Summary of Research
Endothelial and Platelet Function

Disease: Endpoints of interest	First Author	Study Title and Complete Citation	Date	Abstract	Study Type
CVD: oxidation inflammation endothelial function markers	Upritchard JE	Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inf lammatory activity in type 2 diabetes. Upritchard JE, Sutherland WH, Mann JI. Diabetes Care. 2000 Jun;23(6):733-8.	2000	OBJECTIVE: To compare the effects of short-term dietary supplementation with tomato juice, vitamin E, and vitamin C on susceptibility of LDL to oxidation and circulating levels of C-reactive protein (C-RP) and cell adhesion molecules in patients with type 2 diabetes. RESEARCH DESIGN AND METHODS: There were 57 patients with well-controlled type 2 diabetes aged <75 years treated with placebo for 4 weeks and then randomized to receive tomato juice (500 ml/day), vitamin E (800 U/day), vitamin C (500 mg/day), or continued placebo treatment for 4 weeks. Susceptibility of LDL to oxidation (lag time) and plasma concentrations of lycopene, vitamin E, vitamin C, C-RP, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1 were measured at the beginning of the study, after the placebo phase, and at the end of the study. RESULTS: Plasma lycopene levels increased nearly 3-fold (P = 0.001), and the lag time in isolated LDL oxidation by copper ions increased by 42% (P = 0.001) in patients during supplementation with tomato juice. The magnitude of this increase in lag time was comparable with the corresponding increase during supplementation with vitamin E (54%). Plasma C-RP levels decreased significantly (-49% , P = 0.004) in patients who received vitamin E. Circulating levels of cell adhesion molecules and plasma glucose did not change significantly during the study. CONCLUSIONS: This study indicates that consumption of commercial tomato juice increases plasma lycopene levels and the intrinsic resistance of LDL to oxidation almost as effectively as supplementation with a high dose of vitamin E, which also decreases plasma levels of C-RP, a risk factor for myocardial infarction, in patients with diabetes. These findings may be relevant to strategies aimed at reducing risk of myocardial infarction in patients with diabetes.	RCT
CVD: platelet function	O'Kennedy N	Effects of antiplatelet components of tomato	2006	BACKGROUND: Natural antithrombotic agents that influence platelet function are of potential interest for primary prevention of cardiovascular disease. Previous reports	Interv

		extract on platelet function in vitro and ex vivo: a time-course cannulation study in healthy humans. O'Kennedy N, Crosbie L, van Lieshout M, Broom JI, Webb DJ, Duttaroy AK. Am J Clin Nutr. 2006 Sep;84(3):570-9.		showed that tomato extracts inhibit platelet aggregation in vitro, but little is known of the active components, their mode of action, or their efficacy in vivo. OBJECTIVE: The objectives of the study were to examine the antiplatelet activity of specific tomato components by in vitro experimentation and to establish their ex vivo efficacy in healthy humans. DESIGN: The mechanisms of action of antiplatelet components isolated from tomato extracts were examined in vitro. A 7-h time-course study was carried out in cannulated human subjects (n = 23) to determine the ex vivo efficacy of a supplement drink containing tomato extract and the onset and duration of antiplatelet effects. RESULTS: The inhibition of ADP-, collagen-, thrombin-, and arachidonate-mediated platelet aggregation by tomato extract components appears to be linked to the inhibition of glycoprotein IIb/IIIa and platelet secretory mechanisms. We found a significant inhibition of baseline platelet function, from 2.9 +/- 1.4% (optimal ADP concentrations; P = 0.03) to 20.0 +/- 4.9% (suboptimal ADP concentrations; P < 0.001), 3 h after supplementation with a dose of tomato extract equivalent to 6 tomatoes. The observed effects persisted for >12 h. Coagulation variables were not affected. CONCLUSIONS: The ingestion of tomato components with in vitro antiplatelet activity significantly affects ex vivo platelet function. The reported cardioprotective effects of tomatoes are potentially linked to a modulation of platelet function.	

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CVD: platelet function	O'Kennedy N	Effects of tomato extract on platelet function: a double-blinded crossover study in healthy humans. O'Kennedy N, Crosbie L, Whelan S, Luther V, Horgan	2006	BACKGROUND: Aqueous extracts from tomatoes display a range of antiplatelet activities in vitro. We previously showed that the active components also alter ex vivo platelet function in persons with a high response to ADP agonist. OBJECTIVE: The objective was to evaluate the suitability of a tomato extract for use as a dietary supplement to prevent platelet activation. DESIGN: A randomized, double-blinded, placebo-controlled crossover study was conducted in 90 healthy human subjects selected for normal platelet function.	RCT

