

The Effects of Lycopene Intake on Blood Pressure and Lipid Profile of Patients with Metabolic Syndrome; a Randomized Clinical Trial

Mahdi Mirahmadi¹, Malihe Aghasizadeh², Habibollah Esmaily^{3,4}, Hamed Baharara⁵,
Maryam Mohammadi-bajgiran², Reza Assaran-Darban⁶, Gordon A. Ferns⁷,
Farzin Hadizaheh^{1,8,*}, Majid Ghayour Mobarhan^{2,*}

¹Biotechnology Research Center, Pharmaceutical Technology Institute,
Mashhad University of Medical Sciences (MUMS), Mashhad, Iran

²International UNESCO center for Health-Related Basic Sciences and Human Nutrition,
Mashhad University of Medical Sciences, Mashhad, Iran

³Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

⁴Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran

⁶Department of Biology, Mashhad Branch, Islamic Azad University, Mashhad, Iran

⁷Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN19PH, UK

⁸Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran

*Corresponding author: hadizadehf@mums.ac.ir, ghayourm@mums.ac.ir

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Abstract The lycopene has positively affect human health by reducing metabolic disorder, which is a mechanism behind metabolic syndrome (MetS). We developed a method for encapsulating lycopene and designed a randomized clinical trial to assess the effect of lycopene on lipid profile of patients with MetS. In this study, 80 subjects with MetS were randomly assigned to two groups: one group received lycopene at a dose of 30 mg (1 tablet per-day) for 8 weeks. The second group received placebo with similar color, size, and other appearance to lycopene tablets. Participants returned for follow-up visits after 4 and 8 weeks and blood samples were collected for examination of fasting blood glucose and lipid profile. These measurements were taken using an alpha-classic analyzer. The average age of the lycopene and placebo groups were 44.25 ± 11.25 and 41.75 ± 10.05 years, respectively. There were significant differences in systolic blood pressure (SBP), fasting blood glucose (FBG), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG) in the lycopene group before and after treatment, but there was no significant effect of treatment in the placebo group. After adjusting for confounding factors such as age, sex, FBG, LDL, and TC as co-variant, the *P* value of difference between lycopene and placebo groups was significant. Traditionally, lycopene was found to significantly increase serum high-density lipoprotein (HDL) in patients with MetS. This research expands our knowledge about protective effects of lycopene on lipid profile, as an important risk factor for evaluating of cardiovascular disease.

Keywords: metabolic syndrome, lycopene, lipid profile, blood pressure

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1. Introduction

Metabolic syndrome (MetS) is a common metabolic disorder characterized by raised blood pressure, central obesity, insulin resistance, and atherogenic dyslipidemia [1]. MetS is increasingly recognized as a serious, worldwide public health concern. The prevalence of MetS in the Middle East is 20.7-37.2% in men and 32.1-42.7%

in women [2]. However, the prevalence of MetS in Iran is 37.05% [3]. According to several studies, the prevalence of MetS in Brazil [4], Ghana [5], and Indonesia [6] is 34.1%, 69.1%, and 21.6%, respectively.

Several definitions for MetS have been proposed, including those by World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in 2001, and the International Diabetes Foundation (IDF) in 2005. The WHO criteria for MetS include: central obesity (waist/hip

ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m² plus any two of the following four factors: raised triglycerides (≥ 1.695 mmol/L), reduced high density lipoprotein (HDL) cholesterol (≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)), raised blood pressure (BP) ($\geq 140/90$ mmHg), raised fasting blood glucose (FBG) (>5.6 mmol/L) [7,8,9]. Several studies have revealed that atherogenic dyslipidemia is the most common component affecting MetS. The findings suggest that low level of HDL may signal the initiation of pathophysiological processes that contribute to the development of MetS [9,10].

Till now, numerous studies have focused on herbal medicines to reduce the complications of MetS [11]. Chemical drugs have side effects and are often expensive. Due to their minimal side effects and affordable prices, herbal medicines can be used as a very effective option in the management of patients [12]. Lycopene is increasingly applied as a dietary antioxidant from the carotenoid family. Traditionally, Lycopene was first found as a red lipophilic hydrocarbon pigment in tomatoes and other red or pink fruits and vegetables [13,14].

