Nutrition & Diabetes www.nature.com/nutd

ARTICLE **OPEN**

Does partial replacement of animal protein with plant protein in the diet affect components of metabolic syndrome, adropin levels, and the atherogenic index of plasma? Results from a parallel randomized clinical trial in adults with metabolic syndrome

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BACKGROUND: Few studies evaluated the effect of different proportions of dietary plant- and animal-based protein on metabolic syndrome (MetS) and its related biomarkers.
OBJECTIVE: Considering the effect of various types of dietary sources of protein on metabolic health and inconsistent results, this study sought to examine the impact of partially substituting animal protein with plant protein in the diet on the components of MetS, atherogenic index of plasma, and serum adropin values.
METHODS: In this parallel, randomized clinical trial with two arms, 73 participants with MetS were randomly allocated to one of two slightly calorie-restricted intervention diets with different proportions of protein sources, including a plant-based protein diet (70% plant-based protein and 30% animal-based protein) and an animal-based protein diet (30% plant-based protein and 70% animal-based protein) for 10 weeks. All analyses were performed based on both intention-to-treat and per-protocol principles.
RESULTS: Mean age in the plant and animal-based protein groups was 44.0 ± 9.8 and 43.9 ± 9.8 years, respectively. Within each group, weight, body mass index, systolic and diastolic blood pressure, and atherogenic index of plasma significantly decreased, and adropin levels significantly increased after the intervention ($P < 0.05$). However, waist circumference (WC) and triglyceride (TG) levels showed a significant decrease only in the plant protein group, and high-density lipoprotein cholesterol (HDL-c) levels illustrated a significant increase only in the animal protein group ($P < 0.05$). Between-group differences in both crude and adjusted models did not show any significant changes between the two intervention arms ($P > 0.05$). However, findings of per-protocol analyses illustrated a significant difference only in mean adropin values in two study arms.
CONCLUSION: Our findings revealed that both diets based on plant and animal protein were associated with improved in anthropometric indices, MetS components, atherogenic index of plasma, and elevated serum adropin levels. Nevertheless, no statistically significant difference was identified between the two groups.

Nutrition and Diabetes (2025)15:43 ; https://doi.org/10.1038/s41387-025-00401-x

INTRODUCTION

Metabolic syndrome (MetS), as a worldwide public health concern, is related to a cluster of disorders, including abdominal obesity, impaired fasting blood glucose (FBG), dyslipidemia (low high-density lipoprotein cholesterol (HDL-c) and high triglycerides (TG) levels), and high blood pressure [1]. This syndrome is closely linked to an increased risk of non-communicable diseases, including cardiovascular diseases, type 2 diabetes mellitus (T2DM), renal failure, cancers, as well as mortality [2]. The global prevalence of MetS in adults is in the range of 12.5 to 31.4% based on different applied diagnostic criteria, and it has gradually increased in many countries [3].

Recently, the discovery of novel biomarkers, including adropin and the atherogenic index of plasma (AIP), has opened a new era in the diagnosis and management of MetS [4, 5]. Serum adropin levels serve as a significant indicator for predicting metabolic

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Received: 22 October 2024 Revised: 5 October 2025 Accepted: 6 October 2025

state and represent a recently identified peptide that is crucial for maintaining energy homeostasis, obesity, insulin resistance, and nutrient intake [6, 7]. It has been involved in a variety of biological processes and is regulated by carbohydrates and lipids intake [8]. Previous studies suggested that low circulating levels of adropin can elevate the risk of obesity, insulin resistance, MetS, and T2DM [9, 10]. Another index that is related to MetS and obesity is AIP, which is a logarithmically transformed ratio of concentrations of TG to HDL-c [11]. The AIP exhibits a heightened sensitivity in capturing the interaction between atherogenic lipoproteins and protective lipoproteins compared to other atherogenic indices. [5]. Previous investigations revealed that AIP was significantly connected to waist circumference (WC) and body mass index (BMI) [12]. Moreover, elevated AIP levels lead to a higher risk of MetS, diabetes, and high blood pressure [13, 14].

Several modifiable lifestyle factors, especially dietary nutrient content, may have a critical role in the prevalence of MetS, its components, and related biomarkers [15, 16]. In addition to multiple dietary approaches to prevent MetS, the percentage and type of macronutrients could affect the management of MetS and its biomarkers [17, 18]. Among macronutrients, the association of dietary protein with MetS and its related components and biomarkers has received little consideration. Therefore, it is important to examine the effect of partial substitution of dietary animal protein with plant protein on cardiometabolic health, MetS components, atherogenic index of plasma, and adropin.

There are multiple possible reasons for the varying association between animal- and plant-based protein and cardiometabolic risk factors. One potential explanation is that the distinct amino acid compositions found in animal- and plant-based protein sources may account for different associations [19]. Previous evidence has shown that methionine, an essential amino acid, and its metabolic byproduct, homocysteine, may play a role in the progression of chronic diseases, MetS, and its components [20, 21]. On the other hand, glycine, which is abundant in plant-based proteins, is effective in treating metabolic disorders, inflammatory diseases, obesity, diabetes, and cancers [22]. Another explanation is that the various associations of animal-based and plant-based protein foods with cardiometabolic risk factors may be due to additional nutrients in these foods. Plant-based protein sources like nuts, legumes, and whole grains have lower levels of saturated fat but higher levels of monounsaturated and polyunsaturated fats, fiber, polyphenols, antioxidants, and other biologically active compounds. These compounds could have a beneficial effect on metabolic syndrome and its components [23, 24]. In 2021, we conducted a cross-sectional study on a sample of Iranian adults to evaluate the associations between a plant-based diet and MetS, high AIP level, and adropin values [25]. The usual diet of these adult participants consisted of 30% plant protein and 70% animal-based. Our findings showed that more adherence to an unhealthy plant-based diet could increase the odds of MetS, while a healthy plant-based diet could decrease high AIP levels. As cross-sectional investigations could not establish causality, a randomized clinical trial was required to affirm such findings. Due to few number of interventions that assessed the effect of animal and plant protein on MetS and its components, as well as the lack of studies that have investigated this effect on novel biomarkers of MetS, including adropin and AIP in a clinical trial manner, we aimed to conduct a randomized clinical trial in adults with MetS to examine the effect of partial replacement of animal protein with plant protein in the diet on components of MetS, adropin, and atherogenic index of plasma. We hypothesized that substitution of animal protein with plant protein would provide a better metabolic status, higher levels of adropin, and lower levels of AIP.

