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RESEARCH ARTICLE

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Garlic supplementation improves intestinal transit time, lipid accumulation product and cardiometabolic indices in subjects with metabolic syndrome: A randomized controlled trial

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Abstract

Subjects with metabolic syndrome (MetS) are at increased risk for cardiovascular disease (CVD). Altered gut microbiota is involved in the pathogenesis of MetS. It has been hypothesized that garlic can improve intestinal transit time and cardiovascular risks. We investigated the effect of garlic powder supplementation on intestinal transit time, lipid accumulation product (LAP), and cardiometabolic indices in subjects with MetS. A double-blind randomized controlled trial was conducted for 3 months among subjects with MetS. Ninety subjects were randomly assigned to the treatment group (intake of 1,600 mg/d garlic powder) or control group (placebo) using a computer-generated random number table. All participants were asked to follow the common healthy dietary recommendations during follow-up. The primary outcomes included intestinal transit time, LAP, cardiometabolic index (CMI), atherogenic index of plasma (AIP), Castelli risk index I (CRI-I) and Castelli risk index II (CRI-II). Garlic powder compared to the placebo improved intestinal transit time ($p = .001$), LAP (-21.5 ± 23.4 vs. 0.7 ± 21.5; $p < .001$), CMI (-0.85 ± 0.8 vs. 0.13 ± 0.8; $p < .001$), AIP (-0.14 ± 0.1 vs. 0.01 ± 0.1; $p < .001$), CRI-I (-0.69 ± 0.5 vs. 0.16 ± 0.5; $p < .001$) and CRI-II (-0.50 ± 0.3 vs. 0.02 ± 0.3; $p < .001$). Garlic supplementation can improve intestinal transit time, LAP, and cardiometabolic indices.

KEYWORDS
cardiometabolic, garlic, intestinal transit time, lipid accumulation product, metabolic syndrome

1 | INTRODUCTION

The growing prevalence of metabolic syndrome (MetS) has become a major public health problem in both developed and developing countries (Nolan, Carrick-Ranson, Stinear, Reading, & Dalleck, 2017; Ranasinghe, Mathangasinghe, Jayawardena, Hills, & Misra, 2017). The worldwide prevalence of MetS is estimated to be 20%–25% (do Vale Moreira et al., 2020; Ranasinghe et al., 2017), and its prevalence among Iranian people is 30.4% (Kalan Farmanfarma et al., 2019). MetS represents a set of metabolic abnormalities that can increase the risk of cardiovascular atherosclerotic diseases (Tune, Goodwill, Sassoon, & Mather, 2017). The National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) and the International Diabetes Federation (IDF) state different criteria for the diagnosis of MetS (Moy & Bulgiba, 2010; O'Neill & O'Driscoll, 2015). According to the IDF definition, subjects with MetS have central obesity plus any two of the following four factors: a raised triglyceride (TG) level, a reduced high density lipoprotein-cholesterol (HDL-C), raised blood pressure, and raised fasting plasma glucose (FPG), while based on NCEP-ATP III definition, MetS is a clustering of three or more factors, such as central obesity, a raised TG level, a reduced HDL-C, raised blood pressure, and raised FPG (Moy & Bulgiba, 2010; O'Neill &

O'Driscoll, 2015). Components of MetS such as central obesity, dyslipidemia, hypertension, hyperglycemia and insulin resistance are strongly involved in the pathogenesis of non-communicable diseases (Leon, 2015; Sangouni, Ghavamzadeh, & Jamalzehi, 2019). Altered gut microbiota (dysbiosis) through various mechanisms can contribute to the development of MetS components (Festi et al., 2014; Sangouni & Ghavamzadeh, 2019). Dysbiosis changes normal intestinal function and intestinal transit time (Saffouri et al., 2019; Weiss & Hennet, 2017). The Bristol stool scale (BSS) is an available tool for evaluation of stool consistency and intestinal transit time (Vork, Wilms, Penders, & Jonkers, 2019).

Lipid accumulation product (LAP) is a sensitive and available tool to predict cardiovascular risk (Hosseinpanah et al., 2014; Wang et al., 2018). Waist circumference (WC) and TG are used in the equation of LAP to estimate excess lipid accumulation (Sangouni et al., 2021). In addition, the cardiometabolic index (CMI) as a novel scoring system can evaluate the progression of atherosclerosis (Wakabayashi & Daimon, 2015; Wakabayashi, Sotoda, Hirooka, & Orita, 2015). TG/high density lipoprotein-cholesterol (HDL-C) and waist-to-height ratio (WHtR) are variables of the CMI (Wakabayashi & Daimon, 2015). Moreover, atherogenic indices, such as atherogenic index of plasma (AIP), Castelli risk index I (CRI-I) and Castelli risk index II (CRI-II) are accurate and available tools that can assess cardiovascular risk (Fernández-Macías, Ochoa-Martínez, Varela-Silva, & Pérez-Maldonado, 2019; Koca, Tugan, Seyithanoglu, & Kocyigit, 2019; Sujatha & Kavitha, 2017). Indices such as CMI, AIP, CRI-I, and CRI-II can assess cardiovascular risk better than a lipid profile alone (Dursun, Besiroglu, Otunctemur, & Ozbek, 2016; Sasikala & Goswami, 2020).

