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The Effects of Lycopene on Modulating Oxidative Stress and Liver Enzymes Levels in Metabolic Syndrome Patients: A Randomised Clinical Trial

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Abstract

Objective: The pathogenesis of metabolic syndrome (MetS) complications involves the excessive production of reactive oxygen species, inflammation, and endothelial dysfunction. Due to Lycopene, a highly unstable structure and its significant effects on modulating the metabolic system, there is a strong need for a formula that can increase its stability. The aim of this study was to develop an approach for encapsulating Lycopene and investigate its effects on inflammatory markers, oxidative stress, and liver enzymes in patients with MetS.

Materials and Methods: This study is a simple randomized, double-blind, objective-based clinical trial that involved eighty subjects with MetS, who were equally and randomly assigned to two groups: one group received 20 mg of Lycopene per day for 8 weeks, and the Placebo group followed the same protocol as the Lycopene group but received a placebo instead of Lycopene. They were called Lycopene and placebo, respectively. During follow-up visits after 4 and 8 weeks, 20 ml of blood was collected for evaluation of liver enzymes and some inflammatory related markers.

Results: Prior to the assignment of volunteers to their respective groups, there were no notable differences in C-reactive protein (CRP), serum liver enzymes, systolic and diastolic blood pressure, or pro-oxidant-antioxidant balance (PAB) between the Lycopene and placebo groups. However, our subsequent analysis revealed a significant reduction in the serum levels of CRP (P=0.001) and PAB (P=0.004) in the group that received Lycopene. Our encapsulated Lycopene treatment was not associated with a significant difference in serum levels of alanine aminotransferase (ALT), aspartate transferase (AST), or alkaline phosphatase (ALP) between our two groups.

Conclusion: This study investigated the impact of Lycopene on individuals with MetS, revealing a noteworthy modulation effect on PAB and inflammation linked to MetS. However, no significant differences was demonstrated in serum levels of ALT, AST and ALP between the studied group (registration number: IRCT20130507013263N3).

Keywords: Inflammation, Liver Enzyme, Lycopene, Metabolic Syndrome, Oxidative Stress

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Introduction

Oxidative stress, induced by reactive oxygen species (ROS), is a significant risk factor for cardiovascular disease (CVD) in individuals with metabolic syndrome (MetS) (1). MetS disease, a multifactorial disorder, is defined by a combination of altered metabolism of glucose, lipids, obesity and/or arterial pressure elevation. The overproduction of ROS may initiate inflammation and endothelial dysfunction, likely through oxidative modification in the liver, thereby may contribute to

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complications associated with MetS (2). Chronic complications linked to MetS risk factors can arise when there's an imbalance in pro-oxidants and antioxidants, particularly when pro-oxidants are in excess (3). The pro-oxidant-antioxidant balance (PAB) affects the interplay between antioxidant activity, oxidative damage, signal pathway activation, and the progression of pathological conditions such as CVD, insulin resistance, and MetS (4). The serum PAB assay is a simple method for evaluation of pro and antioxidant status in a single test, as reported by Alamdari et al. (5). Recent evidence suggested that an increased serum levels of PAB and C-reactive protein (CRP), along with clinical parameters, are independently associated with MetS (6).

Several cross-sectional studies have demonstrated a relationship between MetS and elevated serum liver enzymes, such as alanine aminotransferase (ALT) and aspartate transferase (AST). It seems that an increased activity of liver enzymes can independently predict the progression of MetS, diabetes mellitus, and cardiovascular events (7, 8). Despite some indications, the association between alcohol intake and liver enzyme levels, including γ-glutamyl transferase (GGT), ALT, and AST, has not been conclusively established (9).

Inflammation plays a crucial role in the pathogenesis of diabetes mellitus and atherosclerosis (10). It is hoped that preventing this condition can significantly reduce CVD mortality. Nutraceutical compounds, nutrients, and dietary patterns have been explored for their beneficial properties and therapeutic potential in treating MetS. Although, several nutrients have been considered as a MetS therapeutic approach, no definitive dietary treatment has been established (11).

Nowadays, Lycopene is recognized for its effectiveness in controlling of various diseases such as obesity, diabetes, metabolic syndrome, cardiovascular diseases, infertility, cancers and respiratory disorders (12-14). It's suggested that dietary carotenoids, particularly Lycopene, may play a crucial role in controlling metabolic issues like obesity, hypertension, diabetes, cardiovascular disease, and cancer (15). The structure of Lycopene contains conjugated double bonds that can react with free radicals, making it the most powerful oxygen quencher among natural carotenoids (16). The reactions between Lycopene and ROS depend on various factors, including Lycopene structure, free radical types, and ROS location in the cell membrane, particularly in biological systems (17).