MATERIALS AND METHODS

Participants

The current intervention study was a parallel randomized clinical trial. This study was carried out as a part of a representative population-based cross-sectional study, which was carried out on adults in Isfahan, Iran, in 2021 [25]. A total of 151 participants with MetS, as determined in the previous cross-sectional study, were asked to take part in this intervention study. According to the Joint Interim Statement (JIS) criteria [26], at least three of the following factors were necessary for a diagnosis of MetS: abdominal obesity (WC ≥ 94 cm in men and ≥80 cm in women), high TG levels (TG ≥ 150 mg/dl (1.7 mmol/L) or on drug treatment for high triglycerides), high blood pressure (systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg or on antihypertensive drug treatment in participants with hypertension), impaired FBG (FBG ≥ 100 mg/dl or on drug treatment for high FBG), and low HDL-c levels (HDL-c < 40 mg/dl (1.03 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women). Participants were teachers aged 20 to 55 years working in Isfahan with a diagnosis of metabolic syndrome based on JIS criteria. Inclusion criteria included a body mass index (BMI) between 25 and 35 kg/m^2 and no adherence to any special diet within the past 6 months. Participants were excluded if they used dietary supplements or had a history of kidney, liver, cardiovascular, thyroid, or cancer diseases. Additional exclusion criteria were use of hormonal drugs (including birth control pills and glucocorticoids), use of medications that could affect blood sugar, blood pressure, or lipid control, being pregnant or lactating, drinking alcohol, or smoking cigarettes or tobacco products. All participants provided informed consent and expressed a desire to participate in the study. Finally, 73 participants with MetS were included at the baseline of the study. A participant's flow diagram is illustrated in Fig. 1. The study received approval from the ethics committee at Isfahan University of Medical Sciences. (No: IR.MUI.RESEARCH.REC.1400.370; 2021/12/04) and was registered on the Iranian Registry of Clinical Trials website (www.irct.ir) (No: IRCT20150909023957N10, 2022/05/16). Informed consent was acquired in written form from all participants.

Study design

This was a parallel study with two arms following two types of diets with different proportions of protein sources, including a plant-based protein diet (70% plant-based protein and 30% animal-based protein) and an animal-based protein diet (30% plant-based protein and 70% animal-based protein). The primary outcomes were adropin levels, MetS components, and probability of having high AIP levels. Participants were randomly allocated to 1 of 2 intervention diets for 10 weeks. This time frame of 10 weeks was chosen based on previous evidence indicating that 8–12 weeks of lifestyle and dietary interventions could lead to significant improvements in MetS components [27, 28]. This duration could provide a balance between allowing enough time to observe measurable changes or improvements and ensuring participants' adherence and feasibility of the study. Random allocation was performed based on a permuted block design with block sizes of 4, using a computer random number generator. On account of the nature of dietary intervention, it was not possible to implement blinding for either the participants or the researchers; however, statisticians were blinded to the treatment assignment. The intervention was only in the form of nutritional and dietary recommendations, and food items were not given to the subjects. These recommendations were personalized for each participant and were designed for each individual by an expert dietician. Participants were visited at the research site every 2 weeks during 10 weeks of the intervention.

Participants were instructed to maintain their regular physical activity levels and to refrain from using any medications or supplements that could potentially influence the study outcomes during the 10-week intervention period. Physical activity was recorded for two days during the study. Dietary intake was evaluated using a 3-day diet record. In addition, diet compliance was evaluated using a 3-day diet record every two weeks. To decrease recall bias and reliance on memory, participants recorded their food intake at the time of food consumption. The food intake (g/day) was analyzed using Nutritionist IV software (Version 7; N-squared computing, OR, USA) to calculate total energy and nutrient intake.

Sample size

Due to a lack of studies assessing the effect of partial replacement of animal-based protein with plant-based protein on adropin levels (as the main outcome), the sample size calculation method for a pilot study was applied to calculate sample size (by considering a power of 90%, two-sided 5% significance, and having a standardized small effect size). According to

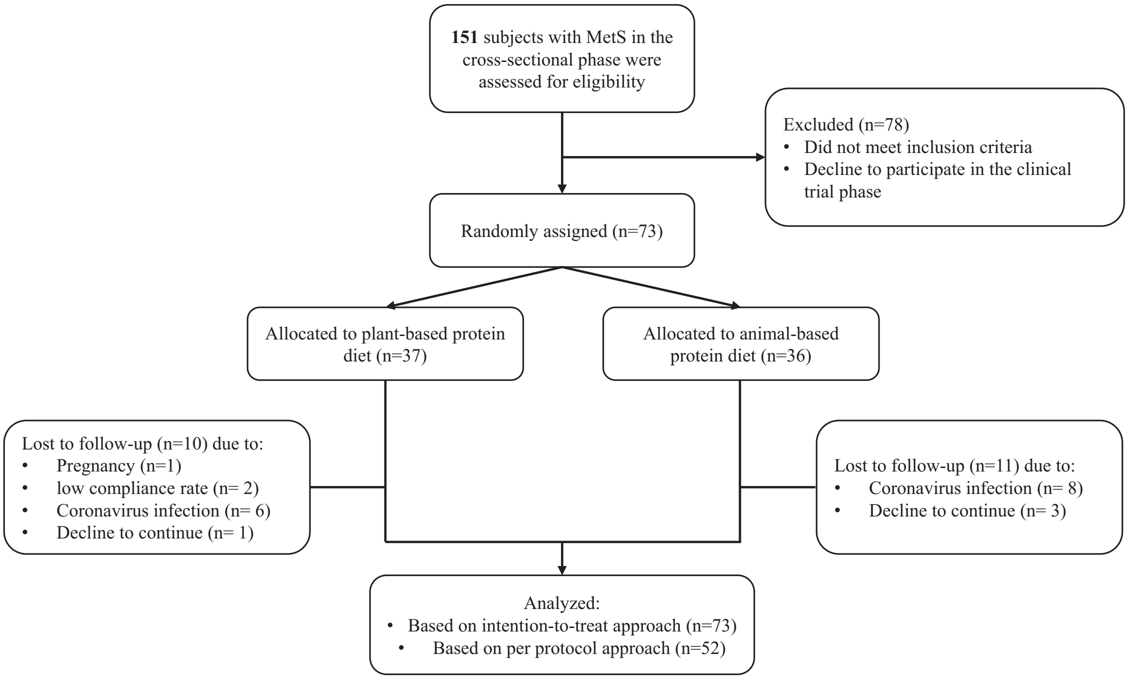

Fig. 1 The study participant flow chart.