Garlic (*Allium sativum L.*) has several bioactive components such as allicin, S-allylcysteine (SAC), ajoene, diallyl disulfide, SAC sulfoxide, and S-methylcysteine sulfoxide (El-Bayoumy, Sinha, Pinto, & Rivlin, 2006; Iciek, Kwiecień, & Włodek, 2009). A review article suggested that allicin can reduce the risk of atherosclerosis through its antiplatelet and fibrinolytic activities (Chan, Yuen, Chan, & Chan, 2013). In addition, garlic acts as a prebiotic by increasing the abundance and activity of beneficial bacteria in the gut (Chen et al., 2019; Filocamo, Nueno-Palop, Bisignano, Mandalari, & Narbad, 2012). It has been demonstrated that garlic has beneficial effects on hypertension, insulin resistance, oxidative stress, lipid profile, and hepatic steatosis (Koseoglu, Isleten, Atay, & Kaplan, 2010; Ried, Travica, & Sali, 2018; Sangouni, Mohammad Hosseini Azar, & Alizadeh, 2020a, 2020b).

Some studies evaluated the effects of garlic consumption among subjects with MetS, but their results were inconsistent (Choudhary, Jani, & Sharma, 2018; Sharifi, Sheikhi, Behdad, & Mousavinasab, 2010). The study of Choudhary et al. (Choudhary et al., 2018) reported that raw crushed garlic significantly reduced WC, systolic and diastolic blood pressure, TG, FPG, and significantly increased serum HDL-C. However, the study by Sharifi et al. (Sharifi et al., 2010) showed that garlic consumption has no effect on lipid profiles and inflammatory biomarkers in women with MetS. It has been suggested that garlic can improve cardiovascular risk factors by inhibiting adipogenesis, decreasing hepatic lipid accumulation, increasing lipolysis, and altering proatherogenic profile to an anti-atherogenic the profile (Ha, Ying, & Kim, 2015; Panyod et al., 2022; Shi et al., 2019). Garlic and its main active ingredients can improve composition of intestinal microbiota, increase the integrity of tight junctions, reduce mucosal damage, and improve the intestinal transit time (Park et al., 2011; Shi et al., 2019). To date, no study has examined the effect of garlic on intestinal transit time, LAP, and cardiometabolic indices in subjects with MetS. Therefore, we conducted a study to determine if garlic powder supplementation can improve these parameters in subjects with MetS.

2 | METHODS

2.1 | Sample size calculation

This article is a part of our study that estimated the optimal sample size (45 participants in each group) based on means and standard deviations of HDL-C (Ashraf, Aamir, Shaikh, & Ahmed, 2005), using the following formula with $\alpha = .05$, power = 95%, and considering a drop-out rate of 20%.

$$n = \frac{\left(Z_{\alpha_2} + Z_{\beta}\right)^2 \times \left({S_1}^2 + {S_2}^2\right)}{\left(\bar{x}_1 - \bar{x}_2\right)^2}$$

To ensure that the sample size was sufficient to detect statistical significance, a retrospective power analysis was performed for all outcomes of the present article, and adequate power (80%) was observed.

2.2 | Recruitment and eligibility screening

A total of 130 individuals who were referred to the Shahid Arefian hospital in Urmia, Iran, between November 2019 and February 2020 were identified and screened. Ninety subjects met the inclusion criteria, defined as follows: subjects with MetS diagnosed by NCEP-ATPIII criteria (Parikh & Mohan, 2012), and an age equal to or greater than 18 years. Participants with clustering of three or more of the following five criteria were included: 1- WC higher than 102 cm for men or higher than 88 cm for women; 2- HDL-C less than 1.0 mmoL/L (40 mg/dL) in men, less than 1.3 mmoL/L (50 mg/dL) in women 3- TG equal to 1.7 mmoL/L (150 mg/dL) or higher than 1.7 mmoL/L (150 mg/dL); 4- Blood pressure equal to 130/85 mmHg or higher than 130/85 mmHg; 5- FPG equal to 5.6 mmoL/L (100 mg/dL) or higher than 5.6 mmoL/L (100 mg/dL) (Parikh & Mohan, 2012). The exclusion criteria were as follows: viral hepatitis, liver cancer, type 2 diabetes mellitus (T2DM), mental disorders, kidney diseases, pregnancy, lactation, low blood pressure, allergy to garlic, and taking blood pressure, lipid and glucose lowering medications. In addition, unwillingness to continue the trial and a compliance rate lower than 80% were considered drop-out criteria.

