BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066740
Article Type:	Protocol
Date Submitted by the Author:	21-Jul-2022
Complete List of Authors:	Hooshiar, Saeedeh Hosseini; Kashan University of Medical Sciences Jafarnejad, Sadegh; Kashan University of Medical Sciences,
Keywords:	GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

The effect of Modified Intermittent Fasting Diet on the severity of Premenstrual Syndrome and Quality of Life in women with overweight or obesity: a study protocol

Saeedeh Hosseini Hooshiar[1]. Sadegh Jafarnejad*[1]

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, IR Iran.

*Corresponding Author. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. E-mail addresses: sjafarnejad@alumnus.tums.ac.ir

ABSTRACT

Introduction: Premenstrual syndrome (PMS) includes a range of behavioral, psychological and physical symptoms and reduces women's quality of life. It has been proposed that increased body mass index (BMI) is associated with menstrual problems and decreased quality of life. Some studies suggest that menstrual problems are caused by increased prostaglandin production. The body fat amount plays a role in menstrual cycles. It can be hypothesized that irregular menstruation and disturbed ovulation can alter the estrogen/progesterone ratio and lead to the production of increased prostaglandin and therefore menstrual problems. Intermittent fasting as an unusual diet results in improvement of anthropometric indices and reduction of body weight. This study aims

to investigate the effect of a daily calorie restriction diet and modified intermittent fasting diet on PMS and Quality of Life.

Methods and analysis: This is an open-label parallel randomized controlled trial to compare the effect of a modified intermittent fasting diet and daily calorie restriction diet on the severity of PMS and Quality of Life in women with obesity or overweight for 8 weeks. Participants will be randomized using stratified randomization based on age and BMI. Then using the random numbers table, they are assigned to one of the two groups fasting (intervention) or daily calorie restriction (control). Primary outcomes were chosen for the study: the difference in the severity of PMS, the quality of life, BMI, fat-free mass (FFM), body fat mass, waist circumference, and the waist-to-hip ratio from baseline to 8 weeks. Secondary outcomes were chosen for the study: the difference in the change of hip- circumference, skeletal muscle mass, percent body fat, and visceral fat area from baseline to 8 weeks.

Ethics and dissemination: The study is approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) (2022-04-17).

Trial registration number: IRCT20220522054958N1

Strengths and limitations of this study

- This is the first study that investigates the effect of modified intermittent fasting diet on the severity of premenstrual syndrome.
- Individuals will be randomized using stratified randomization based on BMI and age, to ensure between-group homogeneity.
- This study is not designed to evaluate the long-term consequences.

INTRODUCTION

PMS is a common disorder among women of reproductive age and reduces their quality of life [1]. The onset of this disorder is in the luteal phase of the menstrual cycle [2]. The worldwide

prevalence of PMS is 47.8 % [3] and among Iranian women is 54·9 % [4]. The PMS symptoms including emotional, behavioral, and physical symptoms can vary from person to person and, may have different causes [5]. In consideration of 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 searching for safer, and more efficient therapies [6]. Therefore, the use of safe approaches such as nutritional interventions for controlling this disorder can be of value [7]. Some studies indicate that family history, age, oral contraceptive pills, stress, smoking, dietary habits, BMI, and exercise can play a role in menstrual problems [8]. Some data propose a positive association between menstrual problems with increased BMI [9]. In addition, Hong et al. indicated a U-shaped association between menstrual problems and BMI. It indicates that both the underweight and overweight + obese women have a higher risk of menstrual problems [10]. Some studies suggest that menstrual problems are caused by increased prostaglandin production [11]. The body fat amount plays a role in menstrual cycles and normal ovulation and can result in menstrual problems [12]. It can be hypothesized that irregular menstruation and disturbed ovulation can alter the estrogen/progesterone ratio, leading to increased prostaglandin production and therefore menstrual problems [13]. Also, in reviews investigating the relationship of obesity to quality of life in various populations, obesity is associated with reduced quality of life [14].

The first-line therapy for weight loss in obese patients is calorie restriction [15]. However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets [16]. Over the past 10 years, an intermittent fasting diet has been proposed as an unconventional method of losing body weight. It improves metabolic health beyond usual calorie restriction [17]. Findings of studies indicate that alternate-day fasting reduces body weight by 3% to 7% within 2 to 3 months [18]. However, what has not yet been determined is whether intermittent fasting or calorie restriction will further improve body composition and fat distribution [15]. Trepanowski et al. (2016) in a systematic review indicated that interventions such as intermittent fasting, reduce waist circumference greater than common weight-loss diets but reduce body weight similar to daily calorie reduction diets [15, 19]. Hutchison et al. (2019) have highlighted that intermittent fasting reduces weight and fat mass more than daily calorie restriction for 8 weeks [20]. The results of other studies demonstrate that attempting weight loss increases the

risk of menstrual problems [21]. 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 [10]. Therefore, we aim to study the effect of a daily calorie restriction diet and modified intermittent fasting diet on PMS and Quality of Life to achieve definitive results in this field.

METHODS AND ANALYSIS

Study design

This is an open-label parallel randomized controlled trial to study the effect of a daily calorie restriction diet and intermittent fasting diet on the severity of PMS and Quality of Life in women with overweight or obesity for 8 weeks. Individuals will be selected from the Health Centers of Kashan University of Medical Sciences. Then, participants are randomly assigned into two groups fasting (intervention) and daily calorie restriction (control) (table 1). The protocol was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) and was registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). Patients will give written consent following a verbal description of the study.

Patient and public involvement

Neither patients nor the public are involved in the conception, design or conduct of the study.

Eligibility criteria

Inclusion criteria: 1) Women in the age range of 18 to 50 years 2) Their BMI is more than or equal to 25 and less than 40 3) regular menstrual cycles of 21–35 d and menstrual bleeding between 3 and 8 d. 4) Having PMS 5) Participants who are willing to comply with study procedures.

Exclusion criteria: 1) Pregnancy 2) Breastfeeding 3) A history of any chronic diseases such as high blood pressure, heart disease, diabetes, gastrointestinal disorders such as gastritis, gastric and duodenal ulcers 4) The habit of smoking 5) Alcohol abuse 6) Weight loss more than 1 to 2 kg in the past month 7) Taking a dietary supplement 8) To follow a specific diet 9) Subjects using any medications (including hormonal contraception) for at least last 2 months 10) having any illness affecting PMS symptoms including mental or psychological diseases such as depression and any

diagnosed clinical condition such as cancer, CVD, renal, hepatic, neurological, infectious, endocrine and gynecological diseases; surgery during the last 6 months. 11) Taking contraceptives and antidepressants 12) B6 supplementation in the last 3 months 13) Suffering from severe stress during the study 14) Failure to complete the questionnaire 3 consecutive days and 5 non-consecutive days.

Sample size calculation

The sample size was estimated using the parameter of a previously published randomized controlled trial that investigated the effect of Ramadan intermittent fasting on gut hormones and body composition in males with obesity [22]. We used the fat-free mass (FFM) data for this study, the standard deviation value of FFM was 63.4 in the intervention group [22]. To detect a clinically significant difference in the outcome measures 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.

Randomization

Individuals will be randomized using stratified randomization based on BMI (40 >BMI≥30; 30 >BMI ≥25) and age (50>age≥30; 30 >age ≥18). This is performed by ranking each subject based on their age and BMI, to have greater between-group homogeneity. Then they are assigned to groups of control and intervention using the random numbers table.

Study hypothesis

- Modified intermittent fasting diet reduces the severity of PMS of the participants in the intervention group.
- Modified intermittent fasting diet increases the quality of life of the participants in the intervention group.

Study outcomes

Primary outcomes

- The effect of daily calorie restriction and modified intermittent fasting on the severity of PMS in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on the quality of life in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on BMI in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on fat-free mass in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on body fat mass in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on waist circumference in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on the waist-to-hip ratio in obese and/or overweight adult women with PMS will be assessed.

Secondary outcomes

- The effect of daily calorie restriction and modified intermittent fasting on hip-circumference in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on percent body fat in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on skeletal muscle mass in obese and/or overweight adult women with PMS will be assessed.
- The effect of daily calorie restriction and modified intermittent fasting on the visceral fat area in obese and/or overweight adult women with PMS will be assessed.

Dietary intervention protocol

Figure 1 shows the flow chart of the participants. 60 women (306 per group) with obesity or overweight and diagnosed with PMS (according to Premenstrual Symptoms Screening Tool (PSST)) are randomly assigned to the 'intermittent fasting' or 'control' group. All individuals follow their diet which will prescribe based on their total energy need and group. The energy requirements for participants will calculate by using the Mifflin equation [23]. Dietary counselling is performed by a professional dietician. Intermittent 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 authorized as lunch between 12.00 and 2.00 pm. 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. In the daily calorie restriction (control) group, subjects consume 63% of the calculated energy requirement each day. Both groups continue their diet for 8 weeks. All participants will prepare their meals at home. Control and intervention group subjects are required to maintain their physical activity routine throughout the study. Daily dietary fat, protein, and carbohydrates respectively account for 30, 15 and 55% of energy requirement.

Adherence to the diet

To control the adherence to the diet by the participants, once every two weeks, food record questionnaires will be completed three days (2 normal days and 1 day off) a week [24] 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 analyzed using N4 software (First Databank Inc.; 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 between 80% to 110% of the prescribed [25].

