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Effects of boron citrate supplementation on cardiometabolic factors, inflammatory biomarkers and anthropometric measures in obese patients: study protocol for a randomised, double-blind clinical trial

Mohammad Naemi ,[1] Sina Naghshi ,[2] Somaye Rostami,[2] Ehsan Safaei,[3] Helda Tutunchi ,[1] Alireza Ostadrahimi[4]

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For numbered affiliations see end of article.

Correspondence to
Dr Helda Tutunchi; helda.nutrition@gmail.com and Dr Alireza Ostadrahimi; ostadrahimi@tbzmed.ac.ir

ABSTRACT

Introduction Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. The efficacy and safety of boron citrate (BC), a novel therapeutic approach, in patients with obesity are not known. The current trial will take place to determine the effects of BC supplementation on cardiometabolic factors, inflammatory biomarkers, anthropometric measures and body composition in obese patients.

Methods and analysis This double-blind, placebo-controlled, randomised clinical trial will involve 60 eligible obese participants aged 18–60 years. Participants will randomly be allocated to receive either BC capsules (containing 10 mg of boron) in the intervention group or placebo capsules (containing 10 mg of maltodextrin) in the placebo group for 12 weeks. Moreover, physical activity and dietary recommendations will be provided for both groups. To assess the dietary intakes of participants, a 3-day food record (2 days of the week and 1 day of the weekend) will be filled. Cardiometabolic factors, inflammatory biomarkers including tumour necrosis factor α, C reactive protein, interleukin-6 and interleukin-10 levels, anthropometric measures and body composition will be assessed at the baseline and end of the intervention. The findings of this study will provide evidence for the effectiveness of BC in the management of obesity.

Ethics and dissemination There are so far no reported adverse effects associated with the use of boron. This trial was approved by the Ethics Committee of Tabriz University of Medical Sciences (approval number: IR.TBZMED.REC.1401.350). Positive as well as negative findings will be published in peer-reviewed journals.

Trial registration number IRCT20220806055624N1.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled clinical trial that will investigate the effects of boron citrate supplementation in obese patients.
⇒ Several outcomes, including anthropometric and biochemical indicators, will be examined at the study baseline and endpoint.
⇒ Given the evaluation of compliance in the current study, low adherence to intervention might be undetectable.
⇒ A single dose of boron citrate will be used in this study; therefore, we cannot explore dose-response effects.
⇒ Obese individuals will be recruited in the study, which may represent a subpopulation that is more adherent to weight management interventions than the general population with obesity.

INTRODUCTION

Obesity, which typically refers to excess body fat, has emerged as a major public health issue. Obesity is associated with numerous comorbidities, including hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease.[1] Existing data show that the prevalence of obesity is rising.[2] In 2016, more than 20% of the world's population were obese.[3] In this way, Iran is not exempt from this issue. About 40.3% and 19.2% of Iranians were overweight or obese, respectively, based on the second national integrated micronutrient study conducted from 2011 to 2015.[4]

Obesity is a complicated multifactorial disease in which genetic, metabolic and environmental factors are thought to play a major role in its development. Moreover, several lines of evidence suggest that low-grade, long-standing adipose tissue inflammation is strongly associated with insulin resistance and excess body fat mass.[5] The excessive adipose tissue stimulates the secretion of

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inflammatory mediators and, consequently, leads to metabolic disorders.[6] Lifestyle interventions (diet and exercise) have long been known as the cornerstone of weight management.[7 8] Additionally, clinical guidelines recommend adjunctive antiobesity medications, but their usage is severely constrained by their unfavourable side effects.[9] Therefore, novel antiobesity and anti-inflammatory approaches focusing on controlling lipid metabolism to limit fat production and storage with minimal side effects have recently attracted substantial attention.[10]

Elemental boron has been known to be an essential micronutrient for plants since the 1920s. Yet, boron appears favourable not only for plant cells but also for most animal and human cells. Boron has been linked to bone development and maintenance, cognitive function, steroid hormone regulation and immune response.[11] Boron deficiency has been documented to have major effects on mammalian metabolic and physiological systems (lipid, bone, mineral, endocrine function and energy metabolism).[10] In previous experimental studies, a low oral dose of boric acid reduced body weight,[12 13] findings that supported further investigation. Furthermore, a meta-analysis of animal studies documented that boron has weight-lowering effects.[14] Boron citrate (BC) could induce weight loss in obese patients by increasing energy metabolism, thermogenesis, lipolysis and inhibition of adiposeness.[14] Findings from a prospective randomised controlled trial study showed that supplementation with different doses of calcium fructoborate lowered inflammatory biomarkers, including C reactive protein (CRP), fibrinogen and erythrocyte sedimentation rate (ESR), in individuals with primary osteoarthritis.[15] Additionally, supplementation with boron was able to decrease inflammatory cytokines in eight healthy men.[16]

