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The effect of lycopene on serum level of cardiac biomarkers in patients undergoing elective percutaneous coronary intervention: A randomized controlled clinical trial

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Original Article

Abstract

BACKGROUND: Myocardial ischemia may recur in a significant subset of patients following percutaneous coronary intervention (PCI). Lycopene, a carotenoid with antioxidant activity, has evidence for beneficial effects on cardiovascular system. In the present study, we aimed to evaluate the possible preventive effect of lycopene against post-PCI myocardial damage by detection of cardiac biomarkers of ischemia.

METHODS: A total of 45 patients who planned to undergo elective PCI were randomly assigned to two groups to receive either lycopene (30 mg 12 hours before PCI as well as 15 mg just before and 8 hours after PCI) along with standard treatment (n = 23) or only standard treatment (n = 22). Standard treatment included aspirin, a statin, and a beta-blocker. The serum levels of creatine kinase-MB (CK-MB), troponin I, and high sensitivity C-reactive protein (hs-CRP) were measured 12 hours before and 12 hours after the procedure and were compared between the two groups.

RESULTS: The use of lycopene significantly prevented the increase of CK-MB following PCI compared to control (P = 0.048). However, it had not any significant effect on serum levels of troponin I (TnI) (P = 0.176) and hs-CRP (P = 0.186) compared to control.

CONCLUSION: Lycopene can prevent the increase of CK-MB following PCI. Therefore, it has the potential for prevention of post-PCI cardiovascular events. However, more studies are needed to confirm such an effect.

Keywords: Lycopene; Troponin I; Creatine Kinase-MB; High Sensitivity C-reactive Protein; Percutaneous Coronary Intervention

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Introduction

Cardiovascular diseases (CVDs) describe a range of several disorders such as high blood pressure, stroke, atherosclerosis, peripheral vascular disease (PVD), and coronary artery disease (CAD). One of every three deaths in the United States and one of every four deaths in Europe are due to CVDs. Atherosclerosis is a condition that causes the death of a majority of patients with CVD.[1]

Overall, CAD refers to the presence of atherosclerosis in coronary arteries.[2] The atherosclerotic plaque gradually causes blockage in the coronary arteries and prevents blood flow.[3]

Percutaneous coronary intervention (PCI) is a procedure for coronary vasodilatation through the destruction of plaque and creating a chamber by the stent.[4] However, PCI itself triggers an inflammatory

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reaction determined by increased plasma C-reactive protein (CRP) concentrations after the procedure.[5]

High sensitivity C-reactive protein (hs-CRP) is one of the most extensively investigated markers of inflammation and has been used to predict the risk of major adverse cardiac events in patients with stable and unstable CAD after PCI.[6] It has been shown that the rate of post-PCI myocardial infarction (MI) increases in patients with higher hs-CRP levels.[7] Hence, periprocedural serum hs-CRP monitoring could be of use in identifying high-risk patients and guiding adjunctive periprocedural therapy to improve PCI outcomes.[6] It should be noted that myocardial damage during PCI can also be characterized by the routine measurement of cardiac biomarkers [troponin I (TnI)] and creatine kinase MB [CK-MB]) in asymptomatic patients; these markers increase in 40% of patients undergoing PCI.[8]

Several epidemiological studies have provided strong and consistent evidence for a beneficial effect of fruits and vegetables on cardiovascular health. Tomato is a rich source of lycopene, a major carotenoid in human plasma with potent antioxidant activity. A recent systematic review of interventional trails has shown that tomato or lycopene supplementation has been successfully associated with improvement of cardiovascular risk factors including low-density lipoprotein (LDL)-cholesterol, interleukin-6 (IL-6), and systolic blood pressure (SBP). In addition, observational cohort studies have reported a positive correlation between tomato or lycopene consumption and a lower risk of CVDs.[9]

Lycopene directly protects endothelial cells from oxidative damage and prevents endothelial monocyte interactions.[10,11] It may also protect the body against neutrophils oxidative response and inflammatory cytokines secretion.[12] Furthermore, the role of carotenoids in preventing CVDs has recently been confirmed in the Framingham Heart-off-Spring study.[13] Therefore, lycopene seems a good candidate among antioxidants for evaluation of effects in cardiac conditions associated with inflammation and oxidative stress.