Assessment of variables

Premenstrual Symptoms Screening Tool

To diagnose PMS and to assess the severity of premenstrual symptoms, we used the PSST questionnaire [26]. It consists of 19 questions which have two parts. The first part includes 14 psychological, physical and behavioral symptoms and the second part measures the effect of these symptoms on people's lives and includes 5 questions. These symptoms are assessed in the five days before menstruation [27]. The severity of each symptom was graded from 1 to 4 (1: none, 4: severe). To define a PMS patient, the following schedule was used: (1) we required a score ≥ 3 in one of the four questions about whether the woman felt "irritable", "tense", "tearful" or "depressed". (2) a score ≥ 3 in one of the five variables of interference with "work performance, relationship with colleagues, family members, in social life or household tasks" was required. (3) a score ≥ 3 in at least four of the first 14 questions (i.e. all questions except the five questions related to interference). Women who did not meet the requirements are excluded from the study [27].

Calendar of Premenstrual Experiences (COPE)

After the selection of participants with PMS, they are expected to record their daily experience of symptoms using the COPE [28] for three 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 behavioral symptoms daily throughout the menstrual cycle [28, 29]. The severity of each item was assessed daily using a 4-point Likert scale (0 = not at all; 1 = a little; 2 = somewhat; 3 = a great deal) [30] . 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 to 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 [31]. This form will be completed by the participants for three months, one month before the start of the intervention, and will be completed for two months during the intervention.

The 12-item Short-Form Health Survey

The Short Form Health Survey SF-36 is a generic health-related quality of life questionnaire that is widely used worldwide [32]. The 12- item Short Form Health Survey (SF-12) is a shorter alternative form of the SF-36 that includes 12 questions and 8 scales: bodily pain, physical functioning, role limitations due to physical problems, general health, vitality, social functioning, role limitations due to emotional problems and perceived mental health [33, 34]. Response categories for items are ranging from 1 to 6-point scales. Then raw scores are transformed to provide eight scale scores each ranging from 0 to 100 [34, 35] And a higher score means a better quality of life.

Physical activity scale

To evaluate physical activity in this trial, the physical activity questionnaire based on the metabolic equivalents (MET) is used. This questionnaire has 9 levels from rest and sleep (METs:0.9) to severe activity (>6 METs) [36].

Anthropometric indices

BMI: weight was measured using the scale 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 calculated as weight in kilograms divided by height squared in square meters.

The waist circumference: The waist circumference is measured during normal expiration at the midpoint between the highest point of the iliac crest and the lowest rib, with a non-stretchable measuring tape [37].

Other anthropometric indices such as percent body fat, fat-free mass, body fat mass, skeletal muscle mass, and visceral fat area 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-square test was used to compare qualitative variables between the two groups (intermittent fasting and control) and an independent t-test is used to detect differences in quantitative factors between groups. Quantitative data are expressed as mean and standard deviation. A paired t-test (in parametric conditions) and Wilcoxon test (in non-parametric conditions) are used to compare the mean of quantitative data within the group at the beginning and end of the intervention (8 weeks later). To compare the mean between the two groups, the t-test (in parametric conditions) and the Mann-Whitney test (in non-parametric conditions) are used. Analysis of covariance (ANCOVA) is used to detect the difference in variable changes between 2 groups after intervention. P-values <0.05 are considered statistically significant and the data are analyzed using SPSS software.

DISCUSSION

Previous studies have shown the association of obesity with premenstrual problems [9] and reduced quality of life [14]. In recent decades, the fasting diet has emerged as a popular weight loss diet. [17]. The results of a study indicated that 8 weeks of intermittent fasting resulted in greater weight and fat mass losses versus daily calorie restriction [18]. 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 [21]. Therefore, this study is performed to further investigate the effect of a modified intermittent fasting diet and daily calorie restriction diet on PMS and quality of life to achieve definitive results in this field. The information gained will enhance our understanding of fasting interventions, which can be used to improve clinical dietary recommendations for women with PMS.

Patient and public involvement

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

Ethics and dissemination

The study is registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). The participants will receive oral and written information about the study before they give written, informed consent. They will be informed that they can decline to participate or can withdraw from the study at any time without explanation. All collected data will be coded and stored in secure, separate locations. There is no physical or psychological harm related to the study. All questionnaires to be used in this study are well established, and participation in the study is voluntary and can be withdrawn at any time. The findings of this study will be published in national and international conferences and scientific journals.

Authors' contributions: All authors contributed to the study design. Saeedeh Hosseini Hooshiar had primary responsibility for writing the study protocol. Sadegh Jafarnejad critically revised the protocol.

Funding statement: This work is funded by Kashan University of Medical Sciences. grant number [400174].

Competing interests statement: The authors declare that they have no competing interests.

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	Study period						
Trial contents	Enrolment	Allocation	Before intervention	After the intervention			Close-out
Timepoint	-t_1	0	1months	2weeks	4weeks	6weeks	8weeks
Enrolments							
Eligibility screen	☐						
Informed consent	☐						
General questionnaire		☐					
Assessments		☐					☐
Anthropometrics		☐					☐
Physical activity questionnaire		☐					☐

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suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers. Journal of occupational health 45(6):335-43.

COPE questionnaire			☐	☐	☐	☐	☐
SF-12 questionnaire		☐					☐
Interventions							
(Intervention)		☐		☐	☐	☐	☐
(control)		☐		☐	☐	☐	☐
Food record				☐	☐	☐	☐

Table 1. Content of Enrolment, Interventions, and Assessments. COPE: Calendar of Premenstrual Experiences, SF-12: The 12- item Short Form Health Survey.

Fig1. Flow chart of the intervention.

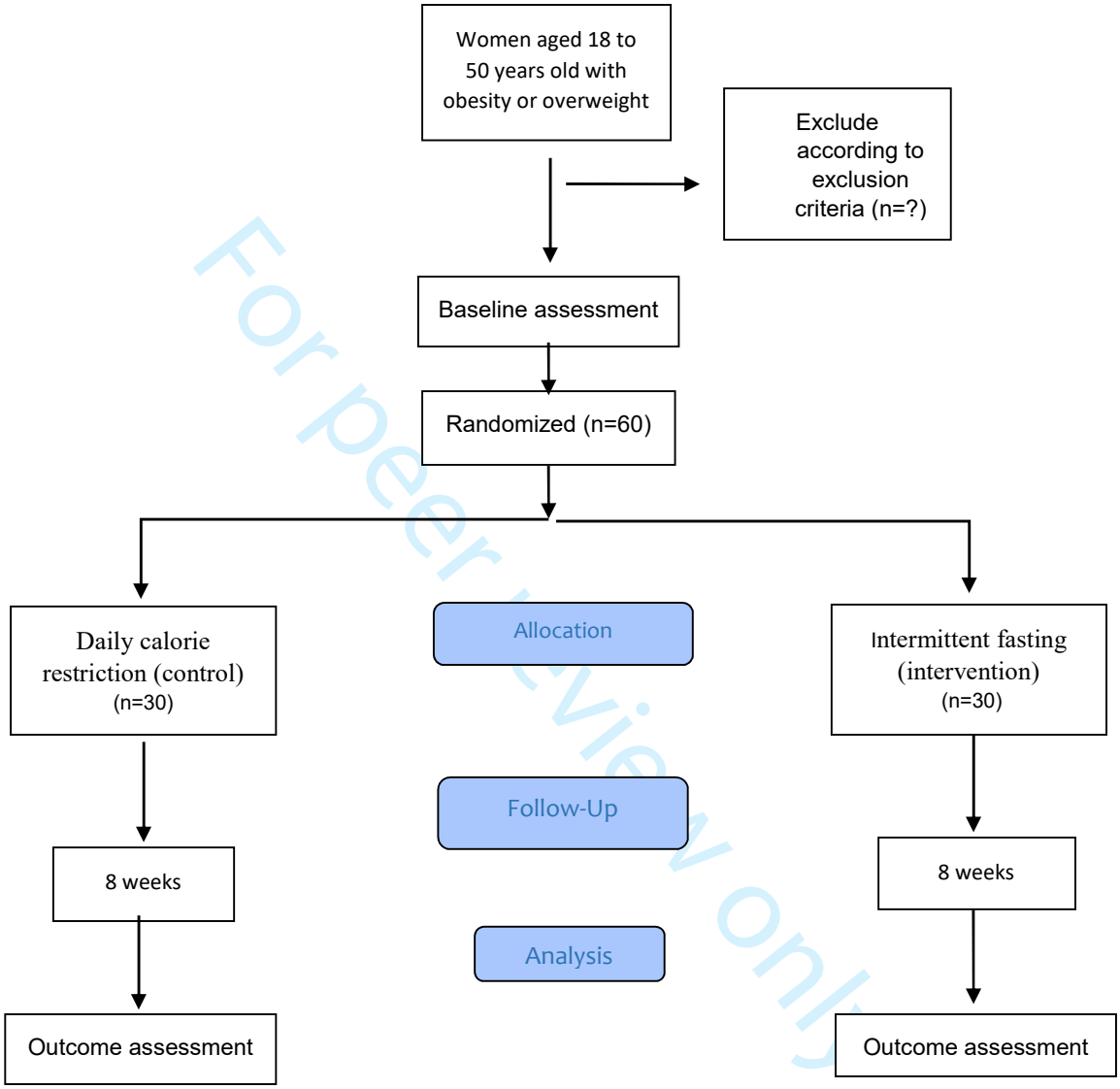

Fig1.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	2
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendices
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The 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 study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066740.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Nov-2022
Complete List of Authors:	Hooshiar, Saeedeh Hosseini; Kashan University of Medical Sciences Yazdani, Akram; Kashan University of Medical Sciences Jafarnejad, Sadegh; Kashan University of Medical Sciences,
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

The 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 study protocol

Saeedeh Hosseini Hooshiar[1]. Akram Yazdani[1]. Sadegh Jafarnejad*[1]

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, IR Iran.