2.3 | Trial design

We conducted a double-blind, placebo-controlled, single-center, randomized clinical trial (RCT) with two parallel study arms (the garlic powder and placebo groups) for 3 months between February 2020 and May 2020. After a detailed description of the potential benefits and side effects of study participation, the participants signed a written informed consent that was confirmed by the Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran, with identifier number: IR.BMSU.REC.1398.120. We registered the study protocol at the Iranian registry of clinical trials website (http://www.irct.ir) with code number: IRCT20180201038585N6. Simple randomization was performed using a random number table that was produced by random allocation software (Saghaei, 2004), then, the participants were assigned to the treatment group or control group. Opaque sealed envelopes were used to perform allocation concealment, and the allocation sequence was concealed from those assigning participants to the intervention groups. The randomized allocation and assignment of participants to intervention groups were performed by a third person. Participants and investigators were blinded to the intervention assignment until the end of the trial.

2.4 | Intervention

The treatment group received four garlic powder tablets (each coated tablet contained 400 mg garlic powder, providing 1.5 mg allicin) daily, and the control group received the same amount and appearance of placebo tablets containing starch. Every month, garlic and placebo tablets were given to the participants. Based on the effective dose of allicin (3.6–7.8 mg/d) (Lawson & Hunsaker, 2018), the optimal dose was determined to be four garlic powder tablets (1,600 mg/d garlic powder) containing 6 mg/d allicin (each coated tablet contained 400 mg garlic powder, providing 1.5 mg allicin). A recent study suggested that the bioavailability of garlic reduces after protein intake (Lawson & Hunsaker, 2018); therefore, the participants consumed two tablets an hour before lunch and two tablets an hour before dinner. All participants were asked to follow the common healthy dietary recommendations throughout the follow-up. Garlic and placebo tablets were prepared by Amin Pharmaceuticals Co., Isfahan, Iran. The compliance rate of participants was monitored every month.

2.5 | Dietary intake and physical activity assessment

To assess average intake of food group servings including dairy, meats, grains, vegetables, fruits, fats, and sugars, we used a 3-day (1 weekend day and 2 nonconsecutive weekdays) 24-h recall questionnaire at the baseline, weeks 6 and 12. In addition, we evaluated the dietary intake of the rich sources of allicin such as garlic, onion, scallion, and leek. Assessment of physical activity was performed at the baseline, weeks 6 and 12 using the metabolic equivalent of task (MET) questionnaire (Ainsworth et al., 2000).

2.6 | Laboratory evaluations

Serum concentrations of total cholesterol (TC), TG, HDL-C and low density lipoprotein-cholesterol (LDL-C) were measured at the baseline, Week 6 and Week 12. An overnight fasting venous blood sample (5 mL) was obtained and centrifuged for 10 min at a speed of 3,600 rpm. The microtubes containing serums were immediately frozen at −80°C. Measuring TC, TG, HDL-C and LDL-C was performed by a commercial kit (Pars Azmoon, Iran) using an autoanalyzer (AVIDA 1800 chemistry system; Siemens, United Kingdom).

2.7 | Anthropometric assessments

Measuring height was performed according to the standard instructions by a stadiometer (Seca, Hamburg, Germany) with an accuracy of 0.5 cm. Weight and WC were measured using a bioelectrical impedance analyzer (BIA) (In Body 770, Korea) at the baseline, weeks 6 and 12 under the standard protocols while participants were with light clothes and without shoes.

2.8 | Intestinal transit time assessment

In order to determine intestinal transit time, participants' stool shape was evaluated using the BSS form (Vork et al., 2019), which demonstrates seven different shapes of fecal excretion with varying scores ranging from severe constipation to severe diarrhea. Participants who reported their stool form as number 1 or 2, which indicate constipation, as well as number 6, or 7, which indicate diarrhea, were classified as having an abnormal intestinal transit time. Participants reporting stool shape as number 3, 4 or 5, which indicate normal form of fecal excretion, were considered as participants with normal intestinal transit time.

