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Association between ischemic heart disease and dietary intake of lycopene: a case–control study

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Aim: The effect of dietary lycopene on ischemic heart disease (IHD) is not clear. Hence, this study aimed to determine the association between dietary lycopene and IHD.

Methods: This case–control study was conducted on 443 patients with physician confirmed diagnosis of IHD as the case group and 443 healthy individuals as the control group. Data on demographic, medical history, anthropometric, and physical activity of the participants were collected. Food intake was evaluated using a 237-item semi-quantitative food frequency questionnaire (FFQ). The dietary intake of lycopene was assessed using Nutritionist IV software.

Results: A negative association was found between IHD and lycopene (OR: 0.98, CI 95%: 0.963–0.996, $p = 0.02$). The results remained significant after adjustment for age and sex, additional adjustment for dietary intake of calorie and fat, further adjustments for BMI, and additional adjustment for smoking, drinking alcohol, and physical activity. The risk of IHD in people with the highest quartile of dietary intake of lycopene was significantly lower than those with the lowest quartile (OR = 0.67, CI 95%: 0.46–0.97, $p = 0.036$).

Conclusion: There was a significant inverse relationship between intake of lycopene and IHD. Further prospective studies in different populations are required to elucidate the roles of lycopene against IHD.

KEYWORDS

ischemic heart disease, lycopene, dietary intake, coronary heart disease, IHD

Introduction

Ischemic heart disease (IHD) is a pathological condition characterized by decreased cardiac blood flow that causes a non-accordance between myocardial oxygen supply and demand (1). The number of patients diagnosed with IHD increased in recent years and the prevalence of IHD was reported to be around 126 million individuals (1,655 per 100,000), approximately 1.72% of the world's population (2). The most common complications of IHD include acute mitral regurgitation (MR) secondary to papillary muscle rupture (PMR), ventricular septal defect (VSD), pseudoaneurysm, and free wall rupture (FWR). Each of these complications are related to increased risk of morbidity, mortality, and length of hospitalization (3, 4).

IHD has several risk factors such as genetic, socioeconomic factors, industrialization, urbanization, increased life expectancy, inadequate physical activity, and alternation of dietary patterns (5, 6). Numerous nutrients in fruits, vegetables, legumes, nuts, and seeds could be protective against IHD including potassium, dietary fibers, carotenoids, and subtypes of polyphenols (i.e., phenolic acids, flavonoids, stilbenes and lignans) (7–13). Lycopene is a member of the carotenoid family, a class of compounds found in fruits and vegetables (14–16). Growing evidence has indicated that lycopene's antioxidant properties protect against cardiovascular disease, diabetes, and inflammatory diseases (17). Some studies suggested that lycopene's antioxidant capabilities cause its cardioprotective effects. Also, Lycopene blocks angiotensin-converting enzyme (ACE) and may acts in reducing oxidative stress caused by angiotensin II and indirectly increasing NO synthesis in the endothelium (18).

Furthermore, Lycopene suppresses reactive oxygen species production, potentially preventing endothelial dysfunction through direct antioxidative actions (19). A recent meta-analysis found an inverse association between fruits and vegetables with risk of IHD (20). Furthermore, randomized controlled trials have shown that increased consumption of fruits and vegetables combinedly reduces blood pressure (21–23). In addition, Numerous studies have shown that higher intakes or blood concentrations of carotenoids have been linked to a reduced risk of CVD (13). A population-based study has shown that a lower risk for acute coronary events or stroke was associated with higher serum lycopene concentration (13). In agreement with the previous reports, the results of one nested case–control study demonstrated that higher plasma lycopene concentrations had been related to a lower risk of CVD in middle-aged and elderly women (24).

There are few studies on the association between lycopene and IHD (25–28). Moreover, the results of these studies have been inconsistent (29). Lycopene's role has been ascribed to its potent antioxidant properties and other functions of lycopene such as gene expression regulation not yet completely understood. Many aspects regarding the roles of lycopene against IHD independent from other environmental and dietary factors are still unknown (13). The aim of the present case–control study was to evaluate the association between lycopene and the risk of of IHD after adjusting a broad range of confounders.