*Corresponding Author. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. E-mail addresses: sjafarnejad@alumnus.tums.ac.ir

Abstract

Introduction: Premenstrual syndrome (PMS) includes a range of behavioral, psychological and physical symptoms and reduces 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 estrogen/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 is an open-label parallel randomized controlled trial to compare the effect of a modified alternate day fasting diet and daily calorie restriction diet on the severity of PMS and HRQoL in women with obesity or overweight for 8 weeks. Women (age: 18 to 50 years, BMI: more than or equal to 25 and less than 40 according to inclusion and exclusion criteria) will be recruited from the Health Centers of Kashan University of Medical Sciences by simple random sampling. Participants will be randomized using stratified randomization based on age and BMI. Then using the random numbers table, they are assigned to one of the two groups fasting (intervention) or daily calorie restriction (control). Outcomes were chosen for the study: the difference in the severity of PMS, HRQoL, BMI, fat-free mass (FFM), body fat mass, waist circumference, and waist-to-hip ratio, hip- circumference, skeletal muscle mass, percent body fat, and visceral fat area from baseline to 8 weeks.

Ethics and dissemination: The study is approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003)(2022-04-17). Results will be published in peer-reviewed academic journals and the participants will be informed via phone calls.

Trial registration: IRCT20220522054958N3

Strengths and limitations of this study

- This is the first study that investigates the effect of a modified alternate day fasting diet on the severity of the premenstrual syndrome.
- Individuals will be randomized using stratified randomization based on BMI and age, to ensure between-group homogeneity.
- This study is not designed to evaluate the long-term consequences.

Introduction

PMS is a common disorder among women of reproductive age and reduces their HRQoL [1]. The onset of this disorder is in the luteal phase of the menstrual cycle [2]. The worldwide prevalence of PMS is 47.8 % [3] and among Iranian women is 54·9 % [4]. The PMS symptoms including emotional, behavioral, and physical symptoms can vary from person to person and, may have different causes [5]. In consideration of 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 searching for safer, and more efficient therapies [6]. Therefore, the use of safe approaches such as nutritional interventions for controlling this disorder can be of value [7]. Some studies indicate that family history, age, oral contraceptive pills, stress, smoking, dietary habits, BMI, and exercise can play a role in menstrual problems [8]. Some data propose a positive association between menstrual problems with increased BMI [9]. 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 [10]. Some studies suggest that menstrual problems are caused by increased prostaglandin production [11]. The body fat amount plays a role in menstrual cycles and regular ovulation and can result in menstrual problems [12]. It can be hypothesized that irregular menstruation and disturbed ovulation can alter the estrogen/progesterone ratio, leading to increased prostaglandin production and therefore menstrual problems [13]. Also, in reviews investigating the relationship of obesity to HRQoL in various populations, obesity is associated with reduced HRQoL [14].

The first-line therapy for weight loss in obese patients is calorie restriction [15]. However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets [16]. Over the past 10 years, an alternate day fasting diet has been proposed as an unconventional method of losing body weight. It improves metabolic health beyond usual calorie restriction [17]. Findings of studies indicate that alternate-day fasting reduces body weight by 3% to 7% within 2 to 3 months [18]. However, what has not yet been determined is whether alternate day fasting or calorie restriction will further improve body composition and fat distribution [15]. Trepanowski et al. (2016) in a systematic review indicated that interventions such as alternate day fasting, reduce waist circumference greater than common weight-loss diets but reduce body weight similar to daily calorie reduction diets [15, 19]. Other studies propose

that alternate-day fasting may preserve fat-free mass and reduces visceral adipose tissue in comparison with calorie restriction [20]. John F et al. (2017) indicated that both alternate-day fasting and calorie restriction increased the fat-free mass, and did not change the visceral adipose tissue [15]. Hutchison et al. (2019) have highlighted that alternate day fasting reduces weight and fat mass more than daily calorie restriction for 8 weeks [21]. The results of other studies demonstrate that attempting weight loss increases the risk of menstrual problems [22]. 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 [10]. Also, Anton et al. (2019) showed that intermittent fasting produced significant weight loss and small but meaningful improvements in HRQoL [23]. Etemadifar et al. (2016) indicated that Fasting Ramadan improved HRQoL in MS patients [24]. A fasting diet correlates with increased HRQoL independent of weight loss [25]. A fasting-mimicking diet is feasible, safe, and potentially increases HRQOL [26]. But a study with 25 young men during Ramadan fasting could not change HRQoL compared to a control group [27]. Therefore, we aim to study the effect of a daily calorie restriction diet and modified alternate day fasting diet on PMS and HRQoL to achieve definitive results in this field.

Methods and analysis

Study design

This is an open-label parallel randomized controlled trial to study the effect of a daily calorie restriction diet and alternate day fasting diet on the severity of PMS and HRQoL in women with overweight or obesity for 8 weeks. Women (age: 18 to 50 years, BMI: more than or equal to 25 and less than 40 according to inclusion and exclusion criteria) will be recruited from the Health Centers of Kashan University of Medical Sciences by simple random sampling. Then, participants are randomly assigned into two groups fasting (intervention) and daily calorie restriction (control) (table 1). The protocol was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) and was registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). Patients will give written consent following a verbal description of the study.

Patient and public involvement

Neither patients nor the public is involved in the conception, design or conduct of the study.

Eligibility criteria

Inclusion criteria: 1) Women in the age range of 18 to 50 years 2) Their BMI is more than or equal to 25 and less than 40 3) regular menstrual cycles of 21–35 d and menstrual bleeding between 3 and 8 d. 4) Having PMS 5) Participants who are willing to comply with study procedures.

Exclusion criteria: 1) Pregnancy 2) Breastfeeding 3) A history of any chronic diseases such as high blood pressure, heart disease, diabetes, gastrointestinal disorders such as gastritis, gastric and duodenal ulcers 4) The habit of smoking 5) Alcohol abuse 6) Weight loss more than 1 to 2 kg in the past month 7) Taking a dietary supplement for weight-loss 8) To follow a specific diet 9) Subjects using any medications (including hormonal contraception) for at least last 2 months 10) having any illness affecting PMS symptoms including mental or psychological diseases such as depression and any diagnosed clinical condition such as cancer, CVD, renal, hepatic, neurological, infectious, endocrine and gynecological diseases; surgery during the last 6 months. 11) Taking contraceptives and antidepressants 12) B6 supplementation in the last 3 months 13) Suffering from severe stress during the study 14) Failure to complete the questionnaire 3 consecutive days and 5 non-consecutive days.

Sample size calculation

The sample size was estimated using the parameter of a previously published randomized controlled trial that investigated the effect of Ramadan alternate day fasting on gut hormones and body composition in males with obesity [28]. We used the fat-free mass (FFM) data for this study, and the mean and the standard deviation value of FFM (kg) were 63.4 and 3.4 respectively in the intervention group [28]. To detect a clinically significant difference in the outcome

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

measures 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% [29], 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 Health Centers of Kashan University of Medical Sciences and are screened based on inclusion and exclusion criteria. Participants that meet the eligibility criteria are invited to take part in the study.

A trained nutritionist and a medical doctor assess patients according to inclusion and exclusion criteria and include patients into 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.

Randomization

56 participants are recruited from the Health Centers of Kashan University of Medical Sciences by Simple Random Sampling according to the inclusion and exclusion criteria. Eligible participants are stratified by age (50>age≥30; 30 >age ≥18) and BMI (40 >BMI≥30; 30 >BMI ≥25) to ensure between-group homogeneity. Participants per stratum are assigned to one of the two groups "modified intermittent fasting" (intervention) and "daily calorie restriction" (control) after baseline investigations. An independent researcher generates the allocation sequence by using random numbers table [30] and a trained nutritionist enrols participants.

Study hypothesis

- Modified alternate day fasting diet reduces the severity of PMS of the participants in the intervention group.

- Modified alternate day fasting diet increases the HRQoL of the participants in the intervention group.

Study outcomes

Primary outcomes

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

Secondary outcomes

The effect of daily calorie restriction and modified alternate day fasting 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. 60 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 [31]. 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 authorized as lunch between 12.00 and 2.00 pm. 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. Control and intervention group subjects are required to maintain their physical activity routine throughout the study.

Adherence to the diet

To control the adherence to the diet by the participants, once every two weeks, food record questionnaires will be completed three days (2 normal days and 1 day off) a week [32] 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 analyzed using N4 software (First Databank Inc.; 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 between 80% to 110% of the prescribed [33].

Plans for participant retention

To control the adherence to the diet, once every two weeks, food record questionnaires will be completed three days (2 normal days and 1 day off) a week. Researchers make regular phone calls to patients to reinforce what they were doing and to encourage them to continue. The data of subjects who deviate or discontinue from intervention protocols for any reason are analyzed with intention-to-treat.