Studies have reported that the use of Lycopene to reduce inflammation and liver disease treatment (18, 19). The bioavailability and absorption of Lycopene are enhanced by trans-to-cis conversion in enterocytes, liver and stomach (20). In the stomach, Lycopene is activated, released from the matrix, internalized into lipid droplets, and then released into the small intestine. Enzymes and bile acids break down the remaining matrix, facilitating the uptake of Lycopene by enterocytes. The majority of Lycopene is packaged into chylomicrons and secreted into the lymphatic system before being released into the circulation from chylomicrons in the liver. The bioactive properties of Lycopene metabolites are produced through enzymatic or oxidative cleavage in the liver (21).

The anti-inflammatory and antioxidant activities of Lycopene play an important role in the maintenance of the liver normal metabolism (18). There are few clinical trials that examined the effects of Lycopene intervention on patients with MetS. The present study was designed to address to Lycopene effect on MetS patients in Iran.

Materials and Methods

The institutional board of the research and Ethics Committee of Iranian Clinical Trials confirmed in this study (IRCT20130507013263N3), and also, we received the confirmation of the Mashhad University of Medical Sciences (Mashhad, Iran) ethics committee (IR.MUMS.SP.1396.214). This clinical trial was performed in the Qhaem Hospital, (Mashhad, Khorasan Razavi, Iran) and the Clinical Nutrition Department (Mashhad University of Medical Sciences, Mashhad, Iran) between October 2022 and January 2023.

Study participants and eligibility criteria

Participants were recruited by email, face-to-face interviews, social media, and campus-based advertisements. All participants provided their written informed-consent. The study initially had 90 participants. However, during the follow-up period, the number decreased to 80. The main inclusion criteria were: having MetS based on the International Diabetes Federation criteria, which is at least two parameters associated with waist circumference (having a waist circumference higher than 94 cm in men and 80 cm in women), having fasting blood sugar higher than 100 mg/dl or having diabetes, having triglycerides higher than 150 mg/dl, having systolic blood pressure (SBP) of 130 mm Hg or diastolic blood pressure (DBP) higher than 85 mm Hg or using antihypertensive drugs, having HDL less than 40 mg/dl in men and less than 50 mg/dl in women patients who aged between 18-60 years at the beginning of the study (22), and lived in the Mashhad city (Khorasan Razavi, Iran). The detailed exclusion criteria were as follows: having a serious disease requiring active treatment, taking any other herbal supplements, being pregnant or breastfeeding and taking medications that may interact with Lycopene. Figure 1 shows the representative flowchart of the study design.

Study design

This double-blind, randomized and placebo-controlled investigation spanned a duration of 8 weeks. According to previous research (23), we considered 8 weeks as the minimum time of Lycopene intake .The anthropometric parameters were measured during the clinical trial, on initial day and in the 4th and 8th week of the study.