Methods

The present case–control study was conducted on 443 patients with physician-confirmed IHD as the cases and 443 individuals without IHD as the controls. The sample size was obtained using Open EPI online software (30) and the odds ratio obtained in similar previous studies (28). A consecutive method was applied for selection of the case group among newly diagnosed subjects who were visited the Shahid Rajaei Hospital and Tehran Heart Center in Tehran, Iran. They all had IHD. Then, an oral explanation was given about the aim, the study's implementation, and the information's confidentiality. The control group was selected among individuals who visited the hospital for general check-up or were from the hospital staff without diagnosed heart disease. All demographic information, medical history, anthropometric measurements, physical activity levels, and food intake information were collected by a trained interviewer. The inclusion criteria for the case group were adults aged 40–80, suffering from IHD, diagnosed in the last three month before the baseline, and consent to participate. The inclusion criteria for the control group were adults aged 40–80, without IHD with the physician's approval, and consent to participate. The exclusion criteria of the case and control groups were a history of mental disorders, cancer, malignant diseases, using lycopene supplements, and failure in gathering the required data.

The participant's body weight was measured with clothing and without shoes and recorded to the nearest 0.1 kg using a digital scale. Their height was measured in a standing position without shoes and with a tapeline with an accuracy of 1 cm. Socio-demographic, medical, and dietary data were collected using a self-administered questionnaire consisted of three parts: first, general information such as age, gender, height, weight, and place of residence. Afterward, medical and lifestyle information including the use of medicine or supplements, smoking and physical was collected. Also, food intake was evaluated using a 237-item semi-quantitative food frequency questionnaire (FFQ) with standard portion sizes commonly consumed by Iranian people. The validity and reliability of FFQ was already confirmed in Iran for the evaluation of nutrients' intake (31). Data on food intake during the last year in the control group and related to food intake in the last year before cancer diagnosis in the case group were collected through a face-to-face interviews by a trained dietitian. All reported consumptions were converted to grams per day by using household measures. Then, the intake of dietary lycopene was analyzed using Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA). Data on biochemical and hematologic indices including red blood cells (RBC), white blood cells (RBC), fasting blood sugar (FBS), SBP (systolic blood pressure), right DBP (diastolic blood pressure), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), the mean corpuscular hemoglobin concentration (MCHC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglycerides (TG) were extracted from participants' file.

Statistical analysis

An independent sample T-test (shown as mean ± sd), and chi-squared test [shown as frequency(percent)] were used for

quantitative and qualitative data, respectively. Normal distribution of continuous data was confirmed using the Kolmogorov–Smirnov test. Logistic regression method [shown as OR and 95% Confidence Interval (CI)] was used for the association between IHD and dietary intake of lycopene and the confounding variables including age at interview, gender, total fat and energy intake, BMI, smoking, using alcohol, and physical activity were adjusted in different models. Data was performed using SPSS software version 21 (IBM Corp., Armonk, NY, USA) and $p < 0.05$ was considered significant in all analyses.

Ethical considerations

The informed written consent was obtained from all participants. This study has been approved by Local ethics review boards at Shahid Beheshti University, Tehran, Iran (Code: IR.SBMU.NNFTRI.REC.1400.030).

Results

Characteristics of the participants are presented in Table 1. No significant difference was found regarding age, sex, physical activity, height, weight, BMI, smoking, and drink alcohol between the groups. Table 2 presents the biochemical measurements of the participants. The cases had lower RBC (4.86 ± 1.66 vs. 4.96 ± 1.52, $p < 0.01$) and higher WBC (6.67 ± 0.53 vs. 6.32 ± 0.56, $p < 0.01$) and FBS (121.11 ± 37.36 vs. 107.96 ± 43.20, $p < 0.01$) than the controls. There was no significant difference in BMI, smoking, drink alcohol, right SBP, right DBP, HGB, HCT, MCV, MCH, MCHC, HDLC, LDLC, TG, and cholesterol.