Lycopene is considered as an important and valuable component, playing a key role in reducing the levels of triglyceride (TG), total cholesterol (TC), and low-density lipoprotein (LDL). Much of the current literature on lycopene pays particular attention to effects of dietary lycopene supplementation on the plasma lipid profile. These studies have reported that the levels of TG and LDL decrease with prolonged consumption of lycopene [15,16]. In an observational study by Baz (2022), it has been reported that a significant increase in the serum level of HDL was observed in the lycopene group compared to the control. This points out that lycopene displayed a beneficial potential to manage MetS and its related pathologies [17]. Several studies have reviewed the evidence literature from the randomized clinical trials (RCTs) and found the beneficial effects of lycopene supplementation on BP levels [18], improving cardiovascular risk factors [19], weight, body mass index (BMI), inflammatory factors [20], and also its efficacy among patients with prostate cancer [21].

Due to the inconsistent results of previous RCTs on the effects of lycopene supplementation on MetS and the high prevalence of hyperlipidemia in Iran, we conducted this randomized controlled double-blinded study to assess the effect of lycopene containing tablets on lipid profile of patients with MetS in Iranian population. The encapsulation method of lycopene explained here for the first time, is the novelty of this paper.

2. Method

2.1. Trial Design

The present study was randomized, double-blinded and placebo-controlled with an 8-week duration. The trial was carried out at the Qaem hospital (Mashhad, Iran) and the department of Clinical Nutrition (Mashhad University of Medical Sciences, Mashhad, Iran) during the period from October 2022 to January 2023. The study was conducted according to approval from the Institutional Ethics Committee

(IR.MUMS.PHARMACY.REC.1399.038) and Iranian Registry of Clinical Trials (IRCT20130507013263N3). Figure 1 presents an overview of the randomized clinical trial on effects of lycopene on MetS patients in the Iranian population.

2.2. Study Participants

Participants were recruited from the eligible patients using face-to-face interviews, email, social media, and campus and dorm-based advertisements. Prior to screening, participants received verbal and written information regarding the purpose of the research, the data to be collected and the duration of the intervention and signed a written informed-consent form to participate. The study included subjects of both genders, aged between 18 and 60 years, residing in the city of Mashhad and had MetS according to “The international Diabetes Federation” guidelines [8]. Exclusion criteria consisted of subjects with prior cardiovascular diseases, pregnant or breastfeeding women, serious disease requiring active treatment and treatment with any other herbal supplements.

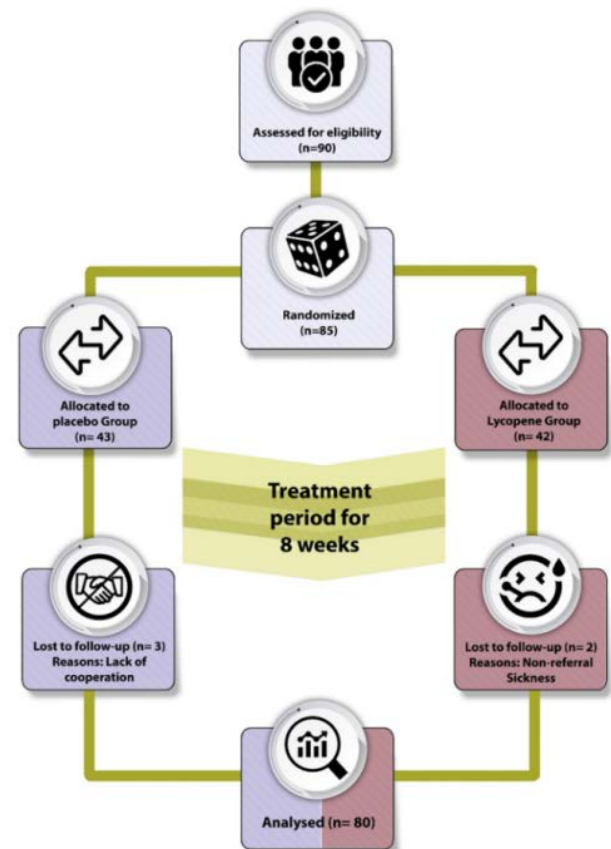


Figure 1. Flowchart of the study

2.3. Interventions

Participants were randomly allocated to the control and intervention groups using computer software (SPSS, version 24 software). To blind the participants, a placebo group received a packaging with color, size, and other appearance characteristics completely similar to lycopene tablets. Subjects were randomly assigned to one of two groups using random number tables. Upon entering the

trial, subjects selected a numbered, sealed envelope containing their randomized allocation to either intervention or the control group. The random allocation sequence was generated by the statistics team, and an employee outside the research team blinded the drugs. Care providers enrolled participants, and the project's physician assigned them to their respective interventions, and both were blinded to the interventions.