Given the role of BC in suppressing inflammation and inducing lipolysis, we hypothesised that administration of BC may reduce body weight and inflammatory markers and improve cardiometabolic factors in obese patients. Therefore, the purpose of the present study is to investigate the effects of BC supplementation on cardiometabolic factors, inflammatory biomarkers, anthropometric measures and body composition in obese patients.

Methods and design

Study design

This parallel-group, randomised, double-blind clinical trial will evaluate the effects of BC supplementation on cardiometabolic factors and inflammatory biomarkers, including tumour necrosis factor α (TNF-α), CRP, interleukin-6 (IL-6) and IL-10 levels, anthropometric measures and body composition in obese patients. The trial was registered on the Iranian Registry of Clinical Trials website (http://www.irct.ir) on 31 August 2022 with code number IRCT20220806055624N1. Moreover, the Ethics Committee of Research Vice-Chancellor of Tabriz University of Medical Sciences ethically approved the study (identifier: IR.TBZMED.REC.1401.350). This trial will be conducted at Tabriz University of Medical Sciences, Tabriz, Iran. Written informed consent will be obtained from the volunteers at the beginning of the study by researchers. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013 checklist) was used to develop the protocol for this study. The schedule of the trial and the progress of the study, along with the registration of volunteers, allocation, intervention and review, are displayed in online supplemental table 1 and figure 1.

Study participants and enrolment

The participants will be recruited through advertisements and referrals from physicians and families. Individuals who want to participate in the present study would be recruited after an initial interview by the researchers and according to the defined inclusion and exclusion criteria. All participants will be assigned a visit time, and their blood samples will be taken following the visit.

Inclusion criteria

In the present study, we will recruit adults aged between 18 and 60 years and with a body mass index (BMI) of 30–40 kg/m^2.

Exclusion criteria

Individuals who are professional athletes; smokers; those consuming alcohol (consuming more than 14 units of alcohol per week for women and more than 21 units per week for men); taking chemical or herbal drugs for weight loss; hepatotoxic drugs such as phenytoin, tamoxifen, lithium, antihypertensive drugs, lipid-lowering drugs, insulin-sensitive drugs, corticosteroid and non-steroidal anti-inflammatory drugs; antibiotics; supplements affecting liver enzyme levels or any supplements over the past 3 months will not be included. We also will not include individuals who are pregnant, lactating, those with menopause, those who have undergone infertility treatment and those who use birth control pills and oestrogen. Individuals who have some pathological conditions such as cardiovascular, liver, thyroid, parathyroid, kidney, gastrointestinal and known autoimmune diseases, as well as suffering from polycystic ovary syndrome, cancer, severe infection, or inflammatory disease, will be excluded. In addition, those who underwent weight loss surgery in the past year or strict weight loss diets in the past 3 months will not be included in the current study. If a participant becomes pregnant during the course of the research, consumes alcohol and/or tobacco or uses multivitamin-mineral supplements, he or she will be excluded.

Sample size calculation

We estimated sample size taking into consideration all primary outcome measures and all yielded similar sample sizes. For example, here, we calculated the sample size based on plasma CRP level. Using a type I error of 5% (α=0.05) and a type II error of 20% (β=0.20, power=80%), the sample size in this study was calculated using the

