

Effect of Time Restricted Feeding on Anthropometric Measures, Body Composition, Eating Behavior, Stress, Brain Derived Neurotrophic Factor (BDNF) and Lipopolysaccharide Binding Protein (LBP) Levels in Food Addicted Over Weight and Obese Women: A Study Protocol for a RRandomized Clinical Trial

Hanieh Irani

Shahid Beheshti University of Medical Sciences

Banafsheh Khodami

Shahid Beheshti University of Medical Sciences

Behnaz Abiri

Shahid Beheshti University of Medical Sciences

Atoosa Saidpour (✉ atoosa.saidpour@gmail.com)

Shahid Beheshti University of Medical Sciences School of Medicine <https://orcid.org/0000-0002-8442-7620>

Research Article

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Abstract

Background: Food addiction, the desire to eat compulsively and excessively palatable foods, is one of the behavioral factors that plays an important role in pathogenesis of obesity. Food addiction, like drug addiction, changes the dopaminergic system in rewards region of brain, but at lower levels. There are evidence suggesting brain-derived neurotrophic factor (BDNF) is synthesized in dopaminergic pathways in the reward regions of the brain and is involved in regulating food intake and body weight. BDNF is also associated with eating disorders in humans and hyperphagia in mice. On the other hand, it has been shown that the intestinal microbiome is effective in eating behavior through the production of neuronal and hormonal mediators, including BDNF. Intestinal microbiome changes greatly under the influence of diet. It has been shown that a time-restricted feeding (TRF) has been able to maintain fluctuations in the intestinal microbiome in response to the body's circadian rhythm. Furthermore, increased pathogens in the gut are associated with increased release of polysaccharides from the bacterial wall, resulting in increased levels of lipopolysaccharide binding protein (LBP). This study will aim to evaluate the effect of TRF on anthropometric measures, body composition, eating behavior, stress level, BDNF and LBP levels in over weight and obese women with food addiction.

Methods/design: we will carry on a randomized clinical trial for 8 weeks to evaluate the effect of a TRF on anthropometric measures, body composition, eating behavior, stress level, BDNF and LBP levels in obese and overweight women with food addiction.

Discussion: Given the effect of BDNF on regulating eating behavior and body weight and the effect of dietary restrictions on BDNF and the gut microbiome, the TRF diet could possibly be a new way to successfully manage weight through modifying BDNF in people with eating disorders, including food addiction.

Trial Registration: Iranian Registry of Clinical Trials. IRCT20131228015968N7. Registered on 2020-10-25.

Introduction

Background and rationale

Despite recent advances in our understanding of the physiological mechanisms that regulate body weight, obesity remains a major health problem worldwide with multiple of consequences, including metabolic and endocrine complications, malignancy diseases and psychosocial problems(1). The global obesity epidemic suggests that obesity is not only triggered by a lack of motivation for weight loss, loss of control over food intake and continued excessive consumption despite knowing negative consequences may also develop in many individuals(2). The term of 'food addiction' is used to describe this compulsive feeding behaviors associated with loss of control of eating(3, 4)with a prevalence rate ranging from 19–56.8% in different populations .(4, 5) The prevalence of food addiction among Iranian obese women was 26.2% based on Iranian version of Yale Food Addiction Scale (6).Feeding behavior can be managed by both homeostatic (associated with energy demands/stores) and hedonic pathways

(brain dopaminergic reward system) which controls energy intake and body weight (7). So, understanding the mechanisms underlying feeding behavior might be helpful in finding the way of being more efficient in obesity management. Some appetite-regulating hormones such as brain derived neurotrophic factor (BDNF) have been shown to play a modulatory role in reward related behaviors through both aforementioned pathways(8, 9). So it seems that modification of eating behavior through modulation of these hormones may play a key role in some cases of weight gain and obesity such as food addicted ones. Gut microbiota modulation is one of the new therapeutic approaches for managing feeding behavior (10). Based on previous studies, gut microbiota may play an important role in regulating obesity, energy balance and also the host eating behavior through affecting appetite and hormone levels such as BDNF(10, 11). BDNF is a neuromodulator playing an important role in the homeostatic control of food intake and energy expenditure regulation(9). The regulatory role of BDNF in hedonic feeding has also documented through the mesolimbic reward pathways(9) including consumption of palatable food. So it is not surprising that disruptions in these aforementioned regulatory roles of BDNF lead to hyperphagic behavior and obesity(12). So far, it seems that gut microbiota improvement might have a modulatory effect on central levels of BDNF (13–16).