Patients received one tablet of lycopene or placebo once daily for a duration of 8 weeks. Subjects returned for follow-up visits at 4 and 8 weeks of study. They were evaluated for efficacy and safety and received a diet for next 4-weeks. At baseline (week 0), 4 and 8 weeks of the trial, body weight (kg), height (cm), waist circumference (cm), body composition, and blood pressure were assessed. After a 12-hour overnight fasting, 20 ml of blood was taken in plain blood collection tubes for examination of FBG, SBP, DBP and lipid profile including triglycerides, HDL-C, LDL-C, and total cholesterol at baseline and after 8 weeks of treatment. At each visit, subjects were screened for the occurrence of adverse drug reactions (ADRs), and any reported ADRs were noted on the case report form.

2.4. Lycopene Extraction

The designed extraction method [22,23,24,25] involves various steps. Initially, we kept tomato paste as the product obtained from tomatoes, at a temperature of 37-40°C for three days, and about 70-80% of its moisture content was dried. Then, using a semi-industrial mill, the dried tomato pastes sheets were turned into dry powder and left for 12 hours to dry, or they were stored at room temperature with low humidity until ready for the extraction process. Then, a mixture of 1:1 acetone and ethyl acetate solvents were added to these powders. The amount of solvent was selected based on the volume of the powder and was about 4 times the volume of the powder. This mixture was agitated using a propeller mixer for 1 to 3 hours in a covered container isolated from air and light. This process was repeated 3 to 5 times, and each time the extract from the powders was separated and filtered, and the fresh solvent was added to the mixing container. In the separation stage, using cloth filters and mechanical pressure over 1 ton per square meter with the help of a device designed for this purpose, the applied solvents contained the separated extract and were transferred to a special container. Next, the collected extract, containing acetone, ethyl acetate, and a lycopene-containing extract, was transferred to a rotary device to recover the solvent and reduce the volume of the extract. Approximately 95% of the solvent was recovered during several stages. This step is one of the main advantages of this method, as the high cost of organic solvents can be reduced significantly by recovering and reusing them, especially with a recovery rate of this magnitude, which reduces the cost of the extraction process significantly. After removing the solvent, the extract obtained in the initial stage contains approximately 30-35% of the weight of the active ingredient, lycopene. This extract should be kept refrigerated at a temperature of 4 °C. After this stage, the extract was kept at room temperature for a short time to be homogenized to increase the lycopene content. Cold 96%

ethanol with a ratio of 10:1 was then added to the extract, causing the desired material (lycopene) to precipitate and unwanted impurities to separate. The resulting sediment was separated using a centrifuge and transferred to a separate container. The ethanol used in this stage can also be recovered at a rate of approximately 70-80%, reducing the consumption of other solvents in the extraction process. The remaining amount of ethyl acetate and acetone in the final extract was measured using the Head-Space method (by GC) to determine the presence of solvents used in the extraction process. The final extract was analyzed and standardized by HPLC, initially using USP-NF (USP 44 – Dietary Supplements – Lycopene). Initially a weighed quantity of USP Lycopene Preparation RS, (USP 1-May-2019) equivalent to approximately 5 mg of lycopene, were transferred into a 250-mL volumetric flask. About 60 units of bacterial alkaline protease preparation or another suitable enzyme and about 25 mg of butylated hydroxytoluene were added. Then 2.5 mL of ammonium hydroxide diluted in water (2 in 100) was poured into the flask, and mixed. Then it was placed in an ultrasonic bath at 50° for 10 min (rotating the flask occasionally to avoid having the material stick to the glass surface is necessary). This continued until the material was dispersed with no lumps. Then 5 mL of tetrahydrofuran, 40 mL of dehydrated alcohol, was added and mixed by placing in an ultrasonic bath for about 1 min, then cooled to room temperature, and diluted with tert-butyl methyl ether to volume. After shaking vigorously, the precipitate was allowed to settle and finally filtered to be analyzed by HPLC. UV Spectroscopy was used as the following to determine the amount of lycopene based on the obtained standard curve and the USP-NF identification method adjusted for Lycopene preparation. Lycopene final extract content was measured to contain at least 35% w: w of pure lycopene, whereas using 1kg of tomato paste as the raw material, gives between 2-3g of the final filtered and dried extract which contains about 1g of pure lycopene. We performed accelerated stability studies of the extract under specific conditions to ensure maximum stability of the lycopene at a refrigerated temperature (4°C) and away from light and oxygen.