A comparison of dietary intake among the case and control groups is presented in Table 3. The case group had a lower intake of lycopene (12.99 + 8.42 vs. 14.234 + 7.28 mg/d, $p = 0.01$) than the control group. No significant difference was found in dietary intake of protein, total fat, carbohydrate, energy, saturated fatty acids, and other micronutrients between the groups.

The association of IHD and dietary intake of lycopene is presented in Table 4. A negative association was found between IHD and lycopene (OR: 0.98, CI 95%: 0.963–0.99, $p = 0.021$) (Model 1). The results remained significant after adjustment for age and sex (OR: 0.980, CI 95%: 0.96–0.99, $p = 0.024$) (Model 2), after additional adjustment for dietary calorie and total fat (OR: 0.98, CI 95%: 0.96–0.99, $p = 0.024$) (Model 3), after further adjustments for BMI (OR: 0.97, CI 95%: 0.96–0.99, $p = 0.016$) (Model 4), and after further adjustments for smoking, drink alcohol, and and physical activity (OR: 0.97, CI 95%: 0.95–0.99, $p = 0.015$) (Model 5). The IHD relationship with the categorical values of the lycopene was also evaluated. The risk of IHD in people with the highest quartile of dietary intake of lycopene was significantly lower than those with the lowest quartile (OR = 0.67, CI 95%: 0.46–0.97, $p = 0.036$). This association remained significant after adjusting the confounders (Table 4).

Discussion

According to this case–control study, the patients with IHD had a lower lycopene intake than the control group. The present study discovered an inverse association between lycopene intake and the risk of IHD. The associations remained significant after age and sex, after additional adjustments for dietary calorie and total fat, after additional adjustments for BMI, and after further adjustments for smoking and physical activity (Figure 1). In line with the present findings, a population-based study has shown that a lower risk for acute coronary events or stroke was associated with higher serum lycopene concentration (13). Data from previous studies suggests that consuming more lycopene-containing foods leads to higher levels of lycopene in the bloodstream (32). Moreover, high serum levels of lycopene were significantly related to low hazard ratios for CVD mortality in a Japanese population-based study (33). In addition, Rissanen et al. demonstrated that a low plasma concentration of lycopene was associated with a 17.8% increase in the carotid intima-media thickness (CIMT) in men compared to subjects with higher plasma concentrations of lycopene after adjustments for cardiovascular risk factors and nutrients intake (34). In addition, a cross-sectional study on 1,028 middle-aged men confirmed that low serum lycopene concentrations were associated with higher CIMT in middle-aged men (35). On the other hand, another study by Bruneck et al. found no association between lycopene plasma levels and atherosclerosis (36). Moreover, a nested case–control study utilizing the PHS database did not find any association between increasing concentrations of plasma lycopene and the risk of CVD (37). It is important to note that the conflicting results on the potential cardioprotective effects of

TABLE 1 General characteristics of the participants.

	Cases (n = 443)	Controls (n = 443)	p value*
Age (y)	55.59 ± 14.43	54.67 ± 11.13	0.106
MET (kcal/kg*h)	37.53 ± 7.72	38.01 ± 8.38	0.391
Height (Cm)	161.48 ± 34.16	161.03 ± 27.61	0.461
Weight (Kg)	74.38 ± 17.31	72.64 ± 15.54	0.057
BMI (Kg/m^2)	28.54 ± 6.3	28.06 ± 6.01	0.135
Smoking (n, %)	108 (24.83)	87 (19.21)	0.064
Male (n, %)	208 (47.92)	204 (45.03)	0.402
Drink Alcohol (n, %)	38 (8.74)	45 (9.94)	0.479

*Independent sample T-test (shown as mean ± sd) and chi-squared test [shown as frequency(percent)]. MET: metabolic equivalent of task, BMI: body mass index.

TABLE 2 Biochemical measurements of the participants.