2.9 | Indices

Calculating LAP (Dai et al., 2017), CMI (Wakabayashi & Daimon, 2015), AIP (Fernández-Macías et al., 2019), CRI-I (Koca et al., 2019), and CRI-II (Koca et al., 2019) was performed using the following equations:

$$\mathrm{LAP_{men}} = (\mathrm{WC} - 65) \times \mathrm{TG}.$$

$$\mathrm{LAP_{women}} = (\mathrm{WC} - 58) \times \mathrm{TG}.$$

$$\mathrm{CMI} = (\mathrm{TG}/\mathrm{HDL} - \mathrm{C}) \times \mathrm{WHtR}.$$

$$AIP = \log (TG/HDL - C).$$

$$CRI - I = TC/HDL - C.$$

$$CRI - II = LDL - C/HDL - C.$$

2.10 | Statistical analysis

Analysis of data was performed using a statistical package for social science (SPSS) software (Chicago, Illinois, USA) version 24. A per-protocol approach was used. The distribution of variables was assessed utilizing the Kolmogorov–Smirnov test. We used an independent *t*-test for continuous variables and a chi-square for categorical variables to compare differences in general characteristics at the baseline between groups. In addition, to compare mean changes of CMI, AIP, CRI-I, and CRI-II between groups, a general linear model of ANOVA for repeated measurements with Bonferroni post hoc analysis was utilized. The groups were regarded as between-subject factors, and time was considered a within-subject factor. Furthermore, we used univariate ANCOVA to control the effects of confounding factors with significant differences between the two groups, such as the mean change in energy intake during follow-up and baseline values of the CRI-II. For all analyses, $p < .05$ was considered significant.

3 | RESULTS

3.1 | Characteristics of the participants

A total of 84 participants completed the study (the compliance rate was higher than 93%). Six participants left the study due to surgery ($n = 1$) and non-referral ($n = 5$) (Figure 1).

General characteristics of participants are shown in Table 1. There were no significant differences between the two groups in baseline characteristics ($p > .05$). No significant difference was observed between the two groups in physical activity ($p > .05$). In addition, no significant difference was found between the two groups in allicin source consumption as well as drugs and supplements intake ($p > .05$). We found a significant difference in mean intake of energy ($p = .01$) between two groups during follow-up. Due to the normal distribution of variables, parametric tests were used to analyze the data.

The participants did not report any serious adverse events related to the supplement intake during follow-up.