this method [29, 30], 25 participants were at least considered for each treatment arm based on the minimum standardized effect size.

Dietary interventions

Two types of dietary plans with different proportions of plant- and animal-based protein were designed. The first was a plant-based protein diet consisting of 70% plant-based protein and 30% animal-based protein. The plant sources of protein were mainly from whole grains, soy protein, legumes, nuts, and seeds. The second diet was an animal-based protein diet containing 30% plant-based protein and 70% animal-based protein. This diet was based on animal sources of protein, including low-fat meat, poultry, fish, eggs, and low-fat dairy products. Details of intervention diets are explained in Supplementary Table 1. Daily calorie requirement was estimated individually using the 2002 Institute of Medicine, Food and Nutrition Board dietary reference intakes for energy in overweight and obese participants [31]. Both groups were instructed to slightly restrict energy intake by 500 Kcal/day. Both diets provided 20% of the total daily energy requirement from protein. In addition, carbohydrate and fat intakes were respectively designed to be 50% and 30% of total daily energy requirements in both diets [32].

Anthropometric, blood pressure, and biochemical assessment

Anthropometric and biochemical measurements were made at baseline and after intervention. Weight measurements were conducted using the body composition analyzer (Tanita MC-780MA, Tokyo, Japan) with an accuracy of 0.01 kg, while the participants were in a fasting condition and light clothing without shoes. Height was assessed using a tape measure affixed to the wall, recorded to the nearest 0.1 cm, with participants positioned in a natural shoulder alignment and standing without shoes. Waist circumference was assessed with an unstretched tape measure at the narrowest point between the top of the iliac crest and the lower margin of the last palpable rib. BMI was calculated as weight (kg)/[height $(m)]^2$.

Arterial blood pressure (BP) was evaluated twice using a digital sphygmomanometer (OMRON, M3, HEM-7154-E, Japan), with a 0.5 mmHg accuracy, on the left arm, after at least 5-min rest in a sitting position. The mean of the first and second measurements was used for the blood pressure report. After an overnight fast (>12 h), a 10-ml peripheral blood sample was taken using venipuncture from each participant before and after the intervention. Serum was separated by a 10-minute centrifuge at 1500 *g*. The levels of FBG and lipid profiles, including serum concentrations of total cholesterol, HDL-c, low-density lipoprotein cholesterol (LDL-c), and TG, were measured using an enzymatic colorimetric method with the BioSystem Kit and the Biosystem A15 auto-analyzer. AIP was computed as a logarithmic transformation of the ratio of TG to HDL-c [33]. Serum adropin levels were quantified utilizing the ELISA kit developed by ZellBio GmbH (Germany), employing the biotin double antibody sandwich methodology. The assay demonstrated a detection range for adropin from 30 to 960 pg/mL, with a sensitivity of 4 pg/mL. The coefficients of variation for intra-assay and inter-assay reproducibility were found to be less than 10% and 12%, respectively.

Statistical analysis

The normal distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Data were illustrated as mean (SD) for quantitative variables and frequency (percentage) for qualitative variables. Independent samples t-tests were employed to compare baseline characteristics and nutrient intakes for continuous variables between the two groups, while Pearson's chi-square tests were applied for categorical variables. A paired samples t-test was applied to assess within-group changes of variables during 10 weeks of intervention. An independent samples t-test was applied to assess differences between two intervention groups for continuous variables. Between-group differences for any variables at the end of the intervention were evaluated using analysis of covariance (ANCOVA). In ANCOVA models, the baseline value of each variable was used as a covariate. In addition, age and gender were considered as other covariates. All analyses were performed based on both per-protocol and intention-to-treat (ITT) principles. For per-protocol analysis, participants who completed the study protocol were included in the analyses. For ITT, the last-observation-carried-forward method was used to treat missing values. SPSS software version 20 (IBM, Chicago, IL) was used to conduct all analyses, and a *p*-value of less than 0.05 (two-tailed) was deemed statistically significant.

RESULTS

Among individuals with MetS in the cross-sectional phase, 73 participants agreed to take part in this randomized clinical trial. At the end of the trial, 52 participants were analyzed in the per-protocol method. By replacing the missing data with the last observed value, all 73 participants were analyzed in the ITT method. Among 73 patients with MetS, 21 participants ($n = 10$ in the plant-based protein diet, and $n = 11$ in the animal-based protein diet) were excluded due to pregnancy ($n = 1$), Coronavirus infection ($n = 14$), low compliance rate ($n = 2$), and decline to

Table 1. Baseline demographic and cardio-metabolic characteristics of all study participants in the two intervention groups ($n = 73$).