Due to the protective effects of lycopene and the risk of cardiac events after PCI, the present study was conducted to determine the possible effect of lycopene on cardiac biomarkers in patients treated with this type of cardiac intervention.

Materials and Methods

This study was a single-center randomized two-arm placebo-controlled clinical trial conducted at Isfahan Cardiovascular Research Center affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from October 2016 to January 2018. The study was registered in the Iranian Registry of Clinical Trials (IRCT) with the registration code of IRCT20191018045149N1. Informed consent was obtained from all patients enrolled in the study.

Sample Size Calculation: In order to calculate the sample size, the following equation was applied. Since serum TnI was one of the main variables of this study, we used the data relating to this parameter from a previous study,[14] so that the mean significant difference (d) between the groups and the standard deviation (SD) for TnI were 0.25 and 0.30, respectively. Considering $\alpha = 0.05$ (type I error) and $\beta = 0.20$ (type II error), the sample size was calculated 18. Therefore, a minimum sample size of 18 patients in each group was considered.

$$n = \frac{(z_\alpha + z_\beta)^2 \times 2 \times (SD)^2}{(d)^2}$$

Patient Selection: Patients were selected from those referring to the cardiology clinic of Isfahan Cardiovascular Research Center. Eligibility criteria for patients in this study included (a) age ≥ 40 years, (b) not using fish oil or omega-3 products within the last week, and (d) not using any antioxidant products (e.g., vitamins C and E, coenzyme Q10, selenium, and anthocyanin and lycopene supplements) within the last week.

Exclusion criteria were (a) irregular use of tablets, (b) allergic reaction to lycopene (c) presence of active bleeding, (d) thrombocytopenia, (e) aneurysm, (f) cardiogenic shock, (g) liver disease, (h) severe renal disease (creatinine clearance < 30 ml/min), (i) rescue PCI after thrombolytic treatment, (j) urgent need for cardiac bypass surgery, (k) not being pregnant or lactating (for woman) (l), uncontrolled hypertension, and (m) life expectancy < 6 months.

Study Protocol, Groups, and Interventions: Patients who were admitted to undergo elective PCI and met the inclusion criteria were randomly assigned to two groups of intervention (lycopene) and control. Simple randomization was used for allocation of the patients to the groups. For this, an online random number generator was used (available at: https://www.random.org/sequences) so that even and odd numbers were considered for drug and control groups, respectively. The control group was given standard treatment (aspirin, statin, and β-blocker), while the intervention group was given standard treatment plus oral lycopene (using 15-mg tablets, Vitabiotics, UK) 30 mg 12 hours before PCI as well as

15 mg just before and 8 hours after the procedure.

Variables and Measurements: In both groups, patients' serum TnI, CK-MB, and hs-CRP were assayed 12 hours before and after PCI. For this, the patients' plasma was obtained from forearm venous blood (approximately 5 ml) by centrifugation at 2000 rpm for 10 minutes and stored at -70 °C until assay. After the collection of all samples, the serum levels of the above-mentioned biomarkers were assayed using specific enzyme-linked immunosorbent assay (ELISA) Kits (Monobind Inc, USA). The primary outcome measures were the change of serum TnI, CK-MB, and hs-CRP, 12 hours after PCI compared to baseline (12 hours before the procedure).

Data were analyzed by Statistical Package for the Social Sciences (SPSS) software (version 23, IBM Corporation, Armonk, NY, USA). Continuous and categorical variables were reported as mean ± SD and number (percent), respectively. Kolmogorov-Smirnov (KS) test was conducted to assess the distribution pattern of continuous quantitative data. Due to non-normal distribution of data, non-parametric statistical tests were used. To compare pre- and post-intervention values within each group, Wilcoxon signed-rank test was conducted. Mann-Whitney U test was employed to compare parameters between the drug and control groups. Chi-square test and independent samples t-test were applied to compare baseline demographic and clinical characteristics of patients in the two groups. $P < 0.050$ was considered statistically significant.