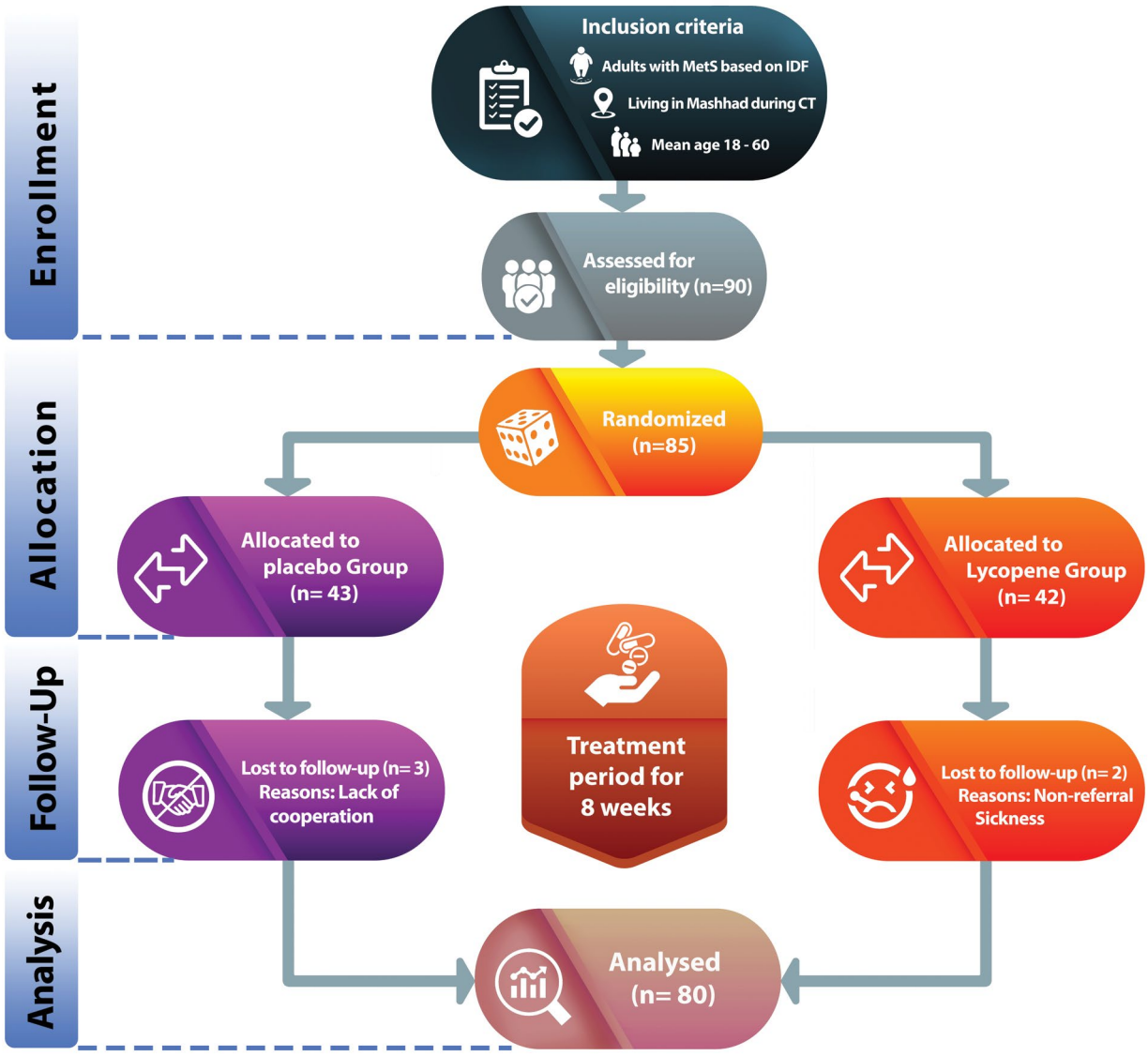

Fig.1: Flowchart of the study.

Interventions

Using SPSS software (version 24.0. Armonk, NY: IBM Corp.), subjects were randomly assigned to either the placebo or intervention groups. Participants chose a sealed envelope containing their random assignment upon entering the trial. All subjects, physicians, care providers, and statisticians were blinded in this study. Also, the placebo group received a preparation that was similar in size, color, and appearance of the treatment group package to maintain blinding. Patients consumed one Lycopene (20 mg) or placebo tablet daily for eight weeks. Assessments were carried out during the fourth and eighth week as a follow-up to determine both the safety and effectiveness. During the trial, evaluations of height, body weight, waist circumference, blood pressure, and body composition were conducted in the first, fourth, and eighth weeks. After a 12-hour overnight fast, SBP and DBP were measured, and also 20 ml blood of each participant was collected to check fasting blood glucose (FBG) and lipid profile, including triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, CRP, and PAB, at weeks one and eight. At each follow-up visit, any adverse drug reactions (ADRs) were documented using a standardized report form.

Lycopene extraction and tablet formulation

A modified method was utilized for the extraction of Lycopene and the production of tablets (24-27). Initially, Lycopene was extracted from tomatoes that were heated to a temperature of 37-40°C for three days and dried to achieve a moisture content of about 70-80%.

The tomatoes, which were dried previously, were ground into a powder using a semi-industrial mill. Then they were subjected to an additional 12 hours of drying and then stored in a low-humidity environment to prepare them for the extraction process. Following this, acetone (100014, Merck Milipore, Germany) and ethyl acetate (PHR1481, Sigma-Aldrich, Germany, 1:1, V/V) were introduced to the tomato powder in a 1:4 (W/V) ratio (approximately four times the volume of the powder). Then, the resulting mixture was slowly mixed by a simple butterfly mixer (C9New, Behan laboratory equipments, Iran) for 1-3 hours in a covered and relatively insulated container.