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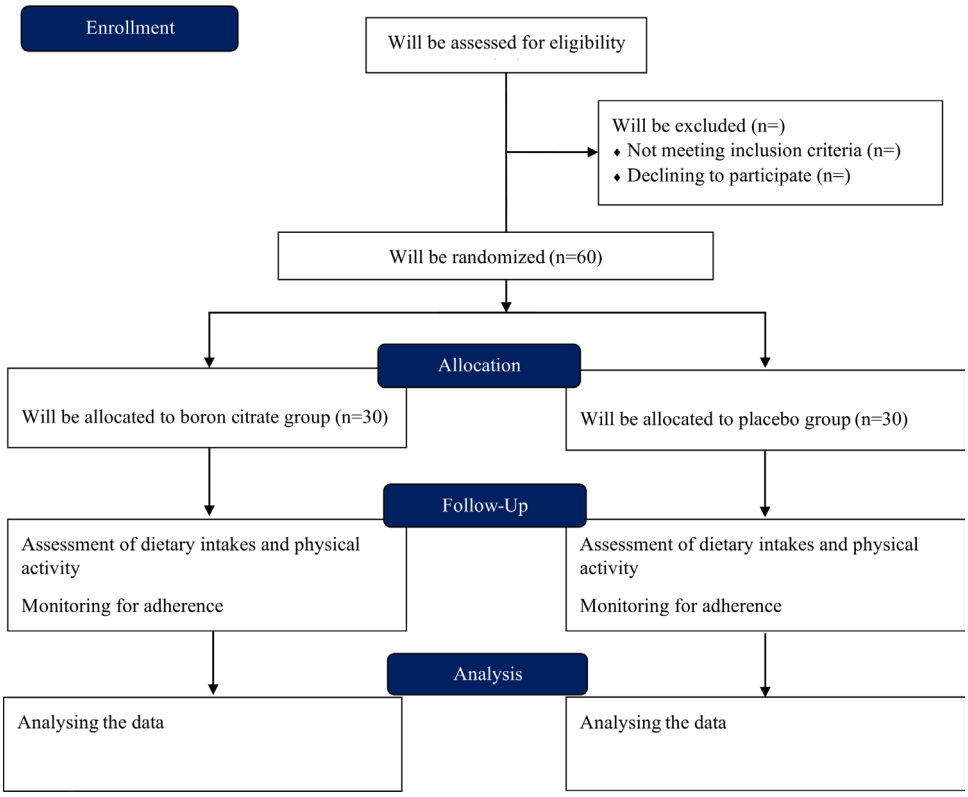

Figure 1 Study flow diagram.

following formula, which has been proposed for parallel clinical trials:

$$n = \frac{\left[\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \sigma^2\right]}{(\mu 1 - \mu 2)^2}$$

n is the sample size for each group.

σ is the variance (SD) for mean CRP, which was considered as 41.5 (the average SDs reported for CRP level in the control and intervention groups of Akbari *et al* study.[17]

$\mu 1$ is the mean difference for CRP level in the intervention group (we considered it as 57.9mg/L based on the study of Akbari *et al*.[17]

$\mu 2$ is the mean difference for CRP level in the control group (which was considered as 34.1mg/L based on the study of Akbari *et al*.[17]

Overall, using this formula and assuming a 20% drop-out rate in each group, we will require a sample size of 30 subjects in each group.

Randomisation

To stratify individuals into distinct strata and blocks, stratified block randomisation will be implemented based on age (18–40 vs 40–60 years) and gender (male vs female). For each individual placed in a given stratum, a matched individual will be considered based on these variables in the same stratum. As a result, two participants with similar characteristics (for age and gender) will be placed in the same stratum. Finally, a research assistant will randomise each stratum into either the BC or placebo group based on a predefined computer-generated number with a 1:1 allocation ratio that will be concealed using serially numbered, opaque, sealed envelopes. Participants and researchers will be blinded to randomisation and allocation until the end of the study. The randomisation list will be provided by the pharmacist of the research centre at the end of the study.

Study interventions

Sixty obese patients will be randomly assigned in a 1:1 allocation ratio to receive either a BC capsule (10mg of boron) or a matched placebo capsule (10mg of maltodextrin) once daily before lunch for 12 weeks. Thirty capsules of BC or placebo will be delivered to patients every 30days (at the study baseline, day 30 and day 60). Patients in the study groups will be asked to consume BC or placebo capsules 30min before lunch or dinner. Patients will be asked to give back the empty packets at the end of the study. Following ethical considerations, the researchers will give physical activity and dietary advice to enhance the lifestyles of patients in both groups. The participants will be requested to follow general healthy eating recommendations, including changing cooking methods to healthier ways and limiting fast foods, saturated fats, high-fat foods, sugar, sweets and sugar-sweetened beverages.