Variables	Plant-based protein diet ($n = 37$)	Animal-based protein diet ($n = 36$)	*P*-value[a]
Age (year)	44 ± 9.8	43.9 ± 9.8	0.65
Body weight (kg)	81.45 ± 13.13	82.33 ± 12.42	0.77
BMI (kg/m^2)	29.23 ± 4.12	29.23 ± 3.41	0.99
WC (cm)	99.31 ± 10.04	96.86 ± 9.42	0.29
Sex			0.82
Male	17 (45.9)	18 (50)	
Female	20 (54.1)	18 (50)	
Education			0.31
Diploma or lower	7 (18.9)	3 (8.3)	
Higher than Diploma	30 (81.1)	33 (91.7)	
Marital status			0.11
Single	1 (2.8)	4 (11.4)	
Married	35 (97.2)	29 (82.9)	
Divorced or widow	0	2 (5.7)	
SBP (mmHg)	125.40 ± 15.68	129.26 ± 17.29	0.32
DBP (mmHg)	85.35 ± 8.71	87.64 ± 11.32	0.33
FBG (mg/dL)	104.62 ± 33.85	99.47 ± 23.21	0.45
TG (mg/dL)	165.78 ± 41.12	180.16 ± 47.24	0.17
TC (mg/dL)	198.35 ± 39.86	191.22 ± 33.15	0.41
LDL-c (mg/dL)	112.54 ± 31.56	107.70 ± 28.03	0.49
HDL-c (mg/dL)	52.65 ± 9.88	47.49 ± 7.72	0.01
LDL-c/HDL-c ratio	2.17 ± 0.63	2.30 ± 0.61	0.38
Adropin (pg/ml)	65.61 ± 55.40	51.11 ± 21.43	0.15
Atherogenic index of plasma	0.49 ± 0.13	0.57 ± 0.14	0.02

[a] Resulted from independent-samples t-test for quantitative variables and chi-square test (fisher's exact test) for categorical variables.
Quantitative variables: mean ± SD. Qualitative variables: frequency (percentage).

continue ($n = 4$). The details of the follow-up process are summarized in Fig. 1.

Demographic characteristics and baseline cardio-metabolic factors of 73 study participants are displayed in Table 1. Mean age in the plant and animal-based protein groups was respectively 44 ± 9.8 and 43.9 ± 9.8 years, with 45.9% and 50% of men. A significantly higher HDL-c (52.65 vs. 47.49, $P = 0.01$) and lower AIP (0.49 vs. 0.57, $P = 0.02$) were found in the plant-based protein group. There were no significant differences in other cardio-metabolic factors and anthropometric indices. Moreover, after per-protocol analysis of 52 participants, only HDL-c levels were significantly higher in the plant protein compared to the animal protein group (53.44 vs. 47.58, $P = 0.02$), as shown in Supplementary Table 2.

Daily dietary intakes of participants at baseline and end of intervention are presented in Table 2. There were no significant differences between the two groups in terms of energy or macronutrient intakes at baseline. During 10 weeks of intervention, the amounts of fiber intake (20.96 vs. 12.74 g/day, $P < 0.001$), polyunsaturated fatty acid (22.67 vs. 19.36 g/day), magnesium (375.55 vs. 324.87 mg/day), and thiamin (1.58 mg vs.1.27 mg/day) in the plant protein group were significantly higher than the animal protein group. Also in this group, elevation of plant protein intake (79.55% vs. 31.85%, $P < 0.001$) was significant that showing great adherence of patients to the prescribed diets. However, intakes of cholesterol, saturated fatty acids, monounsaturated fatty acids, calcium, riboflavin, and niacin were higher in the animal-based protein group ($P < 0.05$).

For physical activity levels, no significant difference was found between the plant-based protein (35.99 ± 5.26 MET-h/day) and animal-based protein groups (38.51 ± 6.04 MET-h/day) throughout the intervention period ($P = 0.12$).

Table 3 and Fig. 2 illustrate the effect of partial animal-based protein replacement in the diet with plant-based protein on anthropometric indices, MetS components, adropin, and AIP (by intention-to-treat analyses, $n = 73$). Within-group analyses revealed that weight, BMI, systolic and diastolic blood pressure, and AIP were significantly decreased, and adropin levels were significantly increased after the intervention in both groups compared to the baseline values ($P < 0.05$). While WC and TG in the plant protein group showed a significant decrease compared to the baseline values, there was no significant difference in the other group. However, higher HDL-c levels just in the animal protein group after 10 weeks. Results of between-group analyses and analysis of covariance (with adjustments for baseline values, age, and sex) showed no statistically significant difference between the two intervention groups in terms of the investigated indicators ($P < 0.05$). Per-protocol analysis on 52 participants illustrated a significant difference only in terms of mean adropin levels in both study groups, as depicted in Supplementary Table 3.

DISCUSSION

The present study was the first randomized clinical trial that investigated the effect of partial replacement of animal-based with plant-based protein in diets with a slight energy restriction on AIP and adropin levels among adults with MetS. Our findings revealed about 2.5% weight loss in both study groups. Moreover, BMI, AIP, and systolic and diastolic blood pressure after intervention decreased in both groups, showing that neither of the two regimes was superior to the other. A reduction in TG levels and waist circumference in the plant-based protein group and an elevation of HDL-c levels in the animal-based protein group after 10 weeks of intervention were significantly found. A significant increase in adropin levels was observed in both groups. However, no statistically significant difference was seen between the two study groups.

In the current intervention, the percentage of protein was considered as 20%, meanwhile participants' diet at baseline indicated that about 13% of their energy intake came from protein; this enhancement in protein intake might have increased satiety and preserved lean body mass during weight loss [34]. Notably, both intervention groups in the present trial experienced an average weight loss of approximately 2.5% over the 10 weeks. The observed weight loss was most likely attributable to the prescribed 500 kcal/day energy restriction in both arms of the intervention. Previous studies showed that a high-protein diet (HPD) could result in weight loss. A meta-analysis of clinical trials revealed that HPD (25–30% of energy) could cause weight loss and improved MetS components, regardless of the source of protein intake, in comparison to a standard diet (12–18%) [35]. Moreover, Ma et al. have indicated that the impact of HPD on weight reduction, body fat, and blood lipid profiles surpasses that of calorie-restricted diets or intermittent fasting [36]. The underlying mechanism might be an increase in satiety and energy expenditure. Increased satiety might be through elevations in

Table 2. Daily energy and nutrient intakes of participants at baseline and end of intervention ($n = 52$).