Results

The CONSORT diagram of the trial is shown in figure 1. Over the study, 45 patients who planned to undergo elective PCI were enrolled, of whom 28 participants were assigned to lycopene group and 25 participants were assigned to control group.

Patients' baseline demographic and clinical data are presented in table 1. As seen, no statistically significant differences were observed between the study groups with regard to basic characteristics including medical and drug history.

The changes in TnI, CK-MB, and hs-CRP levels in study groups are summarized in table 2. As shown, significant increase of TnI in both groups as well as significant increase of hs-CRP in lycopene group was observed; however, these changes were not significantly different between the groups. Regarding CK-MB, although this parameter showed elevation in both groups, only the change in control group was significant; furthermore, the changes were significantly different between the two groups ($P = 0.048$).

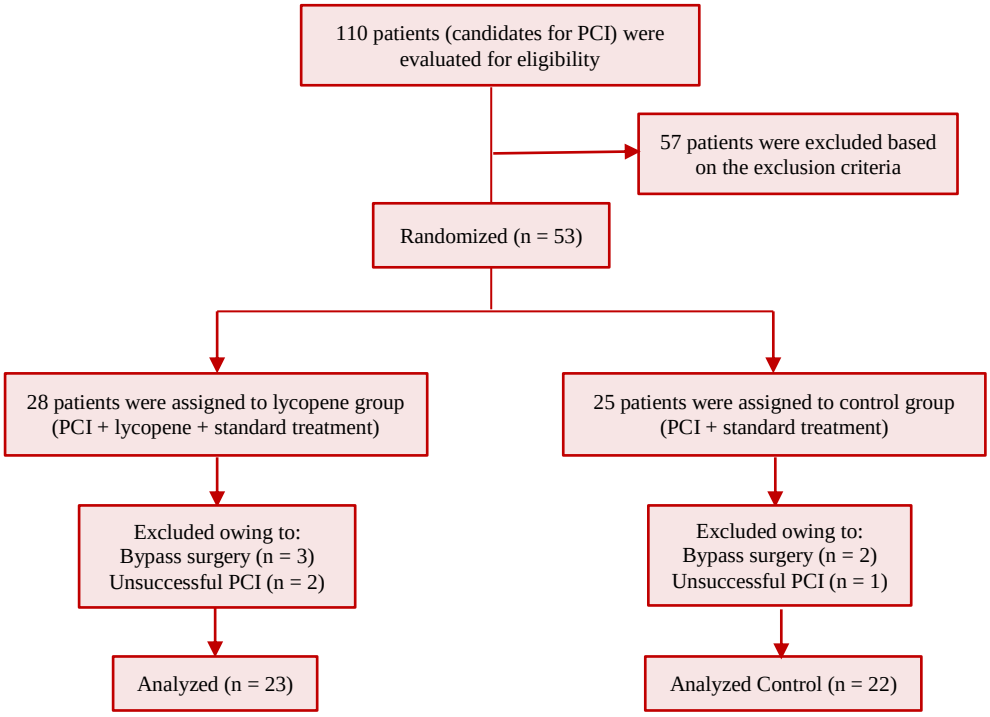

Figure 1. Flowchart of patients' enrollment in the study
PCI: Percutaneous coronary intervention