Several methods have been suggested to modify and improvement of gut microbiota such as probiotic and prebiotic supplementation and fasting(17, 18). Time-restricted feeding (TRF) is kind of fasting recommending individuals to confine the eating window to a specified number of hours per, without altering calorie intake or diet quality (19). TRF could alter the diversity or abundance of the gut microbiome in response to the body's circadian rhythm (20). In turn gut microbiota improvement can also modulate BDNF expression in the brain (21) and also feeding behavior (10). Feeding behavior can be affected by stress level in individuals and significant correlation between food addiction and stress has been seen in overweight and obese patients(22, 23). Lipopolysaccharide (LPS) is an endotoxin produced by altered gut microbiota and is associated with low-grade inflammation in obesity(24, 25). Lipopolysaccharide Binding Protein (LBP) is an acute phase protein produced by the liver which binds to LPS and is a part of LPS-induced inflammation. Serum LBP can be measured to evaluate changes in the gut microbiome(24, 25). On the other hand, two previous clinical trials documented that TRF might have a favorable effects on weight loss, reduction of insulin resistance, systolic blood pressure and fasting glucose levels (26). However some previous studies did not show any advantages of using TRF on body weight management(27, 28). Therefore, these aforementioned discrepancies may be somehow explainable by ignoring the role of feeding behavior disorders such as food addiction on body weight management. Hence, we designed a clinical trial study is to investigate the effect of TRF on anthropometric indices, body composition, stress level, eating behavior and serum BDNF and LBP level in over weight and obese women with food addiction.

Objectives And Hypothesis

The aim of this study is to investigate the effect of TRF on anthropometric indices, body composition, eating behavior, stress, serum levels of BDNF and LBP in over weight and obese women with food

addiction. A TRF is expected to improve these aforementioned indicators.

Methods And Design

Study design

This is a randomized clinical trial. The flow chart of the study is presented in Fig 1. We will conduct a randomized clinical trial for 8 weeks. This intervention is conducting in the nutrition clinic of Shahid Beheshti University of Medical Sciences in Tehran, Iran, to evaluate the effect of TRF on anthropometric indices, body composition, eating behavior, stress, BDNF and LBP levels in over weight and obese women with food addiction.

Sample size

The number of participants was calculated according to the alterations in the main variable weight. Determining the sample size for this study is based on how many samples should be selected so that the difference between the mean weight loss of TRF group from the control group is at least 2.3 kg(29), so that this difference with a probability of 95% ($\alpha=0.05$) and power of 80% ($\beta=20\%$) is statistically significant. Using this method, the number of samples in each group was estimated to be 26, which, taking into account the 20% fall in the samples, will be entered by 30 people in each group.

Study population

Overweight and obese women (Body mass index (BMI) between 26 - 39.9 kg/m²) with food addiction were recruited from nutrition clinic of Shahid Beheshti University of Medical Sciences. the diagnosis of food addiction will be based on Food Addiction Scale(30).Over weight and obese women that obtain the necessary score will be enrolled in the study and written informed consent was obtained at the baseline.

Inclusion and exclusion criteria

For the present study, 60 adult women with the following inclusion criteria will be included: aged 20-65 years, BMI between 26 and 39.9 kg/m², Willingness to participate in the study, Confirmation of food addiction after obtaining the necessary score from the relevant questionnaire.

Patients will be excluded if: 1) they are pregnant or lactating 2) have any diseases such as cancer, diagnosed diabetes, newly diagnosed hypothyroidism, renal or liver failure 3) have a weight loss diet in the last 2 months4) current smokers5) take any antibiotics in the last 1 months 6) take any medication affecting study outcomes regularly, 7) use probiotic products (probiotic supplements, yogurt, cheese, cakes, biscuits and probiotic pasta) continuously (more than once a week) in the last month 8) use weight-loss or appetite-suppressing medications 9) perimenopause women. Also, Participants who refuse to continue the study, have medical conditions needing to take antibiotics or have difficulties in fasting for 14 hours a day in the intervention group will be excluded.