Criteria for discontinuing or modifying allocated interventions

The criteria for discontinuing allocated interventions for a given trial participant include the following:

- individuals with bad adherence are those whose calorie intake is below 80% or above 110% of their recommended calorie intake.
- Participants who experience a severe emotional crisis during the study.
- Getting pregnant during the study.

Data management and protection

DMC is not required for the study as the study involves a small group of patients and is in a single center. Also, data will be stored in SPSS software and kept in local storage as well as in cloud storage. The data does not contain any personal information of the participants. Results will be reported in aggregate. Although every effort will be made to keep study records private, in some cases, patient information in this research study could be reviewed by representatives of the university for purposes such as safety or quality control.

Harms

Adverse events if any, which are directly associated with the study intervention will be monitored, and assessed by researchers involved in the study. The participants will be on continuous monitoring. If any such adverse events arise during the trial, will be reported to Kashan University of Medical Sciences and the Ethics Committee of Kashan University of

Medical Sciences. Any such events are managed by the treating physician and the cost for the same is covered under the trial fund.

Assessment of variables

Premenstrual Symptoms Screening Tool

To diagnose PMS and assess the severity of premenstrual symptoms, we use the PSST questionnaire [34]. It consists of 19 questions which have two parts. The first part includes 14 psychological, physical and behavioral symptoms and the second part measures the effect of these symptoms on people's lives and includes 5 questions. These symptoms are assessed in the five days before menstruation [35]. The severity of each symptom is graded from 1 to 4 (1: none, 4: severe). To define a PMS patient, the following schedule is used: (1) we required a score ≥ 3 in one of the four questions about whether the woman felt "irritable", "tense", "tearful" or "depressed". (2) a score ≥ 3 in one of the five variables of interference with "work performance, relationship with colleagues, family members, in social life or household tasks" was required. (3) a score ≥ 3 in at least four of the first 14 questions (i.e. all questions except the five questions related to interference). Women who do not meet the requirements are excluded from the study [35].

Calendar of Premenstrual Experiences (COPE)

After the selection of participants with PMS, they are expected to record their daily experience of symptoms using the COPE [36] for three 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 behavioral symptoms daily throughout the menstrual cycle [36, 37]. The severity of each item is assessed daily using a 4-point Likert scale (0 = not at all; 1 = a little; 2 = somewhat; 3 = a great deal) [38] . 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 to 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 [39]. This form will be completed by the participants for three months, one month before the start of the intervention, and will be completed for two months during the intervention.

The 12-item Short-Form Health Survey

The Short Form Health Survey SF-36 is a generic HRQoL questionnaire that is widely used worldwide [40]. The 12- item Short Form Health Survey (SF-12) is a shorter alternative form of the SF-36 that includes 12 questions and 8 scales: bodily pain, physical functioning, role limitations due to physical problems, general health, vitality, social functioning, role limitations due to emotional problems and perceived mental health [41, 42]. Response categories for items are ranging from 1 to 6-point scales. Then raw scores are transformed to provide eight scale scores each ranging from 0 to 100 [42, 43] 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 (MET) is used. This questionnaire has 9 levels from rest and sleep (METs:0.9) to severe activity (>6 METs) [44].

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 calculated as weight in kilograms divided by height squared in meters.

The waist circumference: 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. If the deviation is too large, waist circumference is measured twice and a third time [45].

Other anthropometric indices such as percent body fat, fat-free mass, body fat mass, skeletal muscle 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-square test is used to compare qualitative variables between the two groups (alternate day fasting and control) and an independent t-test is used to detect differences in quantitative factors between groups. Quantitative data are expressed as mean and standard deviation. A paired t-test (in parametric conditions) and Wilcoxon test (in non-parametric conditions) are used to compare 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 used to compare the mean between the two groups. Analysis of covariance (ANCOVA) is used to detect the difference in variable changes between 2 groups after intervention. P-values <0.05 are considered statistically significant and the data are analyzed using SPSS software (version 13, IBM). The adjusted p-values correspond to each statistical test used to investigate the intervention effects by using the Bonferroni correction to analyze multiple outcomes.

We will conduct two subgroup analyses, both with strong biological rationale and possible interaction effects. Multiple regression models and Analysis of Covariance (ANCOVA) are used to evaluate whether specific variables are confounders for the treatment effect and whether the treatment effect interacts with specific covariates.

Discussion

This is the first study that investigates the effect of a modified alternate day fasting diet on the severity of the premenstrual syndrome. Previous studies have shown the association of obesity with premenstrual problems [9] and reduced HRQoL [14]. 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. In recent decades, the fasting diet has emerged as a popular weight loss diet. [17]. The results of a study indicated that 8 weeks of alternate day fasting resulted in greater weight and fat mass losses versus daily calorie restriction [18]. 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 [22]. Therefore, this study is performed to further investigate the effect of a modified alternate day fasting diet and daily calorie restriction diet on PMS and HRQoL to achieve definitive results in this field. The information gained will enhance our understanding of fasting interventions, which can be used to improve clinical dietary recommendations for women with PMS. Also, this study will provide important information regarding the effectiveness of alternate day fasting in people with overweight or obesity.

Patient and public involvement

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

Ethics and dissemination

The study is registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). The participants will receive oral and written information about the study before they give written, informed consent. They will be informed that they can decline to participate or can withdraw from the study at any time without explanation. All collected data will be coded and stored in secure, separate locations. There is no physical or psychological harm related to the study. All questionnaires to be used in this study are well established, and participation in the study is

voluntary and can be withdrawn at any time. The findings of this study will be published in national and international conferences and scientific journals.

Consent

A trained nutritionist in the study, assesses the participants, explains the study methodology, and takes informed written consent. For any patient who are injured during this trial, necessary measures will be taken for her and compensation will be paid if necessary, and those events which are directly associated with the study will be managed free of cost. The study data does not include any personal information related to the patient. Patient information which is included in the patient consent form will be kept in a separate folder for future reference if any need arises.

Access to data

The data will be stored in cloud storage and external storage device by a trained nutritionist. The analysis will be done by a statistician who is not involved in the trial. Investigators will not have access to the data until the trial is over. There are no contractual agreements that limit access for researchers.

Authors' contributions

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

Funding statement

This work is funded by Kashan University of Medical Sciences. grant number [400174]. There is no sponsor separate from the funder. The funding body did not have any role in the study design, management, collection, analysis or interpretation of the data, or in writing the report.

Roles and responsibilities

This study is conducted in Shahid Beheshti Hospital, Kashan. The study is run on an individual basis by the principal investigators. The trial will be overseen by the scientific committee every week or when the need arises, in case of any adverse events. Kashan University of Medical Sciences will oversee the overall conductance of the trial and inspection will be done by the Ethics Committee of Kashan University of Medical Sciences as and when needed. In addition, if any adverse events arise, at any point in time which is directly related to the research, they will be reported to the ethics committee.

Protocol amendments

Any change in the conductance of the trial made in the protocol will be informed in the specified format to Kashan University of Medical Sciences and the IRCT. As the study has followed up, the participants who are present in the study will be informed about the protocol changes.

Availability of data and materials

The datasets used and analyzed during the study will be available from the corresponding author upon request.

Competing interest statement

The authors declare that they have no competing interests.

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	Study period						
Trial contents	Enrolment	Allocation	Before intervention	After the intervention			Close-out
Timepoint	-t1	0	1months	2weeks	4weeks	6weeks	8weeks
Enrolments							
Eligibility screen	☐						
Informed consent	☐						
General questionnaire		☐					
Assessments		☐					☐
Anthropometrics		☐					☐
Physical activity questionnaire		☐					☐
COPE questionnaire			☐	☐	☐	☐	☐
SF-12 questionnaire		☐					☐
Interventions							
(Intervention)		☐		☐	☐	☐	☐
(control)		☐		☐	☐	☐	☐
Food record				☐	☐	☐	☐

Table 1. Content of Enrolment, Interventions, and Assessments. COPE: Calendar of Premenstrual Experiences, SF-12: The 12- item Short Form Health Survey.

Fig1. Flow chart of the intervention.