This procedure was performed 3-5 times. Each time, the extract of the powders was separated and filtered, and fresh solvent was added to the container. The separation stage was performed using a modification of previous approaches. A strategy includes using a fabric filter and a device producing a mechanical pressure of more than 1 ton per square meter, the solvents contained in the separated extract and were transferred to a special container. Another method includes the separation of the extract from the powder by using a separator and a vacuum pump.

In our research, we utilized a rotary device to recover the solvent and minimize the volume of the extract, which included acetone, ethyl acetate, and Lycopene. Almost 95% of the solvent was recovered during several stages. A major advantage of this method is the ability to recover and reuse solvents, significantly reducing the high cost of organic solvents. After removing the solvent, 30-35% of the primary extract weight contains the active substance Lycopene. This extract should be restored in a refrigerator at 4°C. To increase the amount of a homogenized Lycopene, the extract was kept at room temperature for a few minutes. To precipitate the Lycopene, cold 96% ethanol was added to the extract with a ratio of 10:1 (W/V). As a result, after centrifugation, the Lycopene was separated from impurities and transferred to another container. The ethanol used in this step was also recovered at a rate of approximately 70-80%. By using the HeadSpace method (by Gas Chromatography), the residual amount of both of ethyl acetate and acetone in the final extract was also analyzed to determine the presence of the used solvents. In particular, the final extract was analyzed by UV Spectroscopy and the amount of Lycopene was determined based on the standard curve. For the tablet formulation, the extract (25-35% Lycopene) and hexane (104374, Merck Milipore, Germany) (medicinal solvent) were added to the microcrystalline cellulose powder (102331, Merck Milipore, Germany) and mixed (using a simple mixer). After removing the solvent, a powder containing Lycopene was created.

The materials used for extraction and formulation have special properties that help to facilitate the extraction. The Avicel has many properties, including uniform mixing of components, excellent absorption of Lycopene extract, high compressibility and outstanding tablet disintegration properties. Another material that is used in the tablet formulation process is the Aerosil (silicon dioxide). Due to its crystalline properties, Aerosil has a low density. As a result, a tablet flow is greatly improved during a direct compression (The Aerosil was used in concentration of 1 to 5%). In addition, the polyvinyl pyrrolidone resulted in a better disintegration, higher compressibility and hardening of tablets. Also, the talc powder (IS29000, CP lab safety, USA) was used in the formulation process (2-5%). The use of Aerosil, talc powder, and a special combination of two types of commercial agents (Polyvinylpyrrolidone K30 and Polyvinylpyrrolidone CL) helped the Lycopene maintenance.

Placebo tablets were formulated using identical excipients as the Lycopene tablets, with the only distinction being that Lycopene was substituted with the Avicel, an inert excipient, in the final formulation. Since the final tablets had a red coat, there was no visible difference between the Lycopene-containing tablets and the placebo tablets. One of the goals of this study was to develop a new formulation of Lycopene tablets that would increase the stability of the Lycopene molecule. Therefore, all of the extraction, purification, and drug formulation methods used in this study are novel and have no prior references.

Statistical analysis

Kolmogorov–Smirnov statistical analysis was used to assess normality of the data. For all variables, descriptive statistics were calculated. This includes the mean and standard deviation (represented as mean ± SD) for data that follows a normal distribution, and the median along with the interquartile range (IQR) for data that does not follow a normal distribution. Normally and non-normally distributed data was analyzed using T student tests and Mann-Whitney, respectively. Normally and non-normally distributed data was analyzed using paired and independent T student tests and Mann-Whitney or Wilcoxon, respectively. Confounding factors such as age and sex were adjusted the analysis of Co-variance (ANCOVA). The $P<0.05$ was considered statistically significant.

Results

The Table 1 demonstrates the main characteristics of the baseline analysis. Totally, 80 patients who participated in this study were classified as belonging to intervention categories. The mean age of the Lycopene and placebo groups was 44.25 ± 11.25 and 41.75 ± 10.05 years, respectively. There were no significant differences in the levels of CRP, serum liver enzymes, systolic and diastolic blood pressure, and PAB between Lycopene and placebo groups before assigning the patients to the Lycopene and placebo groups.