Randomization

Participants will be randomly allocated into two groups: the group receive the time restricted feeding or the control group and will be followed up for 8 weeks. Stratified Blocked Randomization method is used to randomly assign people to two groups. The sequencing will be generating by one of the authors (AS) who is not going to assign participants into the study and allocation concealment will be ensured, as the author will not release the randomization code until the patient has been recruited into the trial by other authors (HI and BKh), which takes place after all baseline measurements have been completed. Participants are classified into over weight (26-29.9), grade 1 (30-34.9) and grade 2 obesity (35-39.9) based on body mass index and randomly assigned to one of control or TRF groups. Separate randomization is performed within each group for each BMI class. The size of the blocks is 4, two allocations are given to TRF group (A) and two allocations to Control Group (B). 6 different permutations of AABB, ABAB, BBAA, BABA, ABBA and BAAB will be created.

Intervention

In this study, patients receive the relevant diets for 8 weeks based on the group they are placed in. In both groups, after calculating the amount of calories required by each individual using the Mifflin formula (31) as much as 300-500 kcal will be deducted from the total energy required for each person and accordingly, the low calorie diet plan is given to each individual. The diet in each group will be consist of 50-55% carbohydrates, 15-20% protein and 30% fat. Patients in the TRF group will receive their meals from 10 hours a day from 10 am to 8 pm(32) while the control group will have less than 12 hours fasting.

Adherence

In order to control the participants in terms of adherence to the regimen and prevent the loss of samples, they will be followed up twice a week by phone call and the data of the patients with more than 90% compliance with the intervention will be analyzed.

Study outcome

The outcome of this clinical trial are the changes in weight, BMI, hip circumferences, Waist-to-hip ratio, fat mass, muscle mass, Stress level, Eating behavior, Plasma BDNF and LBP levels.

Procedure

After obtaining the informed consent, the general profile sheet will be completed for each patient. Also, at the beginning of the study, the weight of each patient with light clothing and with the accuracy of 100 grams and the height of each patient in a shoeless state are measured by the meter mounted on the wall with an accuracy of 0.5 cm. Then, BMI of patients is calculated and waist and hip circumferences are measured using meters with 0.5 cm accuracy. Waist-to-hip ratio is calculated. Then, their fat mass and muscle mass are measured by bioelectrical impedance analysis. The participants' daily physical activity level will be measured using the Standard Physical Activity Questionnaire (MET). The validity of this

questionnaire has been confirmed(33). Stress levels of subjects at the beginning and end of the study will be assessed using the Perceived Stress Questionnaire (PSS-14)(34). The scoring method is that based on the 5-degree spectrum, a score of 0-4 is awarded to each item (never score 0 and most of the time score 4). Phrases 4-5-6-7-10 and 13 are scored inversely (never score 4 to most of the time score 0). Then, by collecting the items, the overall score is 0-56, which the higher score indicates more perceived stress(34). Eating behavior will be measured using three-factor eating questionnaire at the beginning and the end of the study. The questionnaire consists of 18 questions in 3 sections about cognitive factors related to eating, hunger and emotional eating. The questionnaire is scored by questions 1 to 13 on a four-point Likert scale from one (definitely incorrect) to four (definitely correct). Questions 14 to 17 also have a separate Likert scale, and question 18 has an 8-degree Likert scoring scale. The higher rating in the cognitive factors associated with eating indicates greater limitation in receiving calories to control body weight. Also, higher hunger score indicates a person's greater susceptibility to eating in response to hunger and higher emotional eating score indicates a person's greater susceptibility to excessive eating. The validity of this questionnaire has been measured in Iran (35).

In order to measure blood biochemical parameters 5 cc of venous blood samples will be taken from the site of the bracing vein and after 12 to 14 hours fasting by the laboratory technician at the beginning and the end of the study. Blood samples taken in tubes containing sodium citrate anticoagulants will be collected and centrifuged in the laboratory of the Shahid Beheshti Nutrition Faculty for 15 minutes at a speed of 500 round per minute and serums will be stored at -80°C until the tests are performed. Plasma BDNF and LBP levels will be measured by ELISA method with BDNF kit and LBP kit with the intra-assay and inter-assay CV of < 10% and <12%, respectively for both kits in the laboratory of the Nutrition Institute of Shahid Beheshti University of Medical Sciences.

Assessment of dietary intake

In this study, to assess participant's dietary intake, at the beginning of the study, at the end of the fourth and eighth weeks of the study, three days of dietary recall about one holiday and two non-holidays will be completed through face-to-face or telephone interviews. Common household measurement tools (glass, cup, soup bowl, plates, teaspoon and tablespoon) will be provided to assist subjects in estimating the portion size of the food. Dietary intake will be analyzed with Nutritionist IV (N4) software

Assessment of physical activity level

MET physical activity questionnaire will be completed for them(33).