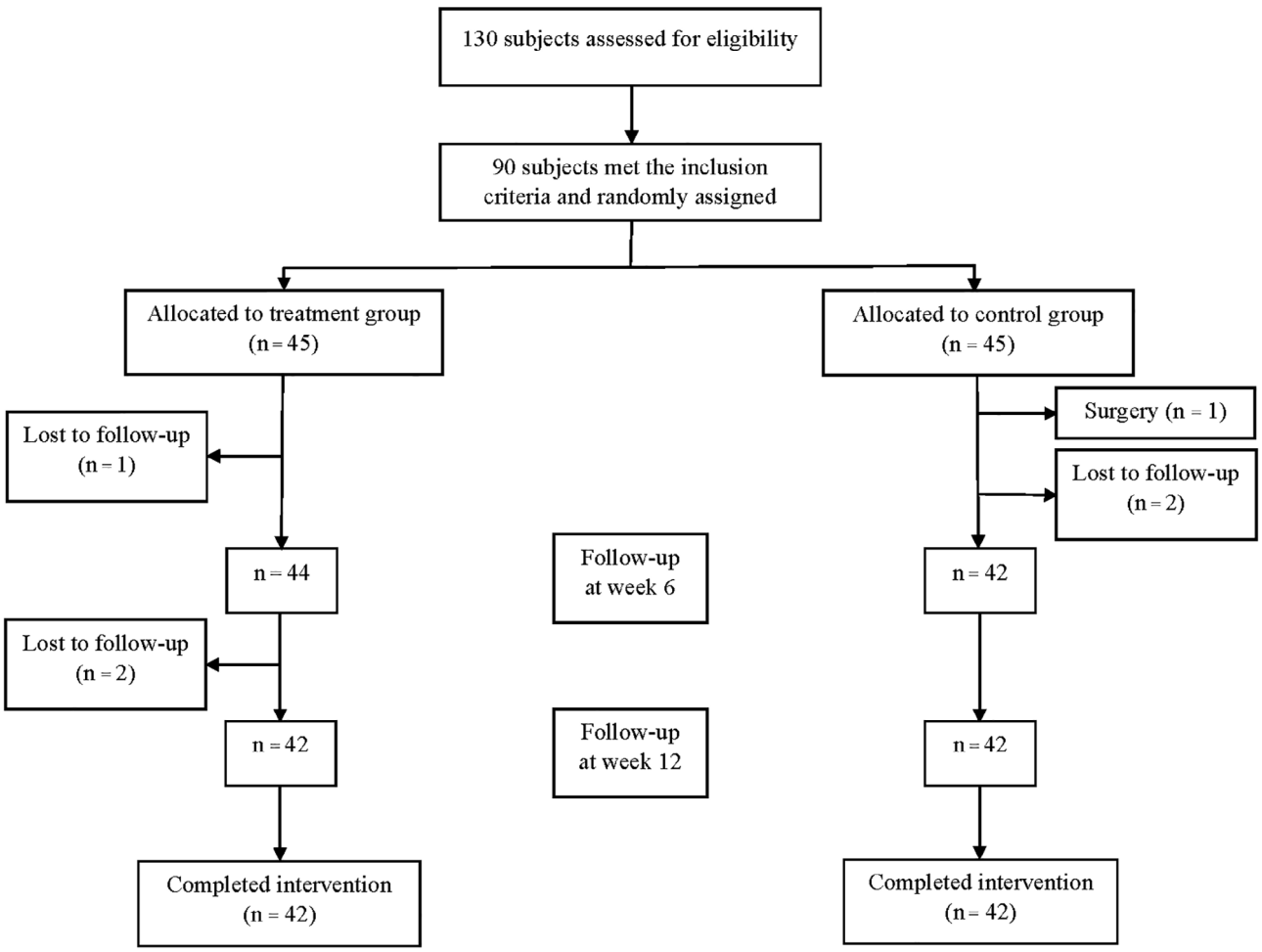

FIGURE 1 Flowchart of eligibility, screening, and follow-up.

TABLE 1 Characteristics of subjects with MetS.

Variable	Treatment group ($n = 45$)	Control group ($n = 45$)	p
Age, *y*	46.8 ± 11.7	44.3 ± 10.5	.28
Sex, *n* (%)			
Male	31 (68.9)	26 (57.8)	.27
Female	14 (31.1)	19 (42.2)	
Smoking, *n* (%)			
Yes	15 (33.3)	12 (26.7)	.49
No	30 (66.7)	33 (73.3)	
Supplement intake, *n* (%)			
Yes	3 (6.7)	3 (6.2)	1.0
No	42 (93.3)	42 (93.3)	
Drug intake, *n* (%)			
Yes	3 (6.7)	6 (13.3)	.29
No	42 (93.3)	39 (86.7)	
Energy intake, kcal/d			
Baseline	2074.0 ± 114.7	2049.1 ± 140.8	.36
After intervention	1946.3 ± 124.9	2005.8 ± 116.8	.02
Mean change	−127.6 ± 142.8	−43.3 ± 142.5	.01
MET-h/d	28.8 ± 3.8	27.7 ± 3.7	.15
Intake of allicin sources, serving	0.07 ± 0.1	0.08 ± 0.1	.81
Height, kg	171.5 ± 9.7	169.3 ± 11.3	.32
TC, mg/dl	202.9 ± 34.4	200.3 ± 39.8	.74
TG, mg/dl	203.5 ± 69.5	234.8 ± 113.1	.11
HDL-C, mg/dl	43.2 ± 7.3	46.3 ± 8.0	.06
LDL-C, mg/dl	121.8 ± 25.3	114.1 ± 25.5	.15
WC, cm	106.3 ± 8.7	108.7 ± 9.0	.20

Note: p values were computed by independent t-test and data are expressed as mean ± standard deviation (SD), while for Sex and Smoking status are computed by chi-square and data are expressed as numbers (percentage).
Abbreviations: HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; MET-h, metabolic equivalent task hours; MetS, metabolic syndrome; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

TABLE 2 Effect of garlic powder supplementation on intestinal transit time in subjects with MetS.

	Treatment group ($n = 42$)		Control group ($n = 42$)				
Variable	Normal	Abnormal (constipation/diarrhea)	Normal	Abnormal (constipation/diarrhea)	$P_{baseline}$	p_{value}[a]	p_{value}[b]
Intestinal function, BSS							
Baseline	22 (52.4)	20 (47.6)	29 (69)	13 (31)	.11	.008	.001
Week 6	38 (90.4)	4 (9.6)	28 (66.6)	14 (33.4)			
Week 12	39 (92.8)	3 (7.2)	27 (64.2)	15 (35.8)			

Note: Data are expressed as numbers (Percentage). p values were computed by chi-square.
Abbreviations: BSS, Bristol stool scale; MetS, metabolic syndrome.
[a]Comparisons between treatment and control groups at Week 6.
[b]Comparisons between treatment and control groups at Week 12.

3.2 | Outcomes

3.2.1 | Intestinal transit time

We reported the effect of garlic powder supplementation on intestinal transit time in Table 2. At the baseline, there was no significant difference between the treatment group and the control group in intestinal transit time (percent of participants with normal stool consistency: 52.4% vs. 69%; $p = .11$). A significant improvement in intestinal transit time was found in the treatment group compared to the control group at Week 6 (percent of participants with normal stool consistency: 90.4% vs. 66.6%; $p = .008$) and after intervention

TABLE 3 Effect of garlic powder supplementation on indices in subjects with MetS.