STUDY OUTCOMES

Primary and secondary outcomes

The primary outcomes of this study are changes in inflammatory factors (CRP, TNF-α, IL-10 and IL-6) and anthropometric indicators (weight, BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio

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(WHR) and waist-to-height ratio (WHtR)). Changes in body composition (total body fat mass (FM) and total body fatfree mass (FFM)), glycaemic parameters (fasting blood sugar (FBS), fasting blood insulin (FBI), haemostatic model assessment of insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI)), lipid profile (triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)) and blood pressure are regarded as secondary outcomes.

Measurements and assessments

Clinical assessments

At the onset of the study, all patients will be asked about their medical history, smoking history, underlying diseases, hormonal problems, alcohol consumption, supplement and drug use history and demographic characteristics (age, gender, education level, employment status and marital status).

Blood pressure

Systolic and diastolic blood pressures will be measured in a seated posture twice with a 15-min interval at the right arm. Before measurement, patients will require to rest for 5 min. The mean of two measurements will be used in the analyses.[18]

Assessment of physical activity and dietary intake

To ensure that the participants' physical activity does not alter throughout the trial, we will monitor their activity. As already validated in Iran,[19] the International Physical Activity Questionnaire-Short Form (IPAQ-SF) will be used to estimate the physical activity level at the beginning and end of the study. According to the IPAQ scoring system, physical activity levels will be classified as low, moderate and high. To assess the dietary intake of each participant, a 3-day food record (2 days of the week and 1 day of the weekend) will be filled at the beginning and end of the study. The 3-day food record booklet will be designed to be entirely self-administered. It will contain instructions for recording the day, time, place, type of meal (breakfast, lunch, dinner and snack), name of the food, ingredients of mixed dishes and recipes, food preparation methods, name of the brand/company and the estimated portion size and any leftovers of all food and drink consumed. The portion sizes of consumed foods will be converted to grams per day using household measures.[20] Then, all gram values of food items will be entered into Nutritionist IV software (First Databank, San Bruno, CA, USA), to obtain daily intake of energy and all nutrients.

Assessment of appetite sensations

Appetite sensations (hunger, satiety, fullness, desire to consume something sweet, fatty or salty) of the patients will be measured using a visual analogue scale (VAS) at the beginning and end of the study after overnight fasting.[21]

Anthropometric measurements

Data on anthropometric measurements will be collected at baseline and end of the trial. The body weight will be recorded in a fasted state, without footwear and wearing light clothing to an accuracy of 100 g. Height will be measured using a stadiometer (Seca, Hamburg, Germany) without shoes at a standing position to the nearest 0.1 cm accuracy. WC will be measured as the smallest horizontal circumference between the costal and iliac crests using a non-stretchable measuring tape with an accuracy of 0.1 cm. The hip circumference (HC) will be measured at the widest point above the great trochanters. Then, WHR will be calculated. BMI is calculated by dividing weight in kilograms by the square of height in metres. Body composition, including FM and FFM, will be measured using Tanita MC780 multifrequency segmental bioelectrical impedance analysis applying three different frequencies (5 kHz/50 kHz/250 kHz).

Blood sampling and biochemical measurements

The blood samples (10 mL) will be taken following a 12-hour overnight fasting at preintervention and postintervention phases. The blood samples will be kept inside a gel tube for 20 min for better precipitation and centrifuged at 3000 rpm for 7 min to extract the serum samples. The serum levels of FBS, TC, TG and HDL-C will be measured instantly on fresh blood samples by enzymatic methods using colorimetric technique by commercial kits (Pars-Azmoon Co., Tehran, Iran). LDL-C will be calculated using the Friedewald equation.[22] The ELISA method will be applied to measure FBI using commercial kits (Monobind, Lake Forest, CA, USA). Serum levels of inflammatory factors (CRP, TNF-α, IL-10 and IL-6) will be assessed using ELISA kits. The following formula will be applied to determine HOMA-IR and QUICKI indexes.

HOMA1-IR = (fasting insulin (μIU/mL) × fasting glucose (mg/dL))/405[23]

QUICKI=1/(log (insulin, U/mL) + log (FBS, mg/dL)

Adherence to the intervention

To assess adherence to the intervention, participants will be asked to document their daily usage of BC supplements on a checklist provided by the researchers. To enhance compliance and prevent participants from forgetting to take supplements, investigators will send daily text messages to participants' cell phones as reminders. In addition, adherence to the intervention will be evaluated by counting the returned capsules at the midpoint and end of the experiment.