Comparing the clinical features of our groups ,after8 weeks of intervention with Lycopene ,we observed some statistically significant differences. The P value of the difference between the Lycopene and placebo groups, after adjusting for confounding factors such as age and sex

was found (Table 2). Interestingly, compared to the initial evaluation, the Lycopene group showed a decrease in the levels of CRP and PAB. However, this reduction was not found to be significant in the placebo group. Additionally, after adjusting for confounding factors, only the P value of the difference in the PAB level between the two groups remained significant. No significant differences were found in the serum levels of ALT, AST, and ALP between our groups.

Table 1: Baseline features in the study groups

Variable	Lycopene (n=40)	Placebo (n=40)	P value
Gender			0.132
Women	22 (55)	28 (70)	
Men	18 (45)	12 (30)	
Age (Y)	44.25 ± 11.25	41.75 ± 10.05	0.214
Systolic blood pressure (mmHg)	125.00 ± 5.774	134.75 ± 12.790	0.108
Diastolic blood pressure (mmHg)	75.00 ± 12.910	35.628 ± 35.628	0.147
hs-CRP (g/dl)	0.46 ± 0.3	0.44 ± 0.27	0.753
PAB (H.K)	162.30 ± 37.42	172.17 ± 28.72	0.155
ALT (U/L)	22.95 ± 16.35	18.03 ± 7.5	0.519
AST (U/L)	23.13 ± 17.06	17.05 ± 6.2	0.149
ALP (U/L)	123.53 ± 34.92	126.87 ± 48.31	0.836
Non-smoker	35 (87.5)	31 (77.5)	0.408
Exposure-smoker	1 (2.5)	3 (7.5)	
Current smoker	4 (10)	6 (15)	

Data presented as mean ± standard deviations or median (interquartile range) or n (%). Independent sample t test was used where appropriate. PAB; Pro-oxidant-antioxidant balance, ALT; Alanine aminotransferase, AST; Aspartate transferase, ALP; Alkaline phosphatase, and hs-CRP; High-sensitivity C-reactive protein.

Table 2: The effect of Lycopene on CRP and liver enzymes in population study

Variable	Lycopene (n=40)			Placebo (n=40)			P value*
	Baseline	Difference	P value	Baseline	Difference	P value	
hs-CRP (g/dl)	0.46 ± 0.3	-0.14	0.004	0.44 ± 0.27	-0.08	0.141	0.340
PAB (H.K)	162.30 ± 37.42	-29.9	<0.001	172.17 ± 28.72	-10.04	0.098	0.002
ALT (U/L)	22.95 ± 16.35	1.2	0.607	18.03 ± 7.5	1.02	0.439	0.252
AST (U/L)	23.13 ± 17.06	-2.2	0.233	17.05 ± 6.2	1.1	0.146	0.792
ALP (U/L)	123.53 ± 34.92	1.2	0.809	126.87 ± 48.31	9.25	0.226	0.406

The P<0.05 was considered statistically significant. *; P value of difference between in Lycopene and placebo groups after adjusting for confounding factors such as age and sex as co-variant, PAB; Pro-oxidant-antioxidant balance, ALT; Alanine aminotransferase, AST; Aspartate transferase, ALP; Alkaline phosphatase, and hs-CRP; High-sensitivity C-reactive protein. Bold numbers are statistically significant.

Discussion

The mechanism of the high-sensitivity CRP (hs-CRP) reduction by the Lycopene is not only exactly known, but also several hypotheses exist. One of them addressed the Lycopene, as a potent antioxidant, that can prevent the oxidation of LDL and consequently, reduce the inflammatory response in the vascular wall. Another hypothesis is that the Lycopene may affect apolipoprotein B (apo B), one of LDL carriers, and reduce its interaction with a CRP. The CRP, an inflammatory protein, may be involved in tissue damage during a heart attack. Therefore, reducing the interaction of CRP and apo B may lead to lower risk of CVD (28, 29).