Indices	Treatment group ($n = 42$)	Control group ($n = 42$)	$P_{baseline}$	$P^{\dagger}$			$P^{\dagger\dagger}$
				P_{Time}	P_{Group}	$P_{Time \times Group}$	
LAP							
Baseline	99.2 ± 42.2	123.5 ± 80.7	.08	<.001[b,c]	.01	<.001	<.001
Week 6	91.8 ± 43.7	127.1 ± 79.4		<.001*	.03*	<.001*	<.001**
Week 12	77.7 ± 34.2	124.2 ± 83.6					
Mean change	−21.5 ± 23.4	0.7 ± 21.5					
CMI							
Baseline	3.05 ± 1.4	3.37 ± 2.4	.47	<.001[a,b]	.05	<.001	<.001
Week 6	2.54 ± 1.4	3.42 ± 2.3		.001*	.13*	<.001*	<.001**
Week 12	2.20 ± 1.1	3.50 ± 2.4					
Mean change	−0.85 ± 0.8	0.13 ± 0.8					
AIP							
Baseline	0.65 ± 0.1	0.65 ± 0.2	.96	<.001[a,b]	.06	<.001	<.001
Week 6	0.56 ± 0.1	0.66 ± 0.2		<.001*	.15*	<.001*	<.001**
Week 12	0.51 ± 0.1	0.66 ± 0.2					
Mean change	−0.14 ± 0.1	0.01 ± 0.1					
CRI-I							
Baseline	4.80 ± 0.9	4.42 ± 1.1	.10	<.001[a,b]	.57	<.001	<.001
Week 6	4.28 ± 0.8	4.55 ± 1.0		<.001*	.97*	<.001*	<.001**
Week 12	4.11 ± 0.8	4.58 ± 1.1					
Mean change	−0.69 ± 0.5	0.16 ± 0.5					
CRI-II							
Baseline	2.87 ± 0.6	2.52 ± 0.6	.01	<.001[a,b]	.61	<.001	<.001
Week 6	2.53 ± 0.6	2.53 ± 0.5		<.001*	<.31*	<.001*	<.001**
Week 12	2.37 ± 0.5	2.54 ± 0.6					
Mean change	−0.50 ± 0.3	0.02 ± 0.3					

Note: Data are expressed as mean ± standard deviation (SD). $P_{baseline}$ were computed by independent *t*-test. $P^{\dagger}$ were computed by general linear model ANOVA for repeated measurements. $P^{\dagger\dagger}$ were computed by univariate ANCOVA for mean change of parameters. Post hoc test: [a]: significant difference between baseline and Week 6; [b]: significant difference between baseline and Week 12; [c]: significant difference between Week 6 and Week 12. *Adjusted based on mean changes of energy intake. **adjusting for mean changes of energy intake and baseline values of CRI-II.
Abbreviations: AIP: atherogenic index of plasma; CMI: cardiometabolic index; CRI: Castelli risk index; LAP: lipid accumulation product; MetS: metabolic syndrome.

(percent of participants with normal stool consistency: 92.8% vs. 64.2%; $p = .001$).

3.2.2 | Lap

The effect of garlic powder supplementation on LAP was demonstrated in Table 3. We found no significant difference between the treatment group and the control group in LAP (99.2 ± 42.2 vs. 123.5 ± 80.7; $p = .08$) at the baseline. Garlic powder supplementation, compared to the placebo, significantly reduced LAP (mean change: −21.5 ± 23.4 vs. 0.7 ± 21.5; $p < .001$). After adjusting for confounding factors, the results remained unchanged.

3.2.3 | CMI and atherogenic indices

We represented the effect of garlic powder intervention on CMI and atherogenic indices in Table 3. There was no significant difference between the groups in CMI (3.05 ± 1.4 vs. 3.37 ± 2.4; $p = .47$), AIP (0.65 ± 0.1 vs. 0.65 ± 0.2; $p = .96$), and CRI-I (4.80 ± 0.9 vs. 4.42 ± 1.1; $p = .10$). However, the level of CRI-II was higher in treatment group compared to the control group (2.87 ± 0.6 vs. 2.52 ± 0.6; $p = .01$) at the baseline. Garlic powder supplementation compared to the placebo reduced the levels of CMI (mean change: −0.85 ± 0.8 vs. 0.13 ± 0.8; $p < .001$), AIP (mean change: −0.14 ± 0.1 vs. 0.01 ± 0.1; $p < .001$), CRI-I (mean change: −0.69 ± 0.5 vs. 0.16 ± 0.5; $p < .001$) and CRI-II (mean change: −0.50 ± 0.3 vs. 0.02 ± 0.3;

$p < .001$). After adjusting for mean changes in energy intake and baseline values of variables, the results remained unchanged.