Table 1. Baseline demographic and clinical characteristics of the study subjects

Parameter (unit)	Lycopene (n = 23)	Control (n = 22)	P
Gender [male; n (%)]	14 (60.9)	16 (72.7)	0.399**
Smoker	8 (34.8)	11 (50.0)	0.361**
PCI [n (%)]			0.192***
None	14 (60.9)	18 (81.8)	
One time	7 (30.4)	4 (18.2)	
Two times	2 (8.7)	0 (0.0)	
Number of balloons [n (%)]			> 0.999***
One	20 (87.0)	19 (86.4)	
Two	2 (8.7)	3 (13.6)	
Three	1 (4.3)	0 (0.0)	
Family history [n (%)]			0.200***
Negative	9 (39.1)	7 (31.8)	
DM	3 (13.0)	1 (4.5)	
CVD	9 (39.1)	10 (45.5)	
HTN	2 (8.7)	0 (0.0)	
DM and CVD	0 (0.0)	3 (13.6)	
DM and HTN	0 (0.0)	1 (4.5)	
Drug history [n (%)]			0.273***
Nitrates	11 (47.8)	7 (31.8)	
ACEI or ARB	12 (52.2)	7 (31.8)	
CCB	3 (13.0)	0 (0.0)	
PPI	8 (34.8)	7 (31.8)	
Age [(mean ± SD) years]	59.52 ± 12.21	59.41 ± 9.51	0.113*
Troponin I [(ng/ml); (mean ± SD)]	1.39 ± 1.69	1.52 ± 2.94	0.592£
CK-MB [(U/l); (mean ± SD)]	26.44 ± 7.51	29.42 ± 18.88	0.153£
hs-CRP [(µg/ml); (mean ± SD)]	5.93 ± 9.20	5.85 ± 8.09	0.820£

* Independent samples t-test; ** Chi-square test; *** Fisher's exact test; £ Mann-Whitney U test
PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; CVD: Cardiovascular disease; HTN: Hypertension ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; PPI: Proton pump inhibitor; CK-MB: Creatine kinase-MB; hs-CRP: High sensitivity C-reactive protein; SD: Standard deviation

Discussion

Our results showed significant preventive effect of lycopene against increase of serum level of CK-MB in patients undergoing PCI. This may be indicative of the potential role of lycopene for prevention of PCI-induced myocardial injury. However, this supplement had not any significant effect against the rise of TnI and hs-CRP levels.

It has been revealed that elevation in post-PCI levels of these markers is associated with short-, intermediate-, and long-term adverse outcomes following PCI.[15,16] Because of this, the guidelines of American College of Cardiology/American Heart Association (ACC/AHA) recommend routine measurement of CK-MB and troponin 8 to 12 hours after PCI in all patients for prognostic evaluation.[17]

Table 2. The effects of interventions on the parameters tested 12 hours after percutaneous coronary intervention (PCI) in the study subjects. The values are presented as mean ± standard deviation (SD).

Parameter (unit)	Lycopene (n = 23)	Control (n = 22)	p**
Troponin I (ng/ml)			0.176
Baseline	1.39 ± 1.69	1.52 ± 2.94	
End	3.37 ± 3.41	2.07 ± 2.46	
P*	0.026	0.049	
CK-MB (U/l)			0.048
Baseline	26.44 ± 7.51	29.42 ± 18.88	
End	29.05 ± 9.61	33.71 ± 12.02	
P*	0.153	0.007	
hs-CRP (µg/ml)			0.184
Baseline	5.93 ± 9.20	5.85 ± 8.09	
End	9.03 ± 10.47	6.78 ± 7.89	
P*	0.002	0.126	

* Intra-group, Wilcoxon Signed Ranks Test; ** Inter-group, Mann-Whitney U test
CK-MB: Creatine kinase-MB; hs-CRP: High sensitivity C-reactive protein

Tomato extract contains carotenoids including lycopene known as an effective antioxidant. Since endothelial cell dysfunction may be related to an increase in cellular oxidative stress, carotenoids could have an antioxidant-mediated tempering influence on endothelial function and inflammation.

To the best of our knowledge, no previous studies have evaluated the effect of lycopene on cardiac markers in post-PCI adult patients. However, some clinical and experimental studies have evaluated the anti-inflammatory and anti-platelet effects of this substance.