	Cases (n = 443)	Controls (n = 443)	p value*
Right SBP (mmHg)	114.47 ± 16.63	114.51 ± 17.37	0.871
Right DBP (mmHg)	71.950 ± 10.40	71.96 ± 10.64	0.842
WBC (K/μL)	6.67 ± 0.53	6.32 ± 0.56	0.001
RBC (M/μL)	4.86 ± 1.66	4.96 ± 1.52	0.003
Hb (gr/dl)	13.99 ± 1.53	14.08 ± 1.55	0.428
HCT (%)	41.04 ± 4.14	41.36 ± 4.29	0.173
MCV (fL)	84.87 ± 5.81	85.002 ± 5.72	0.804
MCH (pg)	28.95 ± 2.59	28.97 ± 2.54	0.852
MCHC (gr)	34.08 ± 1.43	34.05 ± 1.41	0.164
PLT (K/μL)	283.75 ± 67.55	276.68 ± 68.09	0.204
FBS (mg/dl)	121.11 ± 37.36	107.96 ± 43.20	0.001
BUN (mg/dl)	13.58 ± 3.75	13.89 ± 3.82	0.094
Creatinine (mg/ml)	1.08 ± 0.27	1.10 ± 0.216	0.683
TG (mg/dl)	148.33 ± 109.08	144.51 ± 95.82	0.282
Cholesterol (mg/dl)	192.03 ± 40.39	191.26 ± 40.12	0.831
SGOT (IU/L)	19.97 ± 7.39	20.40 ± 10.05	0.091
SGPT (IU/L)	21.95 ± 13.52	22.29 ± 16.61	0.093
ALP (IU/L)	222.07 ± 68.79	222.21 ± 67.23	0.673
HDLC (mg/dl)	52.42 ± 10.54	52.35 ± 10.69	0.876
LDLC (mg/dl)	110.16 ± 34.06	110.40 ± 33.43	0.812

*Independent sample t-test. SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, RBC: red blood cell, FBS: fasting blood sugar, TG: triglyceride, HDL-c: high density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol.

TABLE 3 Dietary nutrient intake among the Cases and the controls.

	Cases (n = 443)	Controls (n = 443)	p value*
Protein (g/day)	78.37 ± 25.76	78.97 ± 26.36	0.452
Fat (g/day)	64.39 ± 24.79	64.59 ± 25.71	0.228
Carbohydrate (g/day)	409.62 ± 135.34	415.49 ± 140.59	0.193
Calorie (Kcal/day)	2482.58 ± 768.69	2511.78 ± 799.43	0.254
Lycopene (mg/day)	12.99 ± 8.42	14.234 ± 7.28	0.011
Galactose (mg/day)	0.192 ± 0.188	0.21 ± 0.216	0.069
Fiber (g/day)	27.11 ± 10.37	28.01 ± 10.12	0.224
Calcium (mg/day)	912.24 ± 328.5	918.67 ± 329.5	0.814
Iron (mg/day)	13.38 ± 4.73	344.82 ± 110.76	0.801
Magnesium (mg/day)	344.8 ± 110.76	343.98 ± 110.69	0.835
Phosphorus (mg/day)	1198.2 ± 389.77	1199.44 ± 398.51	0.417
Potassium (mg/day)	3674.27 ± 1278.79	3642.93 ± 1257.57	0.744
Sodium (mg/day)	4554.7 ± 2054.61	4633.84 ± 2088.36	0.788
Zinc (mg/day)	10.08 ± 3.35	10.08 ± 3.42	0.438
Copper (mg/day)	1.83 ± 0.71	1.83 ± 0.66	0.662
Fluoride (mg/day)	3573.2 ± 2394.6	3576.44 ± 2342.34	0.231
Manganese (mg/day)	5.65 ± 1.95	5.66 ± 1.93	0.916
Selenium (μg/day)	55.78 ± 29.63	54.66 ± 28.13	0.658
Vitamin A (IU/d)	8692.01 ± 5640.81	8720.66 ± 5552.12	0.621
Retinol (IU/d)	338.25 ± 394.44	333.88 ± 281.89	0.553