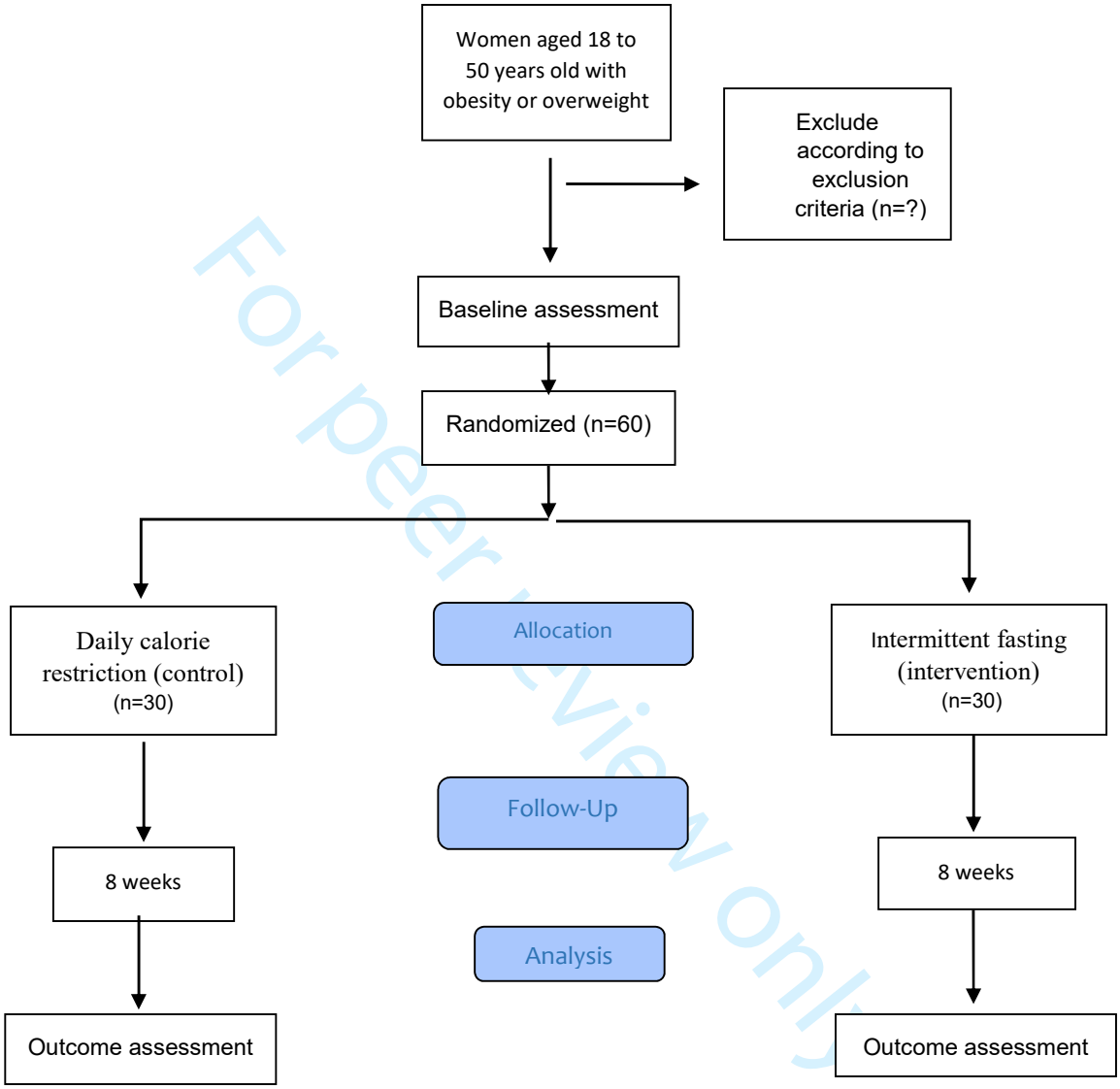

Fig1.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

The 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 study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066740.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Jan-2023
Complete List of Authors:	Hooshiar, Saeedeh Hosseini; Kashan University of Medical Sciences Yazdani, Akram; Kashan University of Medical Sciences Jafarnejad, Sadegh; Kashan University of Medical Sciences,
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

The 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 study protocol

Saeedeh Hosseini Hooshiar[1]. Akram Yazdani[2]. Sadegh Jafarnejad*[1]

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, IR Iran.
[2]Department of Biostatistics and Epidemiology, School of Public Health, Kashan University of Medical Sciences, Kashan, Iran

*Corresponding Author. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. E-mail addresses: sjafarnejad@alumnus.tums.ac.ir

Abstract

Introduction: Premenstrual syndrome (PMS) includes a range of behavioral, psychological and physical symptoms and reduces 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 estrogen/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 is an open-label parallel randomized controlled trial to compare the effect of a modified alternate day fasting diet and daily calorie restriction diet on the severity of PMS and HRQoL in women with obesity or overweight for 8 weeks. Women (age: 18 to 50 years, $25 \leq BMI < 40$, and according to inclusion and exclusion criteria) will be recruited from the Health Centers of Kashan University of Medical Sciences by simple random sampling. Participants will be randomized using stratified randomization based on age and BMI. Then using the random numbers table, they are assigned to one of the two groups fasting (intervention) or daily calorie restriction (control). Outcomes were chosen for the study: the difference in the severity of PMS, HRQoL, BMI, fat-free mass (FFM), body fat mass, waist circumference, waist-to-hip ratio, hip-circumference, skeletal muscle mass, percent body fat, and visceral fat area from baseline to 8 weeks.

Ethics and dissemination: The study is approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) (2022-04-17). Results will be published in peer-reviewed academic journals and the participants will be informed via phone calls.

Trial registration: IRCT20220522054958N3

Strengths and limitations of this study

- This is the first study that investigates the effect of a modified alternate day fasting diet on the severity of premenstrual syndrome.
- Individuals will be randomized using stratified randomization based on BMI and age, to ensure between-group homogeneity.
- This study is not designed to evaluate the long-term consequences.

Introduction

PMS is a common disorder among women of reproductive age and reduces their HRQoL [1]. The onset of this disorder is in the luteal phase of the menstrual cycle [2]. The worldwide prevalence of PMS is 47.8 % [3] and among Iranian women is 33 to 48 % [4]. The emotional, behavioral, and physical symptoms of PMS might change from person to person and may have several reasons. [5]. In consideration of 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 searching for safer, and more efficient therapies [6]. Therefore, the use of safe approaches such as nutritional interventions for controlling this disorder can be of value [7]. Some studies indicate that family history, age, oral contraceptive pills, stress, smoking, dietary habits, BMI, and exercise can play a role in menstrual problems [8]. Some data propose a positive association between menstrual problems with increased BMI [9]. 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 [10]. Some studies suggest that menstrual problems are caused by increased prostaglandin production [11]. The body fat amount plays a role in menstrual cycles and regular ovulation and can result in menstrual problems [12]. It can be hypothesized that irregular menstruation and disturbed ovulation can alter the estrogen/progesterone ratio, leading to increased prostaglandin production and therefore menstrual problems [13]. Also, in reviews investigating the relationship of obesity to HRQoL in various populations, obesity is associated with reduced HRQoL [14].

The first-line therapy for weight loss in obese patients is calorie restriction [15]. However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets [16]. Over the past 10 years, intermittent fasting diet has been proposed as an unconventional method of losing body weight. It improves metabolic health beyond usual calorie restriction [17]. 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 feasting, on an every-other-day basis. Findings of studies indicate that alternate-day fasting reduces body weight by 3% to 7% within 2 to 3 months [18]. However, what has not yet been determined is whether alternate day fasting or calorie restriction will further improve body composition and fat distribution [15]. Trepanowski et al. (2018) in a systematic review indicated that interventions such as alternate day fasting, reduce waist circumference

greater than common weight-loss diets but reduce body weight similar to daily calorie reduction diets [15, 19]. Other studies propose that alternate-day fasting may preserve fat-free mass and reduces visceral adipose tissue in comparison with calorie restriction [20]. Trepanowski et al. (2018) indicated that both alternate-day fasting and calorie restriction increased the fat-free mass, and did not change the visceral adipose tissue [15]. Hutchison et al. (2019) have highlighted that alternate day fasting reduces weight and fat mass more than daily calorie restriction for 8 weeks [21]. The results of other studies demonstrate that attempting weight loss increases the risk of menstrual problems [22]. 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 [10]. Also, Anton et al. (2019) showed that intermittent fasting produced significant weight loss and small but meaningful improvements in HRQoL [23]. Etemadifar et al. (2016) indicated that Fasting Ramadan improved HRQoL in MS patients [24]. A fasting diet correlates with increased HRQoL independent of weight loss [25]. A fasting-mimicking diet is feasible, safe, and potentially increases HRQOL [26]. But a study with 25 young men during Ramadan fasting could not change HRQoL compared to a control group [27]. Therefore, we aim to study the effect of a daily calorie restriction diet and modified alternate day fasting diet on PMS and HRQoL to achieve definitive results in this field.

Methods and analysis

Study design

This is an open-label parallel randomized controlled trial to study the effect of a daily calorie restriction diet and alternate day fasting diet on the severity of PMS and HRQoL in women with overweight or obesity for 8 weeks. Women (age: 18 to 50 years, $25 \leq BMI < 40$, and according to inclusion and exclusion criteria) will be recruited from the Health Centers of Kashan University of Medical Sciences by simple random sampling. Then, participants are randomly assigned into two groups fasting (intervention) and daily calorie restriction (control) (table 1). The protocol was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1401.003) and was registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). Patients will give written consent following a verbal description of the study.

Patient and public involvement

Neither patients nor the public is involved in the conception, design or conduct of the study.

Eligibility criteria

Inclusion criteria: 1) Women in the age range of 18 to 50 years 2) Their BMI is more than or equal to 25 and less than 40 3) regular menstrual cycles of 21–35 d and menstrual bleeding between 3 and 8 d. 4) Having PMS 5) Participants who are willing to comply with study procedures.