Variables	Baseline		P-value[a]	At 10 weeks		P-value[a]
	Plant-based protein diet ($n = 27$)	Animal-based protein diet ($n = 25$)		Plant-based protein diet ($n = 27$)	Animal-based protein diet ($n = 25$)	
Energy (kcal)	2495.72 ± 850.23	2525.06 ± 514.06	0.88	1947.06 ± 342.70	1788.70 ± 304.10	0.08
Carbohydrate (% E)	60.15 ± 7.97	63.89 ± 6.95	0.08	53.79 ± 4.86	52.26 ± 6.15	0.32
Protein (% E)	13.90 ± 2.27	13.73 ± 2.56	0.80	20.30 ± 2.91	19.71 ± 3.21	0.48
Fat (% E)	27.80 ± 5.94	24.67 ± 5.41	0.06	27.71 ± 3.49	29.94 ± 5.45	0.09
Carbohydrate (gr)	369.39 ± 113.11	405.04 ± 99.86	0.24	262.37 ± 53.84	236.76 ± 61.43	0.12
Protein (gr)	86.25 ± 30.74	86.00 ± 21.33	0.97	98.03 ± 16.99	88.55 ± 23.33	0.10
Fat (gr)	81.52 ± 41.86	68.89 ± 19.07	0.17	59.21 ± 8.28	58.31 ± 7.82	0.69
Dietary fiber (gr)	25.17 ± 11.04	26.20 ± 11.17	0.74	20.96 ± 6.23	12.74 ± 3.40	<0.001
Cholesterol (mg)	327.23 ± 183.69	302.96 ± 119.13	0.58	110.79 ± 55.37	290.98 ± 122.80	<0.001
Saturated fatty acids (% E)	9.46 ± 3.50	8.07 ± 2.31	0.10	5.28 ± 0.76	7.80 ± 1.81	<0.001
Monounsaturated fatty acids (% E)	8.70 ± 2.56	7.47 ± 1.64	0.04	7.31 ± 1.26	9.11 ± 1.81	<0.001
Polyunsaturated fatty acids (% E)	6.51 ± 2.63	5.70 ± 2.79	0.28	10.61 ± 2.26	9.99 ± 2.57	0.35
Saturated fatty acids (gr)	27.02 ± 16.48	22.18 ± 5.92	0.16	11.30 ± 1.82	15.21 ± 3.00	<0.001
Monounsaturated fatty acids (gr)	25.21 ± 14.22	20.92 ± 6.08	0.16	15.55 ± 2.40	17.80 ± 3.13	0.01
Polyunsaturated fatty acid (gr)	18.97 ± 12.66	16.31 ± 10.04	0.41	22.67 ± 4.69	19.36 ± 4.00	0.01
Plant-based protein (% Total protein)	42.22 ± 10.39	46.10 ± 9.88	0.17	79.55 ± 8.53	31.85 ± 7.83	<0.001
Magnesium (mg)	304.68 ± 95.84	320.92 ± 113.40	0.58	375.55 ± 81.80	324.87 ± 93.65	0.04
Calcium (mg)	1052.50 ± 400.35	966.17 ± 397.80	0.44	723.16 ± 242.32	1004.47 ± 431.50	0.01
Thiamin (mg)	2.14 ± 0.69	2.37 ± 0.67	0.23	1.58 ± 0.35	1.27 ± 0.30	0.01
Riboflavin (mg)	2.23 ± 0.80	2.09 ± 0.68	0.51	1.47 ± 0.36	2.01 ± 0.67	0.01
Niacin (mg)	23.56 ± 8.71	25.00 ± 5.99	0.49	17.81 ± 4.47	19.54 ± 5.55	0.24

[a] Resulted from independent-samples t-test.

Reported values are means ± SD.

anorexigenic hormones, diet-induced thermogenesis (DIT), blood amino acid levels, hepatic gluconeogenesis, ketogenesis, and decreased levels of orexigenic hormones. Protein is known to increase energy expenditure by a higher increment in DIT than carbohydrates and fat and to prevent the reduction of fat-free mass [37].

We found that both types of studied diets improved anthropometric indices and MetS components, without any significant difference between the two groups. Hill et al. examined the effect of two types of diet (based on plant and animal protein) and indicated a 5% reduction in weight and improvement in MetS components in two groups, without any significant difference between them [38]. The results of the mentioned study were consistent with ours. These findings showed that weight loss, as a result of a slight energy restriction, could play the main role in MetS improvement, regardless of the source of protein intake. In other words, heart-healthy weight-loss dietary patterns based on animal or plant-based protein could improve components of MetS similarly.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported that consuming protein from either plants or animals did not show significant associations with the development of CVDs, ischemic heart disease, or stroke, after considering confounders in analyses [39]. In addition, a study by Sawyer et al. reported that consuming plant-based protein was linked to a reduced risk of MetS, whereas animal-based protein did not have a significant effect on MetS; so that, this research did not suggest reducing animal-based protein intake [40]. A review of the effects of various types of protein on components of MetS and risk factors of CVDs revealed that multiple studies, both observational and intervention-based, have attempted to determine whether plant-based and animal-based proteins have different effects on reducing risk factors for CVDs. However, the current evidence is inconclusive and is likely to remain so, due to challenges in isolating the specific effects of individual proteins. It is important to consider the influence of other components of plant vs. animal foods and the overall dietary pattern [41]. The underlying factors contributing to the specific impacts of plant and animal proteins are multifaceted and diverse; different amino acid composition of these foods, presence of other non-protein compounds in the whole diet, and interactions with gut microbiome may be involved [41–45]. To lower the MetS and CVDs risk factors, previous research suggested that diets emphasizing protein-rich plant foods and incorporating some animal-based protein sources that are low in saturated fat and unprocessed foods, including seafood, poultry, lean meats, low-fat dairy, and eggs, instead of refined carbohydrates and processed meats, might be beneficial [41, 46].

In the current trial, in both intervention arms, participants were advised to consume low-fat dairy products, to reduce their total energy intake by approximately 500 kcal, and to increase their dietary protein to about 20% of total energy. Due to having

Table 3. The effect of partial animal-based protein replacement in the diet with plant-based protein on anthropometric indices, MetS components, adropin, and atherogenic index of plasma (based on intention to treat analyses, *n* = 73).