(Continued)

TABLE 3 (Continued)

	Cases (n = 443)	Controls (n = 443)	p value*
Vitamin A (mg/day)	715.08 ± 508.06	713.19 ± 425.37	0.964
Beta Carotene (μg/day)	4019.38 ± 2739.06	4044.64 ± 2746.80	0.411
Alpha Carotene (μg/day)	665.44 ± 838.02	685.43 ± 856.74	0.206
Alpha tocopherol (mg/day)	7.24 ± 3.28	7.14 ± 3.22	0.654
Vitamin D (IU)	42.91 ± 27.26	42.96 ± 27.10	0.291
Vitamin D2, D3 (mg/day)	1.21 ± 0.703	1.21 ± 0.69	0.239
Vitamin C (mg/day)	143.73 ± 83.78	139.96 ± 78.97	0.448
Vitamin B1 (mg/day)	1.62 ± 0.59	1.64 ± 0.60	0.821
Vitamin B2 (mg/day)	1.76 ± 0.66	1.74 ± 0.626	0.544
Vitamin B3 (mg/day)	18.16 ± 6.53	18.17 ± 6.51	0.682
Vitamin B5 (mg/day)	5.93 ± 1.90	5.90 ± 1.92	0.452
Vitamin B6 (mg/day)	9.77 ± 5.91	10.04 ± 4.91	0.511
Folate (μg/day)	381.07 ± 138.89	377.18 ± 130.77	0.358
Vitamin B12 (μg/day)	6.07 ± 6.43	5.87 ± 4.50	0.257
Vitamin K (mg/day)	164.5 ± 102.65	165.39 ± 100.9	0.542

*Independent sample t-test.

TABLE 4 Odds ratio and CI95% of the association between ischemic heart disease (IHD) and dietary intake of lycopene.

	Trend	Quartile 1 (<7.91 mg/d)	Quartile 2 (7.91–11.64 mg/d)	Quartile 3 (11.64–16.47 mg/d/)	Quartile 4 (16.47 < mg/d)
Model 1	**0.98 (0.96–0.99)**	**1**	**0.79 (0.54–1.15)**	**1.14 (0.78–1.66)**	**0.67 (0.46–0.97)**
Model 2	0.98 (0.96–0.99)	1	0.79 (0.54–1.16)	1.13 (0.77–1.65)	0.67 (0.46–0.99)
Model 3	0.98 (0.96–0.99)	1	0.78 (0.53–1.15)	1.11 (0.75–1.64)	0.65 (0.42–0.99)
Model 4	0.97 (0.96–0.99)	1	0.77 (0.52–1.13)	1.09 (0.73–1.61)	0.63 (0.41–0.97)
Model 5	0.97 (0.95–0.99)	1	0.78 (0.53–1.15)	1.07 (0.72–1.59)	0.64 (0.41–0.99)

* Binominal Logistic regression, Model 1: crude, Model 2: adjusted for Age at interview and gender, Model 3: Additionally adjusted for total fat and energy, Model 4: Additionally adjusted for BMI, Model 5: Further adjusting for smoking, drink alcohol, and physical activity.