The initial question of this study aimed to determine the Lycopene effect on the imbalance of the PAB and hs-CRP in the patient with MetS. The most interesting our finding was that there was a significant difference in PAB levels between our groups, even after adjusting for age and sex. Although, this finding did not align with the previous research. In the study conducted in the United Kingdom with 225 volunteers (94 males and 131 females, aged 40-65 years). They evaluated the Lycopene effects on the modulation of CVD risks after 12 weeks-controlled diet. They considered 3 groups: i. A controlled diet with low consumption of tomato-based food, ii. A high tomato diet (20 to 50 mg Lycopene/day), iii. Controlled diet with Lycopene tablet (10 mg/day). They found that none of the CVD markers, including insulin resistance, sensitivity markers, inflammatory markers, and lipid concentrations, showed significant changes (30). One possible explanation for these results could be the Lycopene low dose used in their study.

As expected, this study found a significant decrease in the hs-CRP levels in the Lycopene group. These results are consistent with Sun and Karin (31) study that showed a daily consumption of Lycopene (29.4 mg/day for one month) reduced the CRP serum level in a population of heart failure patients (23 men, 17 women). Also, Bahcecioglu et al. (32) demonstrated the efficacy of heightened Lycopene intake, derived from tomato products, in ameliorating lipid profiles and inflammatory markers, such as CRP.

Some studies have shown that the Lycopene may be ineffective on liver enzymes and even sometimes have a negative effect on ALT, AST or ALP. The exact mechanism of this process is not clear, but one of the hypotheses is that the Lycopene may affect the activity of other liver enzymes such as CYP450 and cause changes in the metabolism of some drugs. This issue may lead to the liver function dysfunction (33, 34).

The second question this research addressed was the relationship between the Lycopene tablets and liver enzyme serum levels in patients with MetS. We found no difference in the serum level of ALT, AST, and ALP in our groups, which supports the findings of the previous work. In 2020, Negri et al. (35) evaluated the effect of the Lycopene extracts and calorie-restricted regimen in the obese children with fatty liver. This randomized crossover clinical trial examined 61 obese children with fatty with calorie-restricted regimen alone or with a supplement of Lycopene juice for 2 months. A reduction in the body mass index (BMI), cholesterol, triglycerides, and liver size, was more profound in the Lycopene-supplemented group. They suggested that adding Lycopene to a calorie-restricted regimen could be considered preventive and protective support for an obese child (35).

A randomized intervention trial was designed to determine the Lycopene supplementation effect (7 mg daily for 2 months) on healthy volunteers and CVD patients treated by the Statin. In this study by Seki et al. (36), it was indicated that the mentioned treatment resulted in a 53% improvement in the endothelial-dependent arterial vasodilation for patients, while no effect was observed in healthy volunteers. Furthermore, it was shown that a Lycopene supplementation (20 mg/day for 1 year) led to a decrease in the thickness of the intima-media in the144 patients with sub-clinical atherosclerosis (37).

While various nutrients have been explored as potential therapeutic approaches for MetS treatment, no definitive dietary treatment has been established. The Lycopene, a carotenoid recognized for its antioxidant properties, is one such nutrient. However, the relationship between a Lycopene intake and MetS risk factors, such as inflammation and insulin resistance, are not well understood. The majority of these studies reported a significant protective association between Lycopene and MetS. However, the specific components of the MetS influenced by the Lycopene varied across studies (38).

While the evidence generally supports a protective relationship between a Lycopene and MetS, further research is needed to understand the mechanisms behind this effect and to establish evidence-based recommendations for the Lycopene intake. Potential challenges of this study may include ensuring that the study duration is sufficient to observe the long-term effects of Lycopene, and maintaining adherence to the assigned Lycopene dietary intake.

Conclusion

In this investigation, we evaluated the effect of Lycopene on the risk status of patients with MetS. Administrating daily dosage of 20 mg for 8 weeks resulted in no recorded side effects. Our findings indicate that Lycopene has a modulating effect on PAB and inflammation associated with MetS. Additionally, the encapsulated Lycopene treatment did not yield a significant difference in serum levels of ALT, AST, or ALP between the two groups. These results highlight the Lycopene potential therapeutic value. Further research is essential to validate these findings and explore the mechanisms underlying the observed effects.

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Authors' Contributions

M.M.; Project administration, Methodology, and Original draft preparation. M.A.; Visualization, Software, Writing- Reviewing and Editing. F.N, M.G.C., H.H., H.B.; Visualization and Investigation. R.A.-D.: Conceptualization and Validation. S.T.; Investigation and Formal analysis. G.A.F., M.R.M.; Writing - Review, Editing and Original draft preparation. F.H.; Supervision, Project administration, and Funding acquisition. M.G.-M., Supervision and Project administration. All authors read and approved the final manuscript.

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