Statistical analysis

In this study, data analysis is performed by SPSS software version 11.5. Paired t test will be used to compare the mean of quantitative variables with normal distribution in each group between the beginning and the end of the study and the t test will be used to compare their mean between the two groups at the beginning and end of the study. In the case of quantitative variables with non-normal distribution,

Wilcoxon and Mann-Whitney tests are used, respectively. In case of the variables measured three times during the study (beginning, fourth week and eighth week), repeated ANOVA test will be used. Covariance analysis is used to eliminate the effect of quantitative confounding factors. Chi-square test is used to compare the qualitative variables between the two groups and regression analysis is used to eliminate the effect of qualitative confounding.

Ethical considerations

Obese and overweight women who meet the inclusion criteria will be completely informed about the protocol of the study. The protocol of this study was approved by ethics committee of Shahid Beheshti University of medical sciences and is in conformity with the declaration of Helsinki (approved number IR.SBMU.NNFTRI.REC.1399.03).

Modification of study

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by NNFTRI (National Nutrition and Food Technology Institute), and approved by ethics committee of Shahid Beheshti University of medical sciences prior to implementation. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by NNFTRI. The ethics committee of Shahid Beheshti University of medical sciences may be notified of administrative changes at the discretion of NNFTRI.

Discussion

Emerging evidences suggest that intermittent fasting has favorable effects on metabolic health and weight management (19). A TRF is a kind of intermittent fasting that restricts eating window to less than 12 hours per day (19). It is suggested that TRF helps with reducing body weight, fasting blood sugar, systolic blood pressure and blood lipids. Some studies suggest that TRF can also alter the gut microbiota (19, 20).

LPS as an endotoxin and inflammation marker with short half-life, is produced and released to blood circulation by gut microbiome and binds to LBP. High levels of LPS and LBP is representative of altered gut microbiome(24, 25).

Food addiction is one of the behavioral factors that is associated with adiposity and failure in life style changes for weight loss (2, 3, 4). People with higher stress levels are expected to be more susceptible to food addiction (22, 23). In 2018, Bistoletti et al. suggested that dysbiosis can affect BDNF levels differently in ENS and CNS(36). Alteration in BDNF levels can be associated with eating behavior and

weight management (12) and previous studies on mice showed that compounds produced by gut microbiomes can alter brain levels of BDNF (13–16).

Based on previous studies, it seems that alteration in BDNF levels as a result of alteration in gut microbiota caused by TRF may be a novel strategy for management of food addiction and obesity. So, the aim of this study is to investigate the Effect of TRF on anthropometric measures, body composition, eating behavior, stress, BDNF and LBP levels in overweight and obese women with food addiction.

Trial Status

This trial is in the enrolment stage.

Protocol version 1, 8/11/21.

Recruitment began on November 2020 and is expected to be completed on December 2021.

Abbreviations

BMI: Body mass index; TRF: time- restricted feeding; LBP: lipopolysaccharide binding protein; BDNF: brain derived neurotrophic factor.

Declarations

Ethics approval and consent to participate

This protocol has been approved by Medical Ethics Committee of Shahid Beheshti University of Medical Sciences and is in accordance with the Declaration of Helsinki (approval number IR.SBMU.NNFTRI.REC.1399.03). Each subject will sign an informed consent form. The informed consent will be obtained by HI and BKh. Data collected in this study will not be used in any other ancillary studies. This investigation was registered on Iranian Registry of Clinical Trials at 2020-10-25 (IRCT registration number IRCT20131228015968N7).

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Not applicable.

Authors' contributions

AS and HI designed this study. HI and BKh is conducting the study. HI drafted the manuscript of the protocol. AS and BA critically revised the manuscript.

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The funding body has no role in the design of the study, the collection, analysis and interpretation of data, or in the writing of manuscripts.