Exclusion criteria: 1) Pregnancy 2) Breastfeeding 3) A history of any chronic diseases such as high blood pressure, heart disease, diabetes, gastrointestinal disorders such as gastritis, gastric and duodenal ulcers 4) The habit of smoking 5) Alcohol abuse 6) Weight loss more than 1 to 2 kg in the past month 7) Taking a dietary supplement for weight-loss 8) To follow a specific diet 9) Subjects using any medications (including hormonal contraception) for at least last 2 months 10) having any illness affecting PMS symptoms including mental or psychological diseases such as depression and any diagnosed clinical condition such as cancer, CVD, renal, hepatic, neurological, infectious, endocrine and gynecological diseases; surgery during the last 6 months. 11) Taking contraceptives and antidepressants 12) B6 supplementation in the last 3 months 13) Suffering from severe stress during the study 14) Failure to complete the questionnaire 3 consecutive days and 5 non-consecutive days.

Sample size calculation

The sample size was estimated using the parameter of a previously published randomized controlled trial that investigated the effect of Ramadan alternate day fasting on gut hormones and body composition in males with obesity [28]. We used the fat-free mass (FFM) data for this study, and the mean and the standard deviation value of FFM (kg) were 63.4 ± 3.4 in the intervention group [28]. 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% [29], 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 Health Centers of Kashan University of Medical Sciences and are screened based on inclusion and exclusion criteria. Participants that meet the eligibility criteria are invited to take part in the study.

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.

Randomization

56 participants are recruited from the Health Centers of Kashan University of Medical Sciences by Simple Random Sampling according to the inclusion and exclusion criteria. Eligible participants are stratified by age (50>age≥30; 30 >age ≥18) and BMI (40 >BMI≥30; 30 >BMI ≥25) to ensure between-group homogeneity. Participants per stratum are assigned to one of the two groups "modified intermittent fasting" (intervention) and "daily calorie restriction" (control) after baseline investigations. An independent researcher generates the allocation sequence by using random numbers table [30] and a trained nutritionist enrolls participants.

Study hypothesis

- Modified alternate day fasting diet reduces the severity of PMS of the participants in the intervention group.

• Modified alternate day fasting diet increases the HRQoL of the participants in the intervention group.

Study outcomes

Primary outcomes

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

Secondary outcomes

The effect of daily calorie restriction and modified alternate day fasting 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. 60 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 [31]. 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 authorized as lunch

between 12.00 and 2.00 pm. 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. Control and intervention group subjects are required to maintain their physical activity routine throughout the study.

Adherence and participant retention

To control the adherence to the diet by the participants, once every two weeks, food record questionnaires will be completed three days (2 normal days and 1 day off) a week [32] 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 analyzed using N4 software (First Databank Inc.; 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 between 80% to 110% of the prescribed [33]. Researchers make regular phone calls to patients to reinforce what they were doing and to encourage them to continue. The data of subjects who deviate or discontinue from intervention protocols for any reason are analyzed with intention-to-treat.

Criteria for discontinuing or modifying allocated interventions

The criteria for discontinuing allocated interventions for a given trial participant include the following:

- individuals with bad adherence are those whose calorie intake is below 80% or above 110% of their recommended calorie intake.
- Participants who experience a severe emotional crisis during the study.
- Getting pregnant during the study.

Data management and protection

The data monitoring committee (DMC) is not required for the study as the study involves a small group of patients and is in a single center. Also, data will be stored in SPSS software and kept in local storage as well as in cloud storage. The data does not contain any personal information of the participants. Results will be reported in aggregate. Although every effort will be made to keep study records private, in some cases, patient information in this research study could be reviewed by representatives of the university for purposes such as safety or quality control.

Harms

Adverse events if any, which are directly associated with the study intervention will be monitored, and assessed by researchers involved in the study. The participants will be on continuous monitoring. If any such adverse events arise during the trial, will be reported to Kashan University of Medical Sciences and the Ethics Committee of Kashan University of Medical Sciences. Any such events are managed by the treating physician and the cost for the same is covered under the trial fund.

Assessment of variables

Premenstrual Symptoms Screening Tool

To diagnose PMS and assess the severity of premenstrual symptoms, we use the PSST questionnaire [34]. It consists of 19 questions which have two parts. The first part includes 14 psychological, physical and behavioral symptoms and the second part measures the effect of these symptoms on people's lives and includes 5 questions. These symptoms are assessed in the five days before menstruation [35]. The severity of each symptom is graded from 1 to 4 (1: none, 4: severe). To define a PMS patient, the following schedule is used: (1) we required a score ≥ 3 in one of the four questions about whether the woman felt "irritable", "tense", "tearful" or "depressed". (2) a score ≥ 3 in one of the five variables of interference with "work performance, relationship with colleagues, family members, in social life or household tasks" was required. (3) a score ≥ 3 in at least four of the first 14 questions (i.e. all questions except the five questions related to interference). Women who do not meet the requirements are excluded from the study [35].

Calendar of Premenstrual Experiences (COPE)

After the selection of participants with PMS, they are expected to record their daily experience of symptoms using the COPE [36] for three 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 behavioral symptoms daily throughout the menstrual cycle [36, 37]. The severity of each item is assessed daily using a 4-point Likert scale (0 = not at all; 1 = a little; 2 = somewhat; 3 = a great deal) [38]. 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 to 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 [39]. This form will be completed by the participants for three months, one month before the start of the intervention, and will be completed for two months during the intervention.

The 12-item Short-Form Health Survey

The Short Form Health Survey SF-36 is a generic HRQoL questionnaire that is widely used worldwide [40]. The 12- item Short Form Health Survey (SF-12) is a shorter alternative form of the SF-36 that includes 12 questions and 8 scales: bodily pain, physical functioning, role limitations due to physical problems, general health, vitality, social functioning, role limitations due to emotional problems and perceived mental health [41, 42]. Response categories for items are ranging from 1 to 6-point scales. Then raw scores are transformed to provide eight scale scores each ranging from 0 to 100 [42, 43] 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 (MET) is used. This questionnaire has 9 levels from rest and sleep (METs:0.9) to severe activity (>6 METs) [44].

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 calculated as weight in kilograms divided by height squared in meters.

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. If the deviation is too large, waist circumference is measured twice and a third time [45].

Other anthropometric indices such as percent body fat, fat-free mass, body fat mass, skeletal muscle 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-square test is used to compare qualitative variables between the two groups (alternate day fasting and control) and an independent t-test is used to detect differences in quantitative factors between groups. Quantitative data are expressed as mean and standard deviation. A paired t-test (in parametric conditions) and Wilcoxon test (in non-parametric conditions) are used to compare 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 used to compare the mean between the two groups. Analysis of covariance (ANCOVA) is used to detect the difference in variable changes between 2 groups after intervention. P-values <0.05 are considered statistically significant and the data are analyzed using SPSS software (version 13, IBM). The adjusted p-values correspond to each statistical test used to investigate the intervention effects by using the Bonferroni correction to analyze multiple outcomes.

We will conduct two subgroup analyses, both with strong biological rationale and possible interaction effects. Multiple regression models and Analysis of Covariance (ANCOVA) are used to evaluate whether specific variables are confounders for the treatment effect and whether the treatment effect interacts with specific covariates.

Discussion

This is the first study that investigates the effect of a modified alternate day fasting diet on the severity of premenstrual syndrome. Previous studies have shown the association of obesity with premenstrual problems [9] and reduced HRQoL [14]. 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. In recent decades, the fasting diet has emerged as a popular weight loss diet. [17]. The results of a study indicated that 8 weeks of alternate day fasting resulted in greater weight and fat mass losses versus

daily calorie restriction [18]. 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 [22]. Therefore, this study is performed to further investigate the effect of a modified alternate day fasting diet and daily calorie restriction diet on PMS and HRQoL to achieve definitive results in this field. The information gained will enhance our understanding of fasting interventions, which can be used to improve clinical dietary recommendations for women with PMS. Also, this study will provide important information regarding the effectiveness of alternate day fasting in people with overweight or obesity.

Patient and public involvement

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

Ethics and dissemination

The study is registered at the Iranian Registry of Clinical Trials (IRCT20220522054958N1). The participants will receive oral and written information about the study before they give written, informed consent. They will be informed that they can decline to participate or can withdraw from the study at any time without explanation. All collected data will be coded and stored in secure, separate locations. There is no physical or psychological harm related to the study. All questionnaires to be used in this study are well established, and participation in the study is voluntary and can be withdrawn at any time. The findings of this study will be published in national and international conferences and scientific journals.

Consent

A trained nutritionist in the study, assesses the participants, explains the study methodology, and takes informed written consent. For any patient who is injured during this trial, necessary measures will be taken for her and compensation will be paid if necessary, and those events which are directly associated with the study will be managed free of cost. The study data does not include

any personal information related to the patient. Patient information which is included in the patient consent form will be kept in a separate folder for future reference if any need arises.

Access to data

The data will be stored in cloud storage and external storage device by a trained nutritionist. The analysis will be done by a statistician who is not involved in the trial. Investigators will not have access to the data until the trial is over. There are no contractual agreements that limit access for researchers.

Authors' contributions

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

Funding statement

This work is funded by Kashan University of Medical Sciences. grant number [400174]. There is no sponsor separate from the funder. The funding body did not have any role in the study design, management, collection, analysis or interpretation of the data, or in writing the report.

Roles and responsibilities

This study is conducted in Shahid Beheshti Hospital, Kashan. The study is run on an individual basis by the principal investigators. The trial will be overseen by the scientific committee every week or when the need arises, in case of any adverse events. Kashan University of Medical

Sciences will oversee the overall conductance of the trial and inspection will be done by the Ethics Committee of Kashan University of Medical Sciences as and when needed. In addition, if any adverse events arise, at any point in time which is directly related to the research, they will be reported to the ethics committee.