4 | DISCUSSION

For the first time, this RCT found an improvement in intestinal transit time, LAP, CMI, AIP, CRI-I, and CRI-II after garlic powder supplementation for 3 months.

Garlic is known as a prebiotic, and probably through its effects on dysbiosis, it can improve intestinal function and transit time. Garlic can increase the health of the gut by attenuating disturbances of the gut microbiome by increasing the relative abundance of *Lachnospiraceae* and decreasing the relative abundance of *Prevotella* (Chen et al., 2019). There is a direct association between the abundance of *Lachnospiraceae* and antiinflammatory activity and host mucosal integrity (Lin et al., 2018; Reeves, Koenigsknecht, Bergin, & Young, 2012). Garlic can promote gastro-intestinal function by protecting mucosal defense against *Helicobacter pylori* activity and ulcer development (Ghosh & Playford, 2003). Garlic and its main active ingredients, such as allicin, can improve the tightness of tight junctions, increase mucus synthesis, and attenuate villous atrophy (Park et al., 2011; Shi et al., 2019). In addition, allicin significantly increased the villi length and the ratio of villus length to crypt depth, changed the composition of the intestinal microbiota, increased the proportion of beneficial bacteria, and improved intestinal function in high-fat diet-induced obese mice (Shi et al., 2019).

Although the clinical findings in this field are scarce, it seems that even short-term consumption of garlic can improve intestinal transit time. According to our results in this field, garlic consumption can be recommended as a management approach among subjects with MetS (who are not allergic to garlic and also do not have low blood pressure). However, as there is no similar clinical study to confirm our vision, our findings must be interpreted with caution.

We demonstrated a significant reduction of LAP after 12-week supplementation of garlic powder suggesting a significant improvement of cardiovascular risk. There is no previous study investigating the effect of garlic on LAP, but TG and WC are the variables of LAP (Sangouni, Orang, & Mozaffari-Khosravi, 2021), and some studies have shown garlic effects on these parameters.

A study demonstrated that 100 mg/kg body weight of raw, crushed garlic two times a day for 4 weeks could reduce the levels of TG in subjects with MetS (Choudhary et al., 2018). In addition, garlic powder supplementation for 12 weeks led to a significant reduction of TG among patients with non-alcoholic fatty liver disease (NAFLD) (Sangouni et al., 2020a). However, the study by Jung et al. (Jung et al., 2014) showed that aged black garlic intake (6 g/d) has no effect on TG in subjects with mild hypercholesterolemia. Moreover, a study showed that garlic powder intake (920 mg/d) for 12 weeks could not reduce TG among subjects without dyslipidemia (Turner, Mølgaard, & Marckmann, 2004). The health status of participants can explain some conflicting findings. It seems that garlic has no effect on TG in subjects without dyslipidemia, but it can improve TG in subjects with MetS and NAFLD. Besides the effects on TG, garlic can also reduce WC in subjects with MetS (Choudhary et al., 2018). In addition, a RCT confirmed the beneficial effect of garlic powder (1,600 mg/d for 12 weeks) on WC among subjects with NAFLD (Sangouni et al., 2020b). Garlic and its active components, such as allicin, through mechanisms such as attenuating intestinal absorption of TG, inhibiting TG production in the liver, modulating differentiation of human preadipocyte, and increasing the expression of brown adipocyte-related genes and thermogenic genes, can improve body composition and WC (Ha et al., 2015; Joo, Kim, Kim, & Kim, 2013; Keophiphath, Priem, Jacquemond-Collet, Clément, & Lacasa, 2009; Shi et al., 2019) In general, garlic can decrease cardiovascular risk by improving TG and WC in subjects with MetS. Therefore, consumption of garlic can be considered a strategy for management of cardiovascular risk factors, especially among subjects with MetS and patients with non-communicable diseases linked to MetS such as T2DM, NAFLD, and cardiovascular disease (CVD).

The investigations have suggested that garlic and its main components, especially allicin, can improve cardiometabolic and atherogenic indices through various mechanisms, such as inhibiting gene expression of microsomal TG transfer protein in the liver and intestinal cell lines, modulating intestinal fat absorption, decreasing the activity of enzymes involved in the hepatic production of lipids, increasing the clearance of lipids from the liver, and increasing the level of adiponectin (Ha et al., 2015; Joo et al., 2013; Keophiphath et al., 2009).