Availability of data and materials

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Name and contact information for the trial sponsor

National Nutrition and Food Technology Research Institute

e-mail address:nutrition@sbmu.ac.ir

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Figures

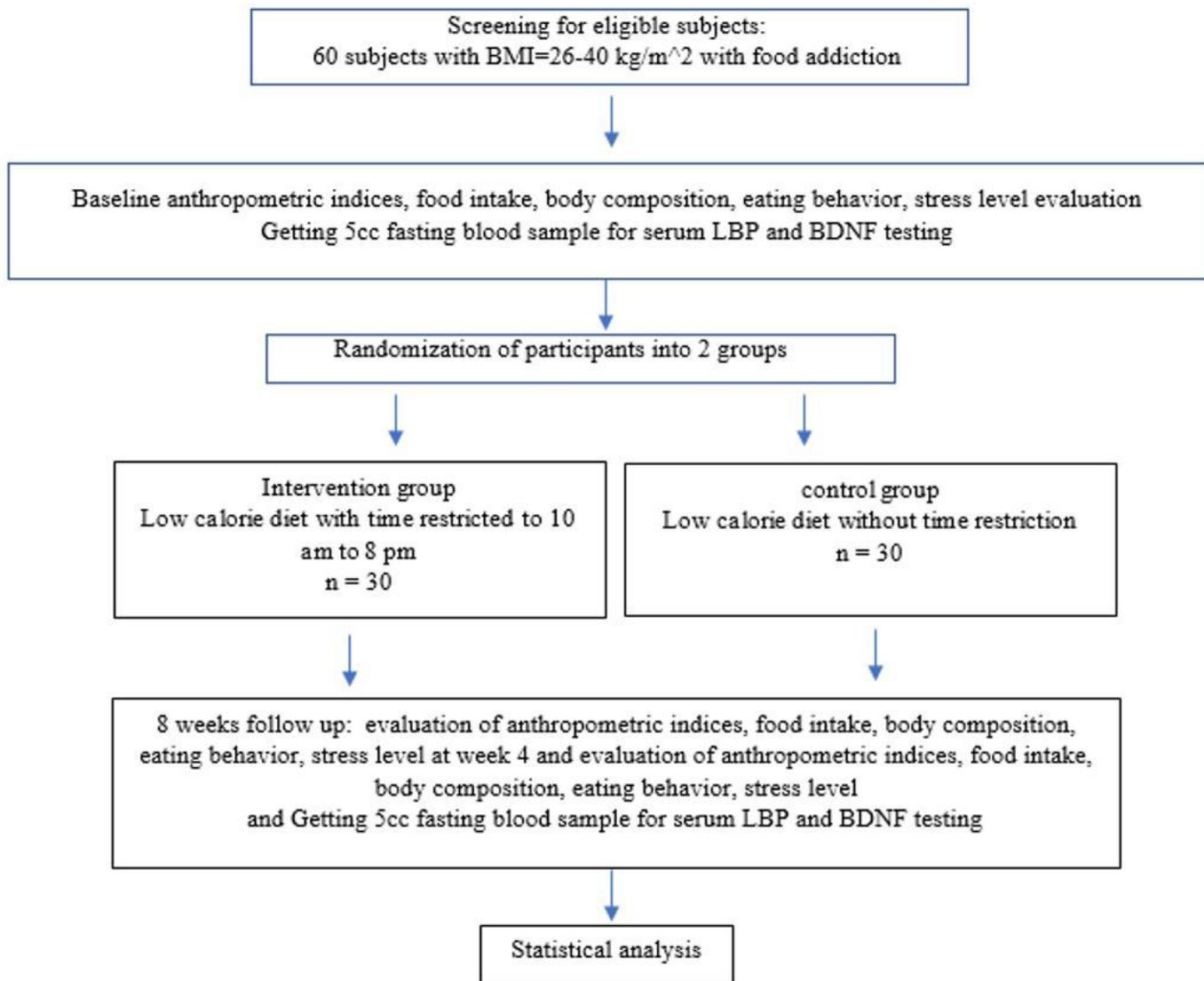


Figure 1

protocol flow diagram; we will carry out an 8-week randomized controlled trial to determine the effects of a time-restricted feeding on anthropometric indices, body composition, eating behavior, stress, brain-derived neurotrophic factor (BDNF) and lipopolysaccharide-binding protein (LBP) levels in over weight and obese women with food addiction.

month																								period (month)	Explanation of proposal activities	
24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1			
																								12	Recruitment and intervention	1
																								-	Presenting the project progress report	2
																								3	Blood biomarkers analysis	3
																								2	Statistical analysis	4
																								4	Writing the final report of intervention	5
																								21	Project Monitoring	6

Figure 2

time line of the study; we expect the duration of trial will be 24 months.