Statistical analysis

Analyses will follow the intention-to-treat (ITT) convention. Multiple imputations with chained equations will be used to assign any missing values.[24] The Shapiro-Wilk normality test will be used to assess distributions of continuous variables for normality, and natural logarithm transformations of skewed variables will be applied before analyses. The findings will be presented as mean (SD) for numerical data, frequency (percentage) for categorical variables and median (25th, 75th) for values with skewed distribution. The independent

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samples t-test and Mann-Whitney U test will be applied to compare quantitative variables with normal and skewed distributions between the two groups, respectively. To do a within-group comparison, we will use the paired-sample t-test and Wilcoxon signed-rank test for normal and skewed distribution values, respectively. We will use the Chi-square test and Fisher's exact test to examine differences in qualitative variables between the two groups. To estimate the intervention effect for all primary and secondary outcomes, an analysis of covariance (ANCOVA) will be used. In this analysis, we will include baseline measurements as a covariate to adjust for potential differences between treatment groups at baseline. Statistical analysis will be carried out using SPSS, version 23. P value <0.05 will be considered statistically significant.

Adverse effects, safety and data monitoring

Although the values of recommended daily intake (RDA), estimated average requirement (EAR) and adequate intake (AI) for boron have not been reported, the tolerable upper level (UL) in adults is 20 mg/day.[25] All participants will be instructed about the potential adverse effects. Each participant will be asked to document all symptoms they experienced during the study period, whether related to boron or not. In case of side effects, more information is required to make a decision for excluding the participants from the study. In such conditions, unbinding is permissible based on the Medical Ethics Committee criteria. The report of any adverse effects will be sent to the Ethics Committee of Tabriz University of Medical Sciences. One of the investigators will check the coding, security and storage of the data. In addition, he/she will assess the data entry and data values twice.

Patient and public involvement

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

DISCUSSION

There is growing evidence that boron plays a multitude of crucial roles in animal and human health. Several experimental research concluded that boron can reduce weight and may even enhance obesity-related markers.[14] It has also been found that boron decreases FBI, FBS and pancreatic beta cell stress.[26 27] Finding from a study demonstrated that oral administration of boric acid reduced the serum levels of TC and LDL-C and increased HDL-C levels in diabetic rats.[28] In a clinical trial in which healthy women consumed diets containing 10 mg more boron than their usual diet for 1 month, a significant reduction was observed in serum levels of TC, LDL-C, very low-density lipoprotein cholesterol (VLDL-C) and TG. Moreover, the body weight, body FM and BMI of the women decreased significantly.[25] In COVID-19 patients, supplementation with BC alone or in combination with oleoylethanolamide resulted in a significant decrease in serum lactate dehydrogenase and ESR levels.[17] In an experimental study, supplementation with boron compounds reduced lipid peroxidation and enhanced the antioxidant defence mechanism in rats.[29] Moreover, a study documented that boron could effectively ameliorate oxidative stress, inflammation and biochemical parameters in rats treated with acrylamide.[30] Concerning the biological mechanisms, the anti-inflammatory effects of boron are thought to be mediated through the inhibition of the oxidative process by activating scavenging cells such as leukocytes and neutrophils.[31] Boron also enhances the inhibition of free radicals by increasing the level of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) in blood and cells.[32] Boron significantly improves magnesium absorption. It has been shown that in magnesium deficiency, the level of proinflammatory cytokines increases.[32] Magnesium also plays an important role in carbohydrate metabolism; its deficiency provokes and worsens insulin resistance.[32] Overall, findings from animal and human studies provide supportive evidence for the beneficial effects of boron on metabolic and inflammatory parameters. To our knowledge, available investigations regarding the effects of BC supplementation on features of obesity in humans are limited. The findings from this study will provide clinical evidence on the effectiveness of BC supplementation in obese patients. The trial results will be disseminated in peer-reviewed scientific and clinical journals.

Strengths and limitations

This is the first randomised controlled clinical trial that will investigate the effects of BC supplementation in obese patients. Using stratified block randomisation, patients will be matched based on a number of characteristics that may impact the final results. Several outcomes, including anthropometric and biochemical indicators, will be examined at the study baseline and endpoint. Moreover, dietary intake, physical activity level and compliance with the intervention will be assessed. Several limitations to this study should be considered. Given the evaluation of compliance in the current study, low adherence to intervention might be undetectable. Moreover, the serum levels of boron will not be measured to examine the compliance of study participants due to financial constraints. A single dose of BC will be used in this study therefore, we cannot explore dose-response effects. As different doses may have different effects, dose-finding trials are needed to identify the lowest safe and effective dose. The 3month intervention period may not be long enough to see a beneficial effect on secondary outcomes. Obese individuals will be recruited in the study, which may represent a subpopulation that is more adherent to weight management interventions than the general population with obesity. Moreover, the efficacy of the same intervention in other metabolic diseases is not known. Future research should explore the effects of boron on such diseases.

