Tomato-rich (Mediterranean) diet does not modify inflammatory markers

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Manuscript submitted 17th November, 2006

Manuscript accepted 29th December, 2006

Clin Invest Med 2007; 30 (2): E70-E74.

Abstract

Background: The Mediterranean diet is rich in lycopene and has been reported to reduce cardiovascular events. The mechanism of prevention of cardiovascular events has not been clearly established. Our aim was to study the effects of a tomatoes-rich diet on markers of vascular inflammation.

Methods: Plasma concentrations of E-selectin, intercellular adhesion molecule 1 (ICAM-1), and high sensitivity C-reactive protein (hs-CRP) were determined by ELISA in 103 apparently healthy volunteers. Volunteers were randomly assigned to two groups: 50 participants ate 300 g tomatoes daily for 1 month, and 53 participants ate their usual diet with tomatoes prohibited during that period. Markers of inflammation were measured before enrollment and 1 month after their assigned diet.

Results: The two diet groups had similar baseline clinical characteristics and similar baseline levels of inflammatory markers. After 30 days of assigned diet concentrations of hs-CRP, E-selectin and ICAM-1 were unchanged compared with baseline in the tomato-rich diet. However, ICAM-1 concentration was increased in the regular diet group from $247.55 \pm 55 \text{ ng/ml}$ to $264.71 \pm 60.42 \text{ ng/ml}$ ($P=0.01$).

Conclusions: The mechanisms of benefit of the tomato-rich diet are not directly related to inhibition of markers of vascular inflammation.

Individuals from the Mediterranean area have a lower risk of coronary heart disease compared to populations based in Western countries.¹⁻⁴ The Mediterranean diet is rich in fruits, vegetables, nuts, olive oil and encourages moderate consumption of fish, poultry and wine.¹ Previous studies have investigated particular components of this diet (nut, wine or fish intake)^{5, 6} but the particular component of the diet associated with improved cardiovascular outcomes remains unclear.⁴

One possibility is that the beneficial effects of the diet are related to intake of certain fruits and vegetables.⁷ In particular, it has been suggested that lycopene-rich diets may have favourable effects on atherosclerosis and carcinogenesis. The mechanism of this benefit has been ascribed to antioxidant effects of lycopenes.⁸

Elevated markers of inflammation have been associated with increased risk of cardiovascular events.^{9, 10} Furthermore, enhanced risk due to inflammation may be modified via statins, exercise, and low-fat diets.¹¹ Thus, modulation of the inflammatory profile may be used as a surrogate marker for improvement in cardiovascular risk.

We hypothesized that tomatoes ingestion could, in part, explain the benefit of the Mediterranean diet.

Thus, we tested this hypothesis via a clinical trial randomly assigning healthy volunteers to a diet rich in tomatoes vs. a regular diet in order to determine if a beneficial effect could be demonstrated by a change in the inflammatory risk profile after 30 days of dietary treatment.

Methods

This was a prospective clinical study that was conducted in our hospital and was approved by the Helsinki Committee of the hospital. Informed consent was obtained and signed before enrollment. 103 healthy volunteers took part in the study: 50 volunteers were randomly assigned to tomato-rich diet (tomatoes 300 g daily for 1 month), and 53 volunteers ate their regular meals with tomatoes prohibited. The average BMI was 28.1 ± 3.15 for the volunteers in the tomatoes-rich diet, and 30.05 ± 1.51 for the regular diet group ($P=NS$). All were considered to be healthy adults (except 4 and 3 in each group that were smoking, and 3 and 4 that had hypertension), active and productive.

The definition of the tomatoes-rich diet was based upon daily intake of tomatoes or tomato related products including tomato-sauce and tomato-juice.

Volunteers were excluded if they had chronic disease that might impact their baseline markers of inflammation including renal failure, heart failure, malignancy, diabetes mellitus, and current cigarette use. Volunteers were also excluded if they could not commit to a tomato-rich diet for the whole month.

Each volunteer was interviewed before enrollment and 30 days after starting the study. Volunteers assigned to both dietary groups kept a daily log of foods ingested in order to determine differences in daily tomatoes ingestion and assess compliance with dietary instructions. Venous blood samples were drawn immediately after dietary assignment and again after 1 month. Every sample was centrifuged and the serum was frozen at -70°C for 4 months until processed as one batch.

We studied the effects of a tomato-rich diet on levels of hs-CRP, ICAM-1 and E-selectin, and compared those effects to the regular diet group. E-

TABLE 1. Volunteers' Baseline Characteristics

P	No Tomatoes diet	Tomatoes rich diet	
NS	53	50	Number
NS	35	33	Females
NS	18	17	Males
NS	45.1 ± 13.5	45.5 ± 14	Age (mean $\pm$ SD)(yr)
NS	3	4	Smoking
NS	4	3	Hypertension
NS	0	0	Diabetes mellitus
NS	0	0	Hyperlipidemia
NS	30.05 ± 1.51	28.1 ± 3.15	BMI
0.01	45.52 ± 21.08	55.37 ± 34.35	E-selectin
0.001	247.55 ± 55	286.47 ± 80	ICAM-1
NS	0.45 ± 0.47	0.43 ± 0.59	hs-CRP

selectin and ICAM-1 were measured with enzyme linked immunoassay (ELISA) kit (R&D Systems Inc., MN, USA). C-reactive protein (CRP) was assayed utilizing a fluorescence polarization immunoassay (FPIA) technology (Abbott Laboratories, Abbott Park, IL, USA).

Statistical analysis: The statistical analysis used in this study was a "paired student t-test" to test for the difference of markers of inflammation before and after 30 days of assigned diet.