Variables	Plant-based protein diet (*n* = 37)	Animal-based protein diet (*n* = 36)	*P*-value[b]	*P*-value[c]	*P*-value[d]
Body weight (kg)					
Baseline	81.45 ± 13.13	82.33 ± 12.42	0.59	0.62	0.58
10th week	79.86 ± 13.06	80.43 ± 12.20			
Mean difference	−1.59 ± 2.24	−1.91 ± 2.70			
P-value[a]	<0.001	<0.001			
BMI (kg/m^2)					
Baseline	29.23 ± 4.12	29.23 ± 3.41	0.42	0.43	0.42
10th week	28.73 ± 4.34	28.55 ± 3.44			
Mean difference	−0.50 ± 0.88	−0.67 ± 0.95			
P-value[a]	0.01	<0.001			
WC (cm)					
Baseline	99.31 ± 10.04	96.86 ± 9.42	0.63	0.92	0.98
10th week	97.67 ± 9.42	95.67 ± 8.72			
Mean difference	−1.63 ± 4.17	−1.19 ± 3.66			
P-value[a]	0.02	0.06			
SBP (mmHg)					
Baseline	125.40 ± 15.68	129.26 ± 17.29	0.54	0.82	0.92
10th week	118.34 ± 16.33	120.39 ± 15.87			
Mean difference	−7.07 ± 13.21	−8.87 ± 11.74			
P-value[a]	0.01	<0.001			
DBP (mmHg)					
Baseline	85.35 ± 8.71	87.64 ± 11.32	0.93	0.55	0.59
10th week	81.43 ± 8.71	83.87 ± 9.94			
Mean difference	−3.91 ± 6.26	−3.76 ± 8.34			
P-value[a]	0.01	0.01			
FBG (mg/dL)					
Baseline	104.62 ± 33.85	99.47 ± 23.21	0.89	0.11	0.12
10th week	104.32 ± 20.11	98.61 ± 9.92			
Mean difference	−0.30 ± 16.87	−0.86 ± 19.03			
P-value[a]	0.91	0.79			
TG (mg/dL)					
Baseline	165.78 ± 41.12	180.16 ± 47.24	0.51	0.15	0.15
10th week	151.84 ± 34.04	171.33 ± 46.95			
Mean difference	−13.94 ± 35.14	−8.83 ± 30.25			
P-value[a]	0.02	0.08			
TC (mg/dL)					
Baseline	198.35 ± 39.86	191.22 ± 33.15	0.83	0.97	0.92
10th week	194.59 ± 40.54	189.01 ± 38.65			
Mean difference	−3.76 ± 34.29	−2.22 ± 24.50			
P-value[a]	0.51	0.59			
LDL-C (mg/dL)					
Baseline	112.54 ± 31.56	107.70 ± 28.03	0.96	0.85	0.82
10th week	109.48 ± 34.51	104.93 ± 31.70			
Mean difference	−3.06 ± 31.45	−2.77 ± 21.46			
P-value[a]	0.56	0.44			
HDL-C (mg/dL)					
Baseline	52.65 ± 9.88	47.49 ± 7.72	0.88	0.30	0.26
10th week	54.75 ± 7.73	49.80 ± 8.80			
Mean difference	2.09 ± 6.72	2.32 ± 6.24			
P-value[a]	0.06	0.03			

Table 3. continued

Variables	Plant-based protein diet ($n = 37$)	Animal-based protein diet ($n = 36$)	P-value[b]	P-value[c]	P-value[d]
LDL-c/HDL-c ratio					
Baseline	2.17 ± 0.63	2.30 ± 0.61	0.99	0.58	0.63
10th week	2.00 ± 0.54	2.12 ± 0.61			
Mean difference	−0.17 ± 0.66	−0.17 ± 0.49			
P-value[a]	0.12	0.04			
Adropin (pg/ml)					
Baseline	65.61 ± 55.40	51.11 ± 21.43	0.31	0.12	0.08
10th week	84.17 ± 56.91	62.36 ± 21.20			
Mean difference	18.56 ± 32.73	11.25 ± 28.53			
P-value[a]	0.01	0.02			
Atherogenic index of plasma					
Baseline	0.49 ± 0.13	0.57 ± 0.14	0.59	0.13	0.07
10th week	0.44 ± 0.11	0.53 ± 0.16			
Mean difference	−0.05 ± 0.11	−0.04 ± 0.09			
P-value[a]	0.01	0.01			

[a] Resulted from a paired t-test for comparison of within-group differences.
[b] Resulted from an independent-samples t-test for comparison of between-group differences.
[c] Resulted from ANCOVA, adjusted for baseline values for comparison of between-group differences.
[d] Resulted from ANCOVA, adjusted for baseline values, age, and sex for comparison of between-group differences.
Reported values are means ± SD.

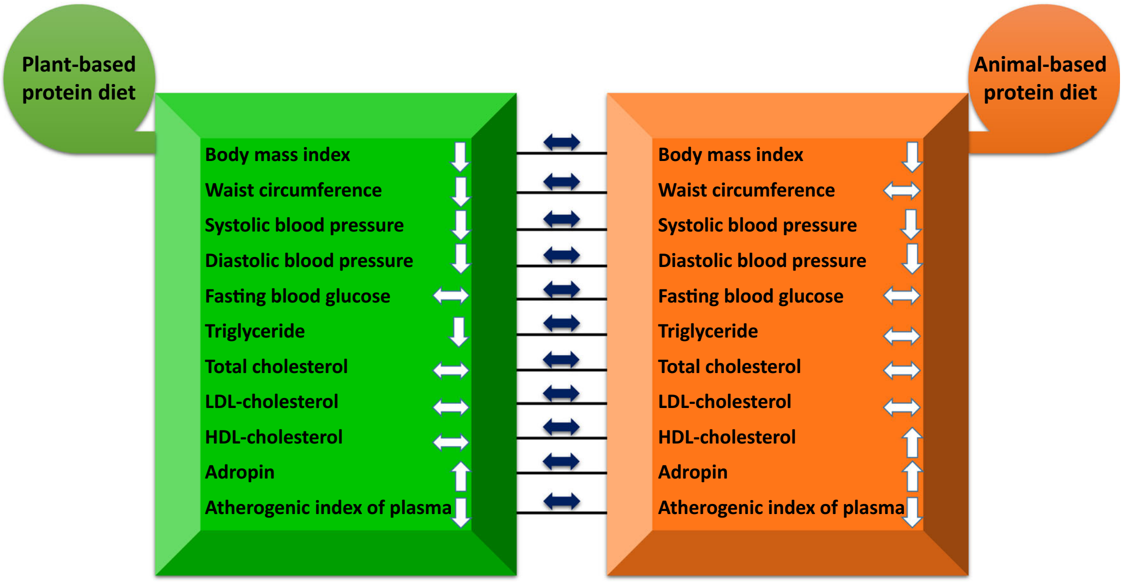

Fig. 2 Schematic summary of the effect of partial animal-based protein replacement in the diet with plant-based protein on anthropometric indices, MetS components, adropin, and AIP (obtained from intention-to-treat analyses, $n = 73$).