Protocol amendments

Any change in the conductance of the trial made in the protocol will be informed in the specified format to Kashan University of Medical Sciences and the IRCT. As the study has followed up, the participants who are present in the study will be informed about the protocol changes.

Availability of data and materials

The datasets used and analyzed during the study will be available from the corresponding author upon request.

Competing interest statement

The authors declare that they have no competing interests.

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	Study period						
Trial contents	Enrolment	Allocation	Before intervention	After the intervention			Close-out
Timepoint	-t1	0	1months	2weeks	4weeks	6weeks	8weeks
Enrolments							
Eligibility screen	☐						
Informed consent	☐						
General questionnaire		☐					
Assessments		☐					☐
Anthropometrics		☐					☐
Physical activity questionnaire		☐					☐
COPE questionnaire			☐	☐	☐	☐	☐
SF-12 questionnaire		☐					☐
Interventions							
(Intervention)		☐		☐	☐	☐	☐
(control)		☐		☐	☐	☐	☐
Food record				☐	☐	☐	☐

Table 1. Content of Enrolment, Interventions, and Assessments. COPE: Calendar of Premenstrual Experiences, SF-12: The 12- item Short Form Health Survey.

Fig1. Flow chart of the intervention.

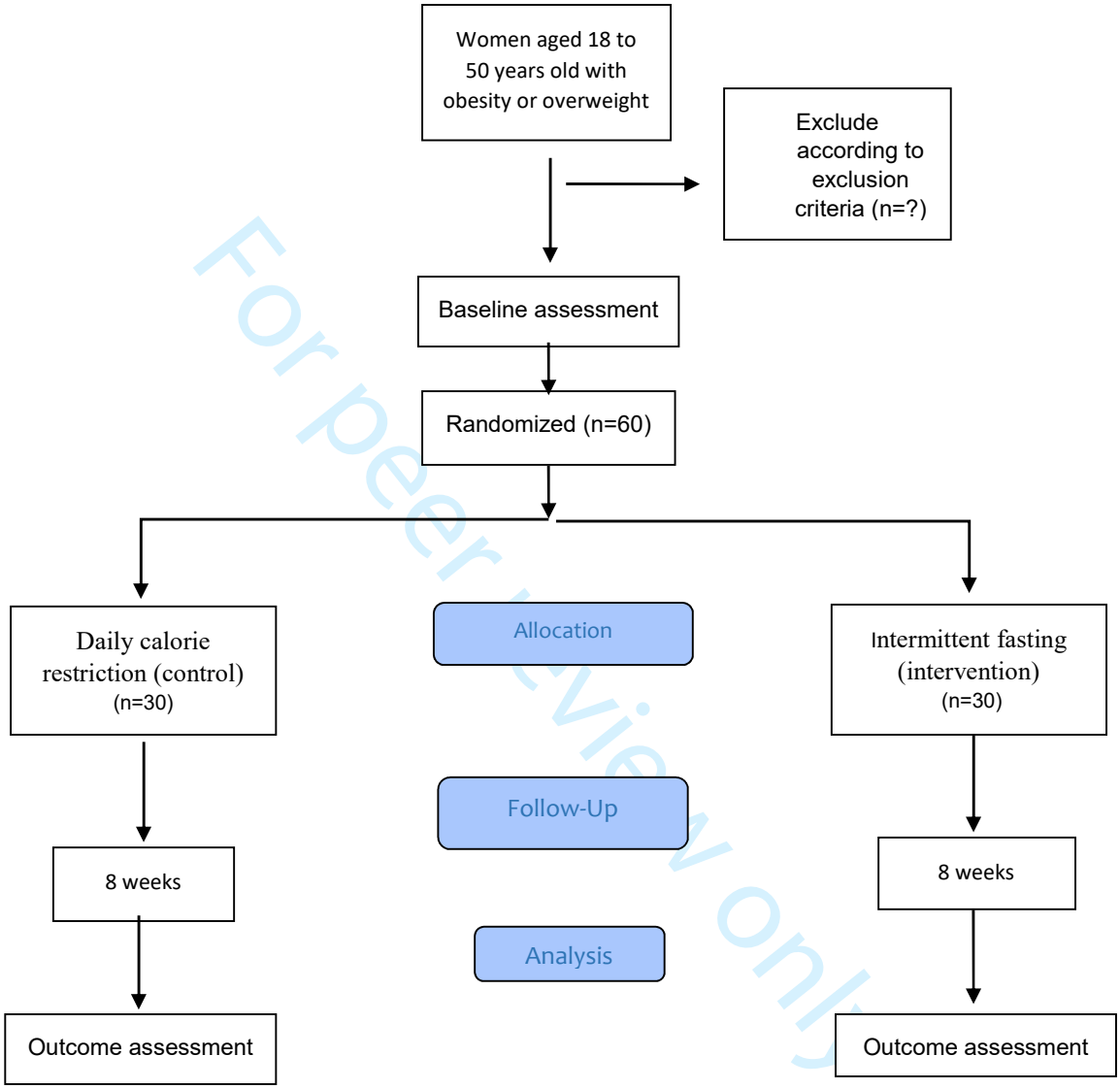

Fig1.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	19

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

The 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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066740.R3
Article Type:	Protocol
Date Submitted by the Author:	18-Mar-2023
Complete List of Authors:	Hooshiar, Saeedeh Hosseini; Kashan University of Medical Sciences Yazdani, Akram; Kashan University of Medical Sciences Jafarnejad, Sadegh; Kashan University of Medical Sciences,
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	GYNAECOLOGY, Community gynaecology < GYNAECOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

The 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

Saeedeh Hosseini Hooshiar[1]. Akram Yazdani[2]. Sadegh Jafarnejad*[1]

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, IR Iran.
[2]Department of Biostatistics and Epidemiology, School of Public Health, Kashan University of Medical Sciences, Kashan, Iran

*Corresponding Author. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. E-mail addresses: sjafarnejad@alumnus.tums.ac.ir

Abstract

Introduction: Premenstrual syndrome (PMS) includes a range of physical, behavioral 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 estrogen/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 eight-week open-label parallel randomized 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 and 50 and 25 ≤ BMI < 40 who meet the inclusion and exclusion criteria will be chosen from the Kashan University of Medical Sciences Center. Patients will be randomized, based on BMI and age through stratified randomization. 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 (FFM), waist-to-hip ratio, waist circumference, hip- circumference, percent 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) (2022-04-17). Results will be published in peer-reviewed academic journals and the participants will be informed via phone calls.

Trial registration: IRCT20220522054958N3

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 randomization based on BMI and age.
- This study is not designed to evaluate the long-term consequences.

Introduction

PMS is a prevalent disorder among women of reproductive age and reduces their HRQoL (1). The onset of this disorder is in the luteal phase of the menstrual cycle (2). The worldwide prevalence of PMS is 47.8 % (3) and among Iranian women is 33 to 48 % (4). The emotional, behavioral, and physical symptoms of PMS might change from woman to woman and may have several reasons. (5). 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 (6). Therefore, the use of safe approaches such as nutritional interventions for controlling this disorder can be of value (7). Some studies indicate that family history, age, oral contraceptive pills, stress, smoking, dietary habits, BMI, and exercise can play a role in menstrual problems (8). Some data propose a positive association between menstrual problems with high BMI (9). 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 (10). Some studies suggest that menstrual problems are caused by increased prostaglandin production (11). The body fat amount plays a role in menstrual cycles and regular ovulation and can result in menstrual problems (12). It can be hypothesized that irregular menstruation and disturbed ovulation can alter the estrogen/progesterone ratio, leading to increased production of prostaglandin and menstrual problems (13). Also, in reviews investigating the relationship of obesity to HRQoL in various populations, obesity is associated with reduced HRQoL (14).

The first-line therapy for weight loss in obese patients is calorie restriction (15). However, because of the daily calorie restriction of conventional weight-loss diets, it is difficult to adhere to these diets (16). 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 (17). 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 feasting, on an every-other-day basis. Findings of studies indicate that alternate-day fasting reduces body weight by 3% to 7% within 2 to 3 months

(18). However, what has not yet been determined is whether calorie restriction or alternate day fasting will further improve anthropometric data and fat distribution (15). Trepanowski et al. (2018) in 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 (15, 19). Several studies indicate that alternate-day fasting diet may preserve muscle mass and reduces visceral fat area compared with calorie restriction (20). Trepanowski et al. (2018) indicated that both alternate-day fasting and calorie restriction preserved the muscle mass, and did not change the visceral fat area (15). Hutchison et al. (2019) highlighted that alternate day fasting reduced weight and fat mass more than daily calorie restriction for 8 weeks (21). The results of other studies demonstrate that attempting weight loss increases the risk of menstrual problems (22). 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 (10). Also, Anton et al. (2019) showed that intermittent fasting produced significant weight loss and small but meaningful improvements in HRQoL (23). Etemadifar et al. (2016) indicated that Fasting Ramadan improved HRQoL in MS patients (24). A fasting diet correlates with increased HRQoL independent of weight loss (25). A fasting-mimicking diet is feasible and safe and can potentially increase HRQOL (26). But Ramadan fasting could not change HRQoL in comparison with control (27). 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 randomized 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 to 50 years, $25 \leq BMI < 40$, and according to inclusion and exclusion criteria) will be recruited from the centers 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 (IRCT20220522054958N1). 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 to 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 to 8 days. 4) Having PMS

Exclusion criteria: 1) Pregnancy 2) Breastfeeding 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 to 2 kg in the past month 7) Taking a dietary supplement for weight-loss 8) To 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, CVD, hepatic, renal, infectious, neurological, endocrine and gynecological 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 14) Failure to complete the questionnaire 3 consecutive days and 5 non-consecutive days.