Author affiliations
[1]Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Food Science and Human Nutrition Department, University of Florida, Gainesville, Florida, USA

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[4]Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition& Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the research question or study design. Patients will also not be involved in the conduct, reporting or dissemination plans of this study. Refer to the Methods section for further details.

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ORCID iDs
Mohammad Naemi http://orcid.org/0000-0002-0456-5258
Sina Naghshi http://orcid.org/0000-0001-6226-7403
Helda Tutunchi http://orcid.org/0000-0002-4795-1757

REFERENCES

1 Flegal KM, Carroll MD, Ogden CL, *et al*. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002;288:1723–7.
2 Aekplakorn W, Inthawong R, Kessomboon P, *et al*. Prevalence and trends of obesity and association with socioeconomic status in Thai adults: national health examination surveys, 1991-2009. *J Obes* 2014;2014:410259.
3 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, Underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017;390:2627–42.
4 Pouraram H, Djazayery A, Mohammad K, *et al*. Second National integrated Micronutrient survey in Iran: study design and preliminary findings. *Arch Iran Med* 2018;21:137–44.
5 Burhans MS, Hagman DK, Kuzma JN, *et al*. Contribution of Adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr Physiol* 2018;9:1–58.
6 Ellulu MS, Patimah I, Khaza'ai H, *et al*. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017;13:851–63.
7 Bazshahi E, Sheikhhossein F, Amini MR, *et al*. The Association of dietary energy density and the risk of obesity, type 2 diabetes and metabolic syndrome: A systematic review and meta-analysis of observational studies. *Int J Clin Pract* 2021;75:e14291.
8 Shahavandi M, Amini MR, Shahinfar H, *et al*. Major dietary patterns and predicted cardiovascular disease risk in an Iranian adult population. *Nutr Health* 2021;27:27–37.
9 Wang L, Yu CC, Li J, *et al*. Mechanism of action of Acupuncture in obesity: A perspective from the hypothalamus. *Front Endocrinol* 2021;12:632324.
10 Abdik EA, Abdik H, Taşlı PN, *et al*. Suppressive role of Boron on Adipogenic differentiation and fat deposition in human Mesenchymal stem cells. *Biol Trace Elem Res* 2019;188:384–92.
11 Nielsen FH, Meacham SL. Growing evidence for human health benefits of Boron. *J Evid Based Complementary Altern Med* 2011;16:169–80.
12 Aysan E, Sahin F, Telci D, *et al*. Mechanism of body weight reducing effect of oral Boric acid intake. *Int J Endocrinol* 2013;2013:914651.
13 Basoglu A, Baspinar N, Tenori L, *et al*. Effects of Boron supplementation on Peripartum dairy cows' health. *Biol Trace Elem Res* 2017;179:218–25.
14 Farrin N, Rezazadeh L, Pourmoradian S, *et al*. Boron compound administration; A novel agent in weight management: A systematic review and Meta- analysis of animal studies. *J Trace Elem Med Biol* 2022;72:126969.
15 Scorei R, Mitrut P, Petrisor I, *et al*. A double-blind, placebo-controlled pilot study to evaluate the effect of calcium Fructoborate on systemic inflammation and Dyslipidemia markers for middle-aged people with primary osteoarthritis. *Biol Trace Elem Res* 2011;144:253–63.
16 Naghii MR, Mofid M, Asgari AR, *et al*. Comparative effects of daily and weekly Boron supplementation on plasma steroid hormones and proinflammatory Cytokines. *J Trace Elem Med Biol* 2011;25:54–8.
17 Akbari N, Ostadrahimi A, Tutunchi H, *et al*. Possible therapeutic effects of Boron citrate and Oleoylethanolamide supplementation in patients with COVID-19: A pilot randomized, double-blind, clinical trial. *J Trace Elem Med Biol* 2022;71:126945.
18 Ogedegbe G, Pickering T. Principles and techniques of blood pressure measurement. *Cardiol Clin* 2010;28:571–86.
19 Moghaddam MHB, Aghdam F, Asghari Jafarabadi M, *et al*. The Iranian version of international physical activity questionnaire (IPAQ) in Iran: content and construct validity, factor structure, internal consistency and stability. *World Applied Sciences Journal* 2012;18:1073–80.
20 Ghaffarpour M, Houshiar-Rad A, Kianfar H. The manual for household measures, cooking yields factors and edible portion of foods. *Tehran: Nashre Olume Keshavarzy* 1999;7:42–58.
21 Flint A, Raben A, Blundell JE, *et al*. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* 2000;24:38–48.
22 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
23 Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
24 Azur MJ, Stuart EA, Frangakis C, *et al*. Multiple imputation by chained equations: what is it and how does it work *Int J Methods Psychiatr Res* 2011;20:40–9.
25 Kuru R, Yilmaz S, Balan G, *et al*. Boron-rich diet may regulate blood lipid profile and prevent obesity: A non-drug and self-controlled clinical trial. *J Trace Elem Med Biol* 2019;54:191–8.
26 Hunt CD. Regulation of enzymatic activity: one possible role of dietary Boron in higher animals and humans. *Biol Trace Elem Res* 1998;66:205–25.
27 Kucukkurt I, Akbel E, Karabag F, *et al*. The effects of dietary Boron compounds in supplemented diet on hormonal activity and some biochemical parameters in rats. *Toxicol Ind Health* 2015;31:255–60.
28 Cakir S, Eren M, Senturk M, *et al*. The effect of Boron on some biochemical parameters in experimental diabetic rats. *Biol Trace Elem Res* 2018;184:165–72.
29 Ince S, Kucukkurt I, Cigerci IH, *et al*. The effects of dietary Boric acid and Borax supplementation on lipid peroxidation, antioxidant activity, and DNA damage in rats. *J Trace Elem Med Biol* 2010;24:161–4.
30 Acaroz U, Ince S, Arslan-Acaroz D, *et al*. The Ameliorative effects of Boron against Acrylamide-induced oxidative stress, inflammatory response, and metabolic changes in rats. *Food Chem Toxicol* 2018;118:745–52.
31 Scorei RI, Ciofrangeanu C, Ion R, *et al*. In vitro effects of calcium Fructoborate upon production of inflammatory mediators by LPS-stimulated RAW 264.7 Macrophages. *Biol Trace Elem Res* 2010;135:334–44.
32 Pizzorno L. Nothing boring about Boron. *Integr Med (Encinitas)* 2015;14:35–48.