different sources of protein in groups, notable differences emerged in the consumption of saturated fats and other macronutrients, which may have influenced the components of MetS, adropin, and AIP. Those in the plant-based protein group had a significantly lower intake of saturated fatty acids (5.28% of energy or 11.30 g/day) compared to the animal-based protein group (7.80% of energy or 15.21 g/day; $P < 0.001$). Additionally, the plant-based group (vs. animal-based protein group) had a higher dietary fiber intake (20.96 vs. 12.74 g/day; $P < 0.001$) and a lower cholesterol intake (110.79 vs. 290.98 g/day; $P < 0.001$). However, during 10 weeks of intervention, the intake of total fat, carbohydrate, and protein was similar in both groups. Recent dietary guidelines recommend reducing saturated fat intake to ≤10% of total daily energy, as more than 10% saturated fat intake is linked to increased LDL cholesterol and a higher risk of atherosclerotic cardiovascular disease (ASCVD) [47]. However, another study revealed that the unhealthy effects of saturated fat might rely on the total dietary context, including carbohydrate intake and food sources of saturated fat [48]. For example, even though whole-fat dairy products and unprocessed meats are rich in saturated fat, their consumption as part of an overall balanced diet does not consistently raise the risk of cardiovascular disease as part of a balanced diet [48].

Epidemiological evidence on the relationship between animal protein intake, particularly red meat intake, and risk of cardiovascular diseases and components of MetS is inconsistent. The study by Chung et al. assessed the association of animal and plant protein intake with MetS and its components in men and women, separately. Their report illustrated that a higher intake of animal-based protein increased the MetS risk factors in men. However, the intake of both animal and plant proteins did not show a significant association with any MetS risk factors in women [49]. One of the reasons for the various effects of animal protein consumption on metabolic parameters in men and women could be related to the different ratios of dietary intake of animal and plant protein. In other words, women consumed a greater proportion of plant-based protein compared to animal-based protein, while men had a higher proportion of animal-based protein that was similar to Western diets. Also, the association between the ratio of animal to plant dietary protein and MetS and its components was investigated in the cross-sectional study [50]. The findings showed that a higher ratio of animal to plant protein intake was linked to components of MetS, such as increased waist circumference and fasting blood glucose levels. Nevertheless, the consumption of plant protein did not appear to have any impact on glucose regulation or body composition [50]. In addition, a study by Vasei et al. evaluated the effects of substituting plant-based- with animal-based proteins in the DASH diet on components of MetS in participants with obesity. The results revealed that the plant-based DASH diet has greater effects on reducing blood sugar and systolic blood pressure, with no significant effect on lipid profiles in both plant- and animal-based DASH diets [51].

While some studies illustrated an adverse effect of animal protein, others report no significant association, particularly when processed and unprocessed meats are examined separately [52–55]. A number of studies have shown a relation between consumption of red meat and MetS due to its saturated fat content, although this relation was not always substantial [56–58]. Red meat is usually limited in heart-healthy diets because of its saturated fat content. However, a study by Damião et al. demonstrated that adjusting the intake of saturated fats disappeared the unfavorable association between red meat and MetS [59]. In our study, the diet in both groups was designed according to a healthy diet, and the type of meat and dairy was considered to be low-fat. Also, patients were advised not to consume processed meat products; these factors reduced the intake of saturated fats. Therefore, the evidence showed that the type of protein that was consumed was not as important as the reduction in energy and saturated fatty acid intake to manage MetS or related risk factors.

Previous studies have reported that eating lean meat or a lower intake of saturated fatty acids can reduce TC and LDL-c levels in hypercholesterolemia participants [60, 61], but we found no significant difference in TC or LDL-c levels in the two study arms. It is worth noting that cholesterol values in both study groups were close to normal ranges; this issue might reduce the effectiveness of the diets [62]. In addition, a study by Meinertz et al. evaluated the effects of different sources of dietary protein (soy as a plant-based vs. casein as an animal-based protein) on plasma lipoproteins in healthy individuals with normal lipid levels. The plasma level of cholesterol and LDL-c reduced in both intervention arms, and the results could not show a substantial difference between the two arms [63]. Therefore, it seems that the type of dietary protein has minimal to no impact on the levels of plasma lipoproteins in healthy individuals. However, a significantly higher HDL-c in the animal protein group was observed after 10 weeks. In this case, the role of saturated fatty acids intake in increasing HDL-c should be highlighted [64, 65]. In addition, the current study showed a decrease in LDL-c/HDL-c ratio in the animal-based protein group. In contrast, Li et al. suggested that the lacto-ovo vegetarian and vegan groups showed notably lower levels of plasma TC, LDL-c, and LDL-c/HDL-c ratio compared to both high- and moderate-meat-eater groups. However, moderate-meat-eaters had significantly higher HDL-c levels than vegans. This study did not recommend that meat eaters switch to a vegetarian diet. However, it might be advisable for meat eaters to reduce their intake of saturated fatty acids to improve their lipid profile [66].