An animal study provided evidence of a novel cardioprotective effect of lycopene in a mouse model of MI. This protection was conferred, at least partially, by its anti-inflammatory and anti-apoptotic actions following myocardial injury.[18]

Another animal study indicated that lycopene improved the cardiac function and ventricular remodeling by inhibiting p38 mitogen-activated protein kinases (MAPK) activation and Matrix metalloproteinase 9 (MMP-9) expression.[19]

In a study that evaluated and compared the anti-atherosclerotic effects of lycopene and fluvastatin in rabbits with a high-fat diet, it was found that lycopene (administered for 8 weeks) had anti-atherogenic effects like fluvastatin.[20] However; this is a long-term effect of lycopene and could not be a mechanism for the effect observed in the current study.

In another study, daily consumption of 15 mg of lycopene for 8 weeks improved endothelial function and decreased systolic blood pressure and hs-CRP levels.[21]

It has been found that low serum levels of lycopene are associated with cardiovascular events. A study suggested that low serum levels of lycopene correlates with increased risk of atherosclerotic vascular events in middle-aged men previously free of coronary heart disease (CHD) and stroke.[22] In a case control study, it was observed that low levels of beta-carotene and lycopene were associated with an increased risk of MI in smokers.[23] Therefore, it seems that maintaining normal serum levels of lycopene could be a prophylactic measure against cardiac events.

In our study, lycopene had not any protective effect against the increase of hs-CRP following PCI. However, in contrast to our finding, some studies have shown such an effect for lycopene. In the study of Biddle et al., the effect of dietary intervention with lycopene on inflammatory markers in patients with heart failure (HF) was evaluated. According to the results, the consumption of 29.4 mg/day of lycopene for 30 days reduced CRP levels in women with HF.[24] In the study of Jacob et al., daily consumption of tomato juice (containing 21 mg of lycopene) for 2 weeks reduced CRP levels in healthy subjects.[25] The differences in the dose of lycopene, duration of intervention, and the study population may be responsible for these variations in the results. Furthermore, considering the results of these studies, it seems that higher dose of lycopene with longer durations might have positive effects regarding hs-CRP changes following PCI.

There are several studies which have evaluated the effects of other antioxidant or anti-inflammatory agents on cardiac biomarkers in patients undergoing PCI. In a recent study on the effect of N-acetylcysteine (NAC), as an antioxidant, on ischemia/reperfusion injury in patients with MI undergoing primary PCI, use of high-dose NAC (loading dose of 100 mg/kg before PCI, 480 mg coronary injection during PCI, and 10 mg/kg infusion for 12 hours after intervention) decreased the serum levels of highly sensitive troponin T (hs-TnT), while it had no significant effect on CK-MB levels compared to control.[26] In another clinical study, administration of omega-3 polyunsaturated fatty acids (PUFAs) with single dose of 3 g 12 hours prior to PCI significantly decreased the serum levels of CK-MB measured 8 and 24 hours after intervention but had not any significant effect on serum TnI levels measured before and 24 hours after the procedure.[27] The authors concluded that omega-3 PUFAs can be considered as a safe adjunctive medication to the standard regimen before PCI for reduction of cardiovascular event after PCI.[27] These results are similar to ours regarding the pattern of effects on the cardiac biomarkers.

Although our study did not show significant lowering effect of lycopene on TnI and hs-CRP levels, considering that high plasma levels of CK-MB after PCI is associated with increased risk of cardiovascular events, it seems that lycopene has the potential for prevention of post-PCI cardiovascular events. However, future long-term clinical trials are required to confirm this effect.

Our study limitations were the small sample size, short duration of the study, lack of placebo, and small number of consumed doses of lycopene (three doses for each patient). It is possible that the use of more frequent doses of lycopene for longer durations (beginning several days before elective PCI) could have more prominent effects on the evaluated biomarkers.

Conclusion

Lycopene can prevent the increase of CK-MB following PCI. Therefore, it has the potential for prevention of post-PCI cardiovascular events. However, more studies are needed to confirm such an effect.

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Conflict of Interests

Authors have no conflict of interests.

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