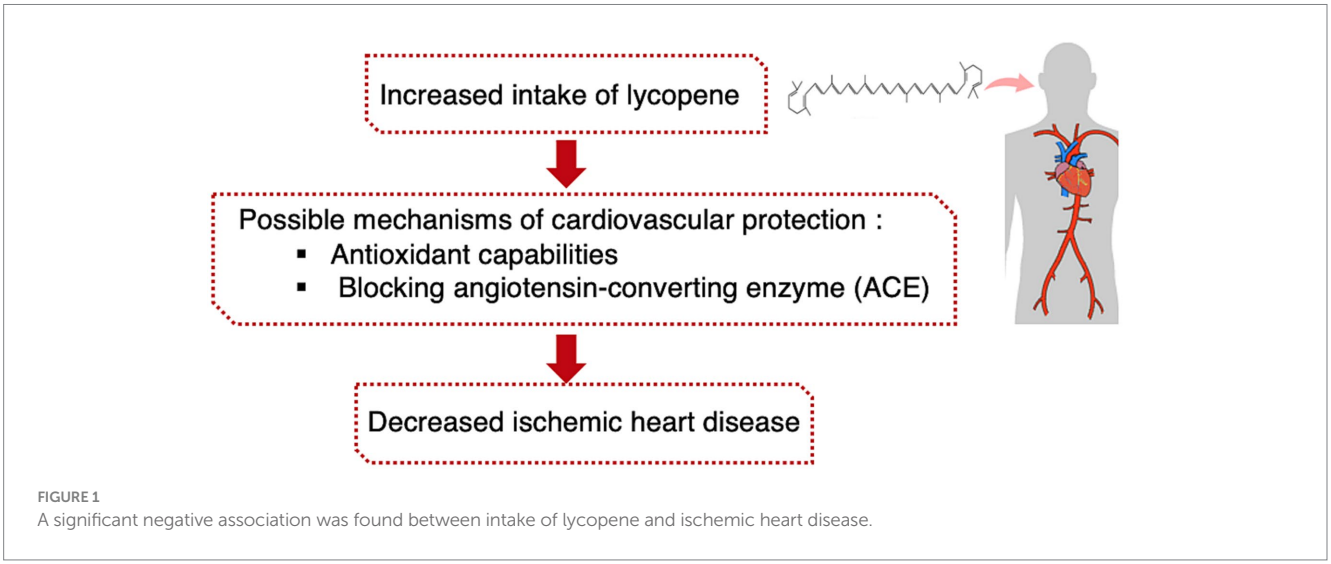

FIGURE 1
A significant negative association was found between intake of lycopene and ischemic heart disease.

lycopene may be caused by the wide variety of experimental protocols used to discover the association between lycopene consumption and cardiovascular disease (38). Pre-existing levels of lycopene, the dietary source of lycopene, and the characteristics of the target populations are essential factors that can affect any association between lycopene consumption and cardiovascular disease (38).

Possible explanations for the effect of lycopene on IHD might be the antithrombotic and antiplatelet effects of lycopene (39, 40), potent antioxidant properties of lycopene (41, 42), induction of detoxifying enzymes (43, 44) and reduction of cell surface adhesion and intima-media thickness (45). Oxidative stress can lead to the production of proinflammatory mediators, including vascular cell adhesion molecules, intracellular adhesion molecules, and chemoattractant proteins, which contribute to the development of early atherosclerosis (46, 47). On the other hand, lycopene is a powerful antioxidant that can effectively reduce levels of reactive oxygen species and eliminate singlet oxygen (48, 49). Thus, lycopene may suppress oxidative stress and acts against IHD. The strength of the present study is the adjustment for a broad range of potential confounding factors. However, this study had some limitations. First, the study design was case–control and did not allow to discover the cause and effect relationship. Second, the FFQ was used to assess food intake in the study, which may lead to over-reporting or under-reporting of dietary intake. Third, the way of cooking food was not investigated in the present study, which can affect the bioavailability of food lycopene.

Conclusion

A significant negative association was found between intake of lycopene and IHD. If this result is confirmed in future studies, high dietary intake of lycopene and lycopene supplementation can be considered complementary strategies against IHD. Further prospective studies in different populations are required to elucidate the roles of lycopene against IHD.

Data availabiulity statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved the study (Ethics Code: IR.SBMU.nnftri.Rec.1400.030). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SD: Formal analysis, Writing – original draft. AA: Data curation, Writing – review & editing. FAl: Data curation, Writing – original draft. MM: Software, Writing – review & editing. RM: Software, Writing – review & editing. FAz: Software, Writing – review & editing. AR: Methodology, Writing – review & editing. ME: Formal analysis, Writing – review & editing. SS: Software, Writing – review & editing. MA: Data curation, Writing – review & editing. SK: Data curation, Writing – review & editing. MA: Data curation, Writing – review & editing. MG: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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