Results

Volunteer characteristics

Characteristics of volunteers assigned to both dietary groups were similar (Table 1). 50 volunteers participated in the tomato-rich arm of the study (33 women) with a mean age of 45.5 ± 14 years old. 53 volunteers (35 women) were enrolled to the regular diet (but without tomatoes), and their mean age was 45.1 ± 13.5 yr. Traditional cardiovascular risk factors were uncommon as per the study design. Compliance with the diet was 100% in both the tomato-rich and the regular

diet groups and there was a complete follow up at 30 days for repeat inflammatory assays.

Inflammatory Markers after 30 days' diet

Tomato-rich diet did not have any effect on markers of vascular inflammation that were studied. There were differences in the basic levels of the inflammatory markers (ICAM-1 and E-selectin) between the two groups of volunteers. Those in the tomato-rich diet had higher E-selectin and ICAM-1 concentrations. No such difference was observed in baseline hs-CRP concentrations.

There were no differences in E-selectin and hs-CRP concentrations before and after one month tomato-rich diet and in the regular diet group as well. However, there was an increase in ICAM-1 concentration in the group of volunteers with the regular diet (without tomatoes), and an increase in ICAM-1 concentration in the tomato-rich group, but the difference did not reach a statistical significance (Table 2).

Discussion

We found no beneficial effects of tomato-rich diet (300 g daily for 1 month) on markers of inflammation that were studied: E-selectin, ICAM-1 and hs-CRP. We expected to find an inhibiting effect of tomatoes on inflammatory markers that could explain tomatoes' clinical-epidemiological beneficial effects but no anti-inflammatory effect was noticed among the inflammatory markers that were studied.

The only difference was in ICAM-1 concentration that was increased after 30 days' regular diet, and did not increase in the tomato-rich diet. This could suggest that tomatoes may have a protective effect on the inflammatory system, represented by ICAM-1, an important adhesion molecule that belongs to the immunoglobulin family of adhesion molecules, and responsible for the moderate (intermediate) phase of adhesion between cells.

We chose to study the effects of tomato-rich diet on specific soluble adhesion molecules because of accumulating evidence suggesting their role as markers of disease activity in patients with coronary and vascular disease: Plasma soluble adhesion molecules

TABLE 2. Inflammatory markers before and 30 days after tomatoes-rich diet compared with the no-tomatoes diet control group

No Tomatoes diet		Tomatoes rich diet		
30 days after	Before	30 days after	Before	
				E-selectin
47.70	45.52	61.20	55.37	Mean
27.27	21.08	40.20	34.35	SD
	0.42		0.14	P
				ICAM-1
264.71	247.55	307.44	286.47	Mean
60.42	55.01	89.80	80.80	SD
	0.01		0.07	P
				hsCRP
0.45	0.45	0.41	0.43	Mean
0.62	0.47	0.40	0.59	SD
	0.96		0.70	P

P – for comparison between levels of cell adhesion molecules and CRP before and 30 days after tomato-rich diet and no-tomato-diet

(ICAM-1, VCAM-1 and E-selectin) were higher in patients with coronary artery disease compared with healthy volunteers, and higher concentrations were found in patients with coronary artery disease who had coronary artery ectasia compared with patients with coronary artery disease without these lesions, suggesting the presence of a more severe and extensive chronic inflammation in the coronary circulation.¹² In patients who underwent coronary artery bypass grafting, high preoperative concentrations of C-reactive protein were associated with long-term risk of cardiovascular events, independent of other risk factors.¹³ The PROVE IT-TIMI 22 study has shown that in patients that were admitted with an acute coronary syndrome, soluble ICAM-1 concentration on admission was the strongest predictor of long term clinical outcome.¹⁴

Our assumption was that an anti-oxidant anti-inflammatory Mediterranean diet would prevent endothelial activation and inhibit vascular inflammation in healthy volunteers. We could not demonstrate such a clear cut effect, even though the lack of increase in ICAM-1 in the tomato-rich group (compared to the significant increase in volunteers of the regular diet group) may suggest that such an effect may have been more evident and could have reached a statistical significance if we had a larger group of volunteers or the study would have continued for a longer period of time.

Lycopene, a carotenoid without provitamin-A activity, is present in many fruits and vegetables; however, tomatoes and processed tomato products constitute the major source of lycopene in North American diet.¹⁵ Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidence is accumulating to suggest other mechanisms (such as modulation of intercellular gap junction communication, hormonal and immune systems and metabolic pathways) may also be involved.⁸ Studies (human and animal cells) have identified a gene, connexin 43 whose expression is up-regulated by lycopene that allows direct intercellular gap junction communication (GJC), which is deficient in many human tumors and its up-regulation is associated with decreased proliferation.¹⁶ Other possible mechanisms may include enhanced LDL degradation, plaque rupture, and altered endothelial functions.¹⁷

In light of the epidemiological studies that suggest a clinical effect on one hand and our results on the other hand, there is a high likelihood that the mechanism of action could be related to anti-oxidative protection of plasma lipoproteins, lymphocyte DNA and serum proteins against oxidative damage, and not related directly to vascular inflammation.¹⁸

Study limitations

The small sample size, the relatively short time of tomato-rich diet, the lack of measurement of lycopene concentrations in the blood, and the fact that the majority of volunteers were females - could limit our observations and conclusions.

Conclusions

Tomato consumption has been demonstrated in epidemiological studies to have beneficial protective effects regarding coronary artery disease and several cancers. We tried to find out a possible mechanism through inflammatory inhibition, however, we could not demonstrate clearly such an effect. A larger, longer, and a multi center study is needed in order to confirm our findings.

Acknowledgments

Supported by a grant donated by Danone-Strauss, Israel. We would like to thank Mrs. Dina Binyamin for her excellent technical and secretarial support.

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