2.5. Tablets Formulation

Firstly, an oil extract containing 30 to 35% of lycopene, along with hexane as a pharmaceutical-grade solvent, was added to microcrystalline cellulose (Avicel) powder and thoroughly mixed using a simple mixer. The powder containing lycopene was obtained after removing the solvent. Avicel has very special physicochemical properties that have been of interest in the pharmaceutical industry. Some of these properties utilized in this formulation include excellent absorption of the lycopene extract, uniform mixing of the components, assistance in the flow and compressibility of the directly compressible tablet powder, and an outstanding tablet disintegration property demonstrated in various formulations in relevant tests, as well as other desirable properties, such as excellent compressibility. In the following step, suitable primary powder obtained for direct compression in the following ratios, using Aerosil, Talc powder, and a specific combination of two types of commercial agents

(Polyvinylpyrrolidone K30 and Polyvinylpyrrolidone CL). Aerosil (silicon dioxide) is a substance with a very low density, which greatly assists the flow of the tablet during direct compression due to its crystalline properties. This powder is used in low percentages (1 to 5%). Talc powder is also used for this purpose in small amounts (between 2 and 5%), and its properties have been utilized in various formulations before. Other agents (polyvinylpyrrolidone,

etc.) are used with the aim of achieving suitable disintegration properties, as well as assisting in the compressibility and hardness of the tablets using a combination of 10 to 30%. For tablet compression, plates were first prepared using this powder and the direct compression method and then crushed and mixed to compress to the final product of 12mm diameter and ~500 mg of weight, film coated tablets.

Table 1. Baseline features in the study groups

		Lycopene n= 40	Placebo n= 40	P value
Gender	Women %	22 (55%)	28 (70%)	0.1
	Men %	18 (45%)	12 (30%)	
Age (year)		44.25±11.25	41.75 ±10.05	0.2
Systolic blood pressure (mmHg)		125.00±5.77	134.75±12.79	0.1
Diastolic blood pressure (mmHg)		75.12±12.91	75.62±15.62	0.1
FBG (mg/dl)		117.45±34.7	98.6±15.7	0.001
HDL-C (mg/dl)		54.2±10.1	54.05±9.2	0.2
LDL-C (mg/dl)		112.5±35.6	105.5±24.6	0.04
TG (mg/dl)		178.2±92.5	168.6±97.36	0.3
TC (mg/dl)		200.68±46.6	189.85±32.53	0.03
Non-smoker, N (%)		35(87.5)	31 (77.5)	0.4
Ex-smoker, N (%)		1(2.5)	3(7.5)	
Current smoker, N (%)		4(10)	6 (15)	

Data presented as mean ± standard deviations or median (interquartile range). Independent sample t-test was used where appropriate.

Table 2. Lycopene's effects on lipid profile in population study

Variable	Normal Range		Treatment (N= 40)			Control (N= 40)			*P value
	Male	Female	Baseline	Diff	P value	Baseline	Diff	P value	
SBP (mmHg)	<120 Normal 120-139 Prehypertension >140 Hypertension		125.00±5.77	- 1.05	0.006	134.75±12.79	0.8	0.420	0.052
DBP (mmHg)	<80 Normal 80-89 Prehypertension >90 Hypertension		75.12±12.91	0.25	0.415	75.62±15.62	0.4	0.602	0.325
FBG (mg/dl)	74-106		117.45±34.7	-13.2	0.001	98.6±15.7	-1.2	0.525	0.244
HDL-C (mg/dl)	30 – 70	30 - 85	54.2±10.1	3.07	0.009	54.05±9.2	0.3	0.823	0.179
LDL-C (mg/dl)	<130		112.5±35.6	-8.7	0.010	105.5±24.6	0.7	0.817	0.343
TG (mg/dl)	<200 Normal 200-400 High Risk >400 Abnormal		178.2±92.5	-31.4	0.002	168.6±97.3	-35.8	0.01	0.400
TC (mg/dl)	<200 Normal 200-240 High Risk >240 Abnormal		200.68±46.6	-18.2	0.001	189.85±32.53	-3.6	0.503	0.229

Data presented as mean ± standard deviations or median (interquartile range). Independent sample t-test was used where appropriate. SBP; Systolic blood pressure, DBP; Diastolic blood pressure, FBG; fasting blood glucose, HDL; high density lipoprotein, LDL; low density lipoprotein, TG; triglyceride, TC; total cholesterol, * P value of difference between diff in lycopene and placebo group after adjusting for confounding factors such as age, sex, FBG, LDL, and TC as co-variant.

2.6. Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the data. Descriptive statistics, including mean and standard deviation (mean ± SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data, were calculated for all variables. The Mann-Whitney test was used for non-normally distributed data, while the T-student test was used for normally distributed data. A P value of less than 0.05 was considered statistically significant.