Values of TG in the plant protein group were significantly decreased after the intervention. It is necessary to know that the amount of polyunsaturated fats might be higher in the plant-based protein diet because of higher nut consumption. A network meta-analysis of clinical trials reported that pistachio and walnut-enriched diets could lower TG, TC, and LDL-c [67]. Another meta-analysis suggested that incorporating nuts into the diet can positively affect serum TG and LDL-c in healthy adults with overweight or obesity [68]. Nuts are rich in unsaturated fats and many bioactive compounds such as antioxidants, dietary fiber, and plant sterols [69]. In the animal-based protein group, our findings revealed that the levels of TG decreased after 10 weeks of intervention, but the result was not significant. A previous cross-sectional study showed that an increase in overall protein consumption was linked to a lower likelihood of elevated TG levels in both men and women. When the types of protein were categorized, it was found that consuming animal protein was only associated with a reduced risk of elevated TG levels in men, but not in women [70]. Weight loss, as a result of increased dietary protein intake (especially with low saturated fatty acids intake), could be considered as a potential mechanism for improving TG levels [71]. In addition, polyunsaturated fats, especially omega-3 fats, could lower TG. Omega-3 could also reduce the de novo synthesis of fatty acids and TG, increase TG catabolism in adipose and muscle tissue, and increase the clearance of TG-rich lipoproteins through activation of the peroxisome proliferator-activated receptors (PPARs) gene [72].

In the current study, the AIP levels decreased in both groups after 10 weeks of intervention. A case-control study evaluated the AIP values in vegetarian and non-vegetarians groups. The mentioned study did not find any variation in AIP levels between different groups. Therefore, the mentioned research did not suggest that a vegetarian diet would be superior in the management and prevention of heart disease risk factors [73]. In addition, a cross-sectional study evaluated the association between different types of plant-based dietary indices and AIP levels. The results showed that greater compliance with the overall plant-based diet index and moderate adherence to the healthful plant-based diet index were linked to reduced likelihood of elevated AIP levels [25]. It is worth noting that the effect of different types of dietary protein on triglycerides and HDL-c, as components of AIP, could predict AIP levels. In the current study, plant-based protein intake decreased TG, and animal-based protein intake increased HDL-c levels that resulting in decreased AIP levels in both intervention groups.

In both groups of the present trial, there was no difference in fasting blood sugar (FBS) after 10 weeks of intervention. Although previous studies suggested that decreased energy intake and subsequent weight loss could be associated with lower FBS, our study could not obtain such a result. Some studies illustrated that blood glucose reduction might be greater in people with higher initial blood sugar than normal or near-normal blood sugar [38, 74]. On the other hand, an elevation in fiber intake might be related to lower blood sugar [75, 76]. In the present study, neither group could meet the recommended amount of fiber intake, which is equivalent to 14 grams per 1000 kcal per day, and this could be a reason for no positive changes in blood sugar.

The intake of macronutrients plays a significant role in the prevention and treatment of MetS and its components. A community-based, large genomic study by Park et al. illustrated that individuals with MetS exhibited reduced consumption of animal-source proteins, along with elevated consumption of plant-source carbohydrates and proteins [77]. This finding might be related to the correlation of dietary plant-based protein and carbohydrates that could alter the association between plant-based protein and MetS [78].

There was a significant increase in adropin levels in both intervention groups, and after adjustment for baseline adropin concentrations, age, and sex, the levels of adropin were higher in the plant protein group than in the animal protein. Onge et al., in a crossover trial, investigated the effect of regular and limited sleep combined with a controlled meal, 30% of energy from fat, 55% from carbohydrate, and 15% from protein, during 4 days. Their results showed that adropin could not be affected by sleep status. However, adropin was correlated with food choices in women. Such that plasma adropin was directly correlated with total and saturated fat and inversely with carbohydrate intake [79]. Furthermore, a study on mice illustrated that a diet consisting of low carbohydrate and high fat was associated with higher levels of adropin, whereas a high-carbohydrate low-fat diet was associated with lower adropin values [80].

Strengths and limitations

The present study contains some strengths. It is the first study that examined the effect of replacing animal-based with plant-based protein on the aforesaid parameters. Also, participants had high adherence to the prescribed diet due to being motivated and somewhat educated. However, we acknowledge some limitations. A great percentage of participants dropped out due to conducting the study during the COVID-19 epidemic, as well as the long duration of the study. Since we live in a developing country, it was not possible to feed the participants and only diets were recommended to them. Due to financial constraints, both the duration and the sample size of the study were relatively limited. While the 10-week intervention period allowed us to observe meaningful improvements in metabolic syndrome parameters, a longer duration might have resulted in more pronounced or sustained effects. It is worth noting that a longer dietary intervention, on the other hand, might result in lower participants' adherence to dietary recommendations. The relatively modest sample size of 60 participants could also limit the statistical power to detect small differences between groups and might restrict the generalizability of our findings. In addition, diet compliance was evaluated using a 3-day diet record every two weeks, and self-reported dietary intake might increase measurement error and information bias. Also, this study could not establish a difference between various types of dietary protein intake and components of MetS; further studies with optimized designs are needed to evaluate the effect of different types of dietary protein on components of MetS and its novel biomarkers.

In conclusion, our findings revealed that both diets based on plant and animal protein were associated with improvement in anthropometric indices, MetS components, plasma atherogenic index, and elevated serum adropin levels. Apart from adropin values, no significant difference was observed between the two intervention groups. Further prospective studies, as well as intervention studies with a larger sample size and a longer period of time,e are needed.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ACKNOWLEDGEMENTS

This study was extracted from Ph.D. dissertation, which was approved by Isfahan University of Medical Sciences (no: 3400603).

AUTHOR CONTRIBUTIONS

FS, MR, PR, AF, GA, ZM, PS, and SMS were involved in the conception and design of the study, data collection and interpretation, drafting of the manuscript, approval of the final version, and consented to all aspects of the research.

FUNDING

The funding for conception, design, data analysis, and manuscript preparation was provided by Isfahan University of Medical Sciences in Isfahan, Iran.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The research methodology was conducted in accordance with the Declaration of Helsinki and complied with the CONSORT guidelines. All participants provided informed written consent prior to their inclusion in the study. The protocol was also reviewed and approved by the Ethics Committee at Isfahan University of Medical Sciences.

CONSENT TO PARTICIPATE

Informed consent was obtained from all participants involved in the study.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41387-025-00401-x.

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