Sample size calculation

In the study of Fathizadeh et al. (2016), a significant difference in terms of muscle mass between the PMS and healthy groups ($p<0.05$) was reported (28). 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 (29). We used the fat-free mass (FFM) data for this study and the mean and the standard deviation value of FFM (kg) were 63.4 ± 3.4 in the intervention

group (29). 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% (30), 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 centers 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.

Randomization

56 participants are recruited from the centers 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 table (31) and a trained nutritionist enrolls 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, fat-free mass, 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. 60 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 authorized as lunch between 12.00 and 2.00 pm. 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 two weeks, one day off and two 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 analyzed using N4 software (First Databank Inc.; 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% to 110% of the prescribed (34). Researchers will make phone calls to patients every two 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 (DMC) is not necessary. Moreover, data will be retained in local and cloud storage as well as SPSS program. 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 participant s' 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 (35). It consists of 19 questions which have two parts. A part includes 14 psychological, behavioral 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 five days before menstruation (36). The intensity of symptoms is graded from 1 to 4 (1: none, 4:

severe). To recognize 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" (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 (36).

Calendar of Premenstrual Experiences (COPE)

After the selection of participants with PMS, they are expected to record their daily experience of symptoms using the COPE (37) for three 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 behavioral symptoms daily within the menstrual cycle (37, 38). 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) (39). 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 to 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 (40). This form will be completed by the participants for three months, one month before the start of the intervention, and will be completed for two months during the intervention.

The 12-item Short-Form Health Survey

The Short Form Health Survey SF-36 is a generic HRQoL questionnaire that is widely used worldwide (41). SF-12 (the 12- item Short Form Health Survey) 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 (42, 43). 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 (43, 44) And a higher score means a better HRQoL.

Physical activity scale

To evaluate physical activity in this trial, the physical activity questionnaire based on MET (the metabolic equivalents) is used. This questionnaire has 9 levels from sleep and rest (METs:0.9) to severe activity (>6 METs) (45).

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 meters.

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 (>1cm) it is measured a third time(46).

Other anthropometric indices such as percent body fat, fat-free mass, 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-square 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 standard deviation. 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 2 groups before and after the study. P-values <0.05 are considered statistically significant and the data are analyzed using SPSS software (version 13, IBM). Two subgroup analyses will be conducted, with possible interaction effects and strong biological rationale. ANCOVA (Analysis of Covariance) 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 (9) and reduced HRQoL (14). 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 (17). 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 (18). 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 (22). 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.

Patient and public involvement

Neither the patients nor the public is involved in the conduct, design, reporting, or dissemination plans of this trial.

Ethics and dissemination

The investigation has been registered in the Iranian Registry of Clinical Trials. (IRCT20220522054958N1). 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 separate, 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) (2022-04-17).

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 contains 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 analyze the data. Throughout the trial, data will not be accessible to researchers. There is no arrangement to restrict access for researchers.

Authors' contributions

SJ conceived the trial. SHH and AY contributed to the development of the research protocol. SHH contributed to acquiring ethical approval for the trial. SJ, SHH, and AY help in data collection, analysis and interpretation. AY conducts the statistical analysis. SJ is the dietician of the research. All authors contributed to the writing of the final manuscript.

Funding statement

This work is funded by Kashan University of Medical Sciences. grant number [400174]. The funder serves as both the sponsor and the fund. The sponsor played no part in the planning of the study, data collecting, management, interpretation, or analysis, or in the preparation of the report.

Roles and obligations

This research will perform in Shahid Beheshti Hospital, Kashan. Every week or when the need arises, the trial will be overseen by the scientific committee. Kashan University of Medical Sciences will monitor the overall conductance of the trial and inspection will be done by the Ethics Committee of Kashan University of Medical Sciences as and when needed. If any adverse events related to the research arise, at any time, they will be reported to the ethics committee.

Protocol amendments

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In case of any changes in the protocol study, Kashan University of Medical Sciences and the IRCT will be informed. The study patients will be also informed about the changes in the study.

Availability of data and materials

The datasets used and analyzed in this trial will be available from the corresponding author upon request.

Competing interest statement

All authors declare that they have no competing interests.

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	Study period						
Trial contents	Enrolment	Allocation	Before intervention	After the intervention			Close-out
Timepoint	-t1	0	1months	2weeks	4weeks	6weeks	8weeks
Enrolments							
Eligibility screen	☐						
Informed consent	☐						
General questionnaire		☐					
Assessments		☐					☐
Anthropometrics		☐					☐
Physical activity questionnaire		☐					☐
COPE questionnaire			☐	☐	☐	☐	☐

SF-12 questionnaire		☐					☐
Interventions							
(Intervention)		☐		☐	☐	☐	☐
(control)		☐		☐	☐	☐	☐
Food record				☐	☐	☐	☐

Table 1. Content of Enrolment, Interventions, and Assessments. COPE: Calendar of Premenstrual Experiences, SF-12: The 12- item Short Form Health Survey.

Fig1. Flow chart of the intervention.

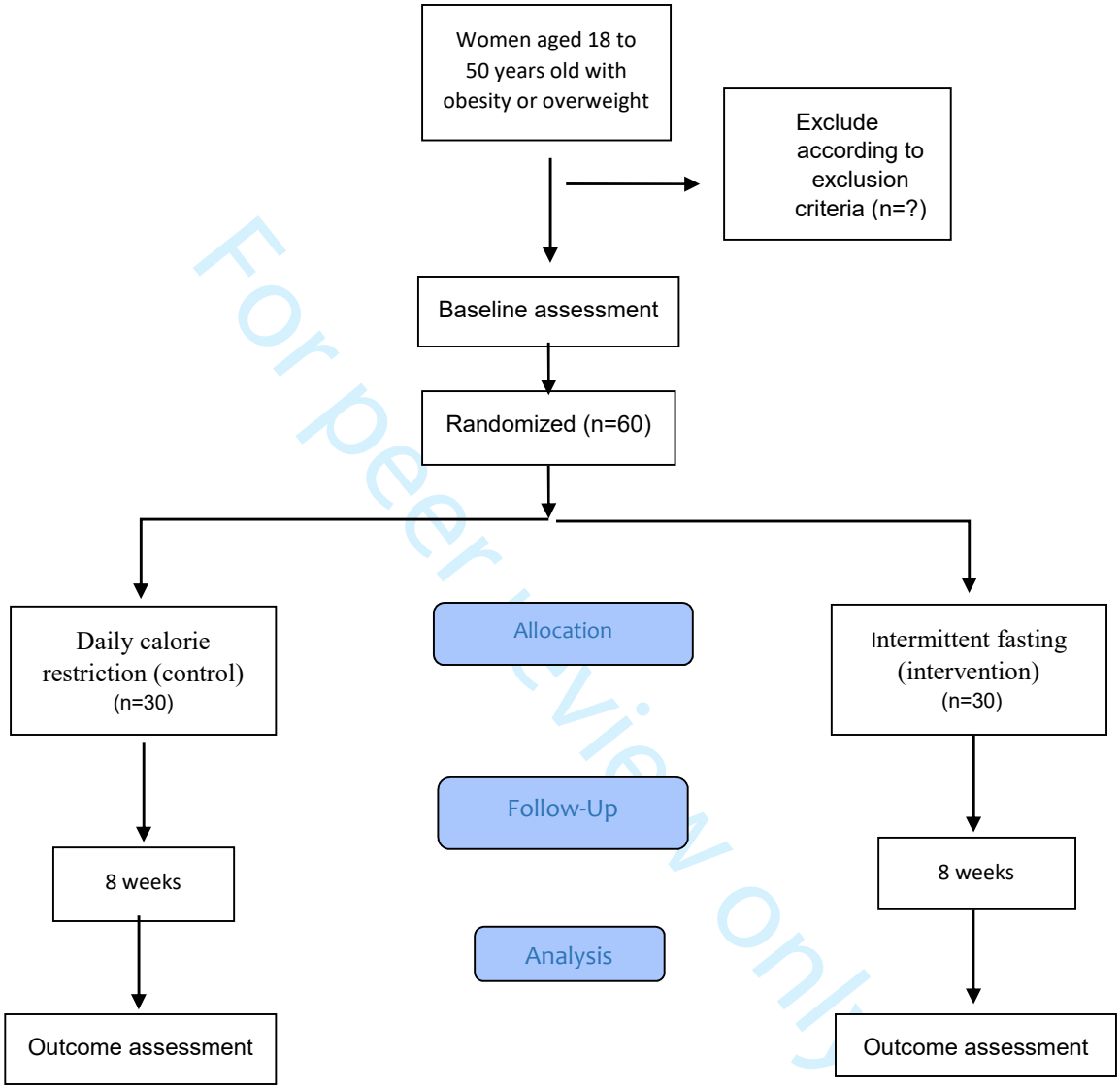

Fig1.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	19

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.