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Supplementary Table 1: Timeline of the trial

Explanation of the trial activities	Time (months)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Material preparation	*															
Recruitment		*	*	*	*	*	*									
Clinical assessments at baseline		*	*	*	*	*	*									
Nutritional assessments at baseline		*	*	*	*	*	*									
Biochemical assessments at baseline		*	*	*	*	*	*									
Intervention								*	*	*	*	*				
Clinical assessments after intervention													*	*		
Nutritional assessments after intervention													*	*		
Biochemical assessments after intervention													*	*		
Data analysis															*	
Writing the final report of the trial																*
The expected time	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

"Consent Form"

I ..... hereby agree to participate in a research project entitled "Effects of boron citrate supplementation on cardiometabolic factors, inflammatory biomarkers, nutritional status, and anthropometric measures in obese patients: study protocol for a randomized double-blind clinical trial" under the supervision of Dr. Helda Tutunchi.

It was explained to me about the effect boron citrate supplementation on cardiometabolic factors, inflammatory biomarkers, nutritional status, and anthropometric measures will be studied.

In this research, I will answer the questions about my characteristics and dietary intakes, and blood sample will be taken from me at the beginning and end of the intervention. The present study is designed to be 12 weeks. During the research period, I will be consumed boron citrate supplements during the intervention.

My name and all information that is taken from me will be remained confidential (in writing) and the research results will be published as the general answer of the studied group and the individual results will be presented without mentioning names.

The researcher has answered all my questions, so I agree to participate in this research. By mentioning this, this agreement will not prevent legal actions - in case of illegal action or inhumane method.

Name and surname of the person being studied:

Study address:

Date and signature of the participant:

Statement of the research officer: I have informed the participant about the nature of the above plan process and the treatment used and the possible risks. I have answered all questions to the

best of my ability. I will inform the participant of any changes in possible risks and benefits during the study or information that will depend on the participant's willingness to continue treatment in this study.