3. Result

The results obtained from the baseline analysis of this study are summarized in Table 1. A total of 80 patients were categorized to two groups; the mean age of the

lycopene and placebo groups were 44.25±11.25 and 41.75 ±10.05 years, respectively. It is apparent from this table that there were significant differences in FBG, LDL-C, and TC between lycopene and placebo groups. Accordingly, no significant differences were found in the other clinical features between two groups.

The results of the clinical differential analysis of treatment (as lycopene) and non-treatment (as placebo) groups can be compared in Table 2. In this table, the baseline level of lipid profile, its difference (diff) after 8 weeks of intervention with lycopene, as well as its last column of the table, the P value of the difference between the lycopene and placebo groups was shown after adjusting for confounding factors such as age, sex, FBG, LDL, and TC as covariants. The most surprising aspect of the data in this study is that lycopene was found to increase serum HDL in patients with MetS. The adjusted

difference of HDL level in lycopene group was significantly more than the placebo group.

Strong evidence of differences was found in SBP, FBG, HDL, LDL, TC, and TG in lycopene group (Table 2). But there were no significant differences between the above-mentioned parameters in placebo group. Also only, *P* value of difference between diff in HDL level in studied groups after adjusting for confounding factors was remained significant.

4. Discussion

This is the first randomized clinical trial that evaluated the effects of lycopene on lipid profile in Iranian patients with MetS. Apparently, it has been shown that lycopene supplementation (30 mg for 8 weeks) increased the serum HDL level in Iranian patients with MetS.

The most important clinically relevant finding of lycopene effect was found to increasing serum HDL in patients with MetS. The present findings seem to be consistent with other research which have found that supplementation with lycopene was correlated strongly with levels of LDL and HDL and reduced HDL oxidation. These results support the hypothesis that carotenoids including lycopene, may show protective effects on cardiovascular disease [26]. This result may be explained by the fact that lycopene acts as an inhibitor of endothelial injury by preventing oxidation of HDL. It also improves HDL function [27] and prevents the inflammatory activity of macrophages cells [28]. There are similarities between the attitudes expressed by a clinical randomized trial of 225 subjects by Thies, 2012. The authors found that there was a positive correlation in tomato-based products consumption and lipid, vascular markers, and HDL functionality improvement [29]. In another clinical trial on MetS subjects, Saberi et. Al (2021) showed that herbal medicine administration improved the serum HDL functionality [30]. Similarly, Karimian (2022) found that that lycopene supplement can reduce the TG levels and subsequently increase endothelial function in ischemic patients. The result of this study on lipid profile including HDL-C, LDL-C, and TC have not shown significant findings [31]. It can be concluded on a meta-analysis study on humans' lipid profile that a significant cholesterol lowering effect on TC and LDL-C by supplementing of lycopene (dosages of more than 25 mg daily) was found [32]. However, the clinical trial studies on effect of lycopene in MetS patient were limited to comparison and therefore would not represent similar result.

A number of clinical trials have focused on the effect of lycopene supplementation on blood pressure; however, the controversy about this evidence has undiminished for over a century. Some researchers have suggested that lycopene had beneficial effects on BP [33,34,35] On the contrary, some researcher found that there are no changes in BP [36,37].

The pooled data from review analysis including 688 participants (438 case and 250 control) showed that lycopene supplementation could be significantly decreased systolic blood pressure [38]. Wolok et al. showed that treatment with standardized amount of lycopene (15 or 30 mg) was associated with statistically

significant reductions in SBP [39]. According to our result, the clinical differential analysis of lycopene and placebo groups was not significantly in DBP. These results agree with the findings of other studies, in which effects on DBP were not significantly observed in individuals (intervention with lycopene dosages of ≥ 15 mg, duration ≥ 8 weeks). [40].

This is the first study reporting a randomized clinical trial to assess an advantage of lycopene containing tablets in Iranian people who have metabolic syndrome disorder and was limited by sample size.

5. Conclusion

For the first time, this project was undertaken to design a randomized clinical trial to assess the effects of a new lycopene preparation on lipid profile and blood pressure of Iranian patients with metabolic syndrome. The lycopene administration (30 mg for a period of 8 weeks) increases serum HDL in patients with MetS. As well, no side effects were observed. Taken together, the adjust difference of HDL level in lycopene group was reported significantly more than the placebo group. A significantly differences in SBP, FBG, LDL, TC, and TG were also shown in lycopene group, but not in placebo group. Also, this result is not significant after removing confounders parameters. This research extends our knowledge about protective effects of lycopene on lipid profile as a most important risk factor for evaluation of cardiovascular disease. It is recommended that future studies investigate these effects on a larger patient population over a longer period of time. Additionally, it would be worthwhile to evaluate the impact of lycopene on other CVD risk factors.

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