Serum lipids are the main variables in the equation of CMI and atherogenic indices (AIP, CRI-I, and CRI-II) (Fernández-Macías et al., 2019; Koca et al., 2019; Wakabayashi & Daimon, 2015). A study demonstrated a significant improvement in TC, LDL-C, and HDL-C in patients with T2DM and dyslipidemia who consumed 600 mg/d raw garlic for 12 weeks (Ashraf et al., 2005). It has been found that garlic powder supplementation (1,600 mg/d) for 12 weeks can reduce TG, TC, and LDL-C, and increase the level of HDL-C in patients with NAFLD (Sangouni et al., 2020a). In addition, the study of Kojuri et al. (Kojuri, Vosoughi, & Akrami, 2007) examined the effect of garlic powder intake (800 mg/d for 6 weeks) on lipid profile among subjects with hypercholesterolemia, and reported a significant improvement of TC, LDL-C, and HDL-C. However, Jung et al. (Jung et al., 2014) reported that 12-week supplementation of aged black garlic (6 g/d) in subjects with mild hypercholesterolemia had only a beneficial effect on HDL-C, but could not improve TG, TC, and LDL-C. In addition, Turner et al. (Turner et al., 2004) showed that garlic powder (920 mg/d) for 12 weeks could not change serum lipids in volunteers without dyslipidemia. These discrepancies suggest that intervention duration, type, and dosage of garlic and the health status of participants have a strong influence on treatment outcome. Generally, garlic has lipid modifying effects among subjects with dyslipidemia, but it has no effect on the lipid profile in subjects without dyslipidemia. Therefore, garlic consumption can be a therapeutic option for subjects with dyslipidemia.

It should be noted that energy intake can affect the levels of cardiometabolic risk factors. In other words, energy intake reduction can improve visceral obesity and cardiometabolic indices. We have

previously shown that garlic can reduce appetite and energy intake (Sangouni, Alizadeh, Jamalzehi, & Parastouei, 2021), and the mean reduction of energy intake in our intervention group was significantly lower than in the control group after 12 weeks, corroborating these results. In order to find a more realistic effect of garlic powder supplementation (independent of energy intake reduction), the mean change in energy intake was considered a confounding factor in the analysis of covariance (ANCOVA), and the findings remained unchanged.

We declare that recently our research group reported the effect of garlic powder supplementation on MetS components, insulin resistance, fatty liver index, and appetite (Sangouni, Alizadeh, et al., 2021). We used the same data for the present article. To follow the principles of ethics in research, we clarify that Figure 1 and the baseline characteristics of our previous article (Sangouni, Alizadeh, et al., 2021) have been added to the present article.

Our study has important strengths. This study was the first RCT that assessed the effect of garlic on intestinal transit time, LAP, and cardiometabolic indices in subjects with MetS. In addition, we assessed dietary consumption of garlic and evaluated the garlic effect on a short duration intervention (Week 6). However, as limitations, the intervention duration of this study was relatively short, and we did not evaluate the types and abundance of gut microbiota before and after the garlic intervention. In addition, an assessment of garlic concentration to evaluate the bioavailability of garlic and the reliability of the results was not performed. Finally, although we evaluated dietary intakes at the baseline, Week 6, and after the intervention, studies with more controlled research environments are more appropriate to evaluate the realistic effect of garlic on constipation and diarrhea events.

5 | CONCLUSIONS

In conclusion, garlic powder supplementation for 12 weeks improved intestinal transit time and cardiovascular risks. Clinical studies evaluating the effect of garlic on outcomes similar to the ones of the present study are scarce, and several studies are needed to confirm our results. Therefore, our findings should be interpreted with caution. Further well-designed studies with longer intervention durations are required to reach a firm conclusion. In addition, to clarify the effects of garlic on gut microbiota in future studies, we suggest evaluating the types and abundance of bacteria in the gut microbiota before and after garlic intervention.

AUTHOR CONTRIBUTIONS

The authors' responsibilities were as follows—Abbas Ali Sangouni, Mohammad Alizadeh, Atena Jamalzehi and Karim Parastouei: conceived and designed the study; Abbas Ali Sangouni and Mahdieh Hosseinzadeh analyzed the data; Mohammad Alizadeh: provided material and technical support, Abbas Ali Sangouni and Mahdieh Hosseinzadeh: wrote the manuscript; Karim Parastouei: critically revised the manuscript for important intellectual content; Karim Parastouei: had primary responsibility; and all authors: read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interests.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was confirmed by Baqiyatallah University of Medical Sciences and Health Services. In addition, the Ethical Committee of Baqiyatallah University of Medical Sciences and Health Services in Tehran, approved the written informed consent, which was obtained from all subjects before the data collection, was approved under code number: IR.BMSU.REC.1398.120. All methods were performed in accordance with the Helsinki Declaration.

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