		G, Broom JI, Webb DJ, Duttaroy AK. Am J Clin Nutr. 2006 Sep;84(3):561-9.		Changes from baseline hemostatic function were measured 3 h after consumption of extract-enriched or control supplements. RESULTS: Significant reductions in ex vivo platelet aggregation induced by ADP and collagen were observed 3 h after supplementation with doses of tomato extract equivalent to 6 (6TE) and 2 (2TE) tomatoes [3 micromol ADP/L: 6TE (high dose), -21.3% ; 2TE (low dose), -12.7% ; P < 0.001; 7.5 micromol ADP/L: 6TE, -7.8% , 2TE, -7.6% ; P < 0.001; 3 mg collagen/L: 6TE, -17.5% ; 2TE, -14.6% ; P = 0.007]. No significant effects were observed for control supplements. A dose response to tomato extract was found at low levels of platelet stimulation. Inhibition of platelet function was greatest in a subgroup with the highest plasma homocysteine (P < 0.05) and C-reactive protein concentrations (P < 0.001). CONCLUSION: As a functional food or dietary supplement, tomato extract may have a role in primary prevention of cardiovascular disease by reducing platelet activation, which could contribute to a reduction in thrombotic events.	
CVD: inflammation endothelial function markers	Blum A	Tomato-rich (Mediterranean) diet does not modify inflammatory markers. Blum A, Monir M, Khazim K, Peleg A, Blum N. Clin Invest Med. 2007;30(2):E70-4.	2007	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	RCT

				the tomato-rich diet. However, ICAM-1 concentration was increased in the regular diet group from 247.55+/-55 ng/ml to 264.71+/-60.42 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	

Disease: Endpoints of interest	First Author	Study Title and Complete Citation	Date	Abstract	Study Type
CVD: oxidation inflammation endothelial function markers	Denniss SG	Effect of short-term lycopene supplementation and postprandial dyslipidemia on plasma antioxidants and biomarkers of endothelial health in young, healthy individuals. Denniss SG, Haffner TD, Kroetsch JT, Davidson SR, Rush JW, Hughson RL. Vasc Health Risk Manag. 2008;4(1):213-22.	2008	The objective of this study was to test the hypothesis that the effect of a high-fat meal (HFm) on plasma lipid-soluble antioxidants and biomarkers of vascular oxidative stress and inflammation would be attenuated by short-term lycopene supplementation in young healthy subjects. Following restriction of lycopene-containing foods for 1-wk (LYr), blood was collected in a fasting state and 3 h after a HFm and a low-fat meal (LFm) in N = 18 men aged 23 +/- 2 years, and after a HFm only in N = 9 women aged 23 +/- 1 years. Blood was also sampled pre- and post-meals following 1-wk of 80 mg/day lycopene supplementation (LYs) under continued dietary LYr. In the fasting state, LYs compared with LYr not only evoked a >2-fold increase in plasma lycopene but also increased plasma beta-carotene and alpha-tocopherol ($p < 0.01$), though LYs did not affect plasma nitrate/nitrite (biomarker of nitric oxide), malondialdehyde (biomarker of lipid oxidative stress), vascular- and intercellular-adhesion molecules or C-reactive protein (biomarkers of inflammation). Contrary to the hypothesis, the HFm-induced dyslipidemic state did not affect plasma malondialdehyde, C-reactive protein, or adhesion molecules in either LYr or LYs. Both the HFm and LFm were associated with decreases in the nitric oxide metabolites nitrate/nitrite and lipid-soluble antioxidants ($p < 0.05$). The data revealed that 1-wk of LYs increased plasma lycopene, beta-carotene, and alpha-tocopherol yet despite these marked changes to the plasma lipid-soluble antioxidant pool, biomarkers of vascular oxidative stress and inflammation were	Interv

				unaffected in the fasted state as well as during dyslipidemia induced by a HFm in young healthy subjects.	
CVD: oxidation lipids endothelial function BP	Kim JY	Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. Kim JY, Paik JK, Kim OY, Park HW, Lee JH, Jang Y, Lee JH. Atherosclerosis. 2011 Mar;215(1):189-95. Epub 2010 Dec 9.	2011	OBJECTIVE: The objective was to determine the effects of lycopene supplementation on endothelial function assessed by reactive hyperemia peripheral arterial tonometry (RH-PAT) and oxidative stress. METHODS: Healthy men (n=126) were randomized to receive placebo (n=38), 6 mg (n=41), or 15 mg (n=37) lycopene daily for 8-week. RESULTS: Serum lycopene increased in a dose-dependent manner after 8-week supplementation (P<0.001). The 15 mg/day group had greater increase in plasma SOD activity (P=0.014) and reduction in lymphocyte DNA comet tail length (P=0.042) than the placebo group. Intragroup comparison revealed a 23% increase in RH-PAT index from baseline (1.45±0.09 vs. 1.79±0.12; P=0.032) in the 15 mg/day group after 8-week. hs-CRP, systolic blood pressure, sICAM-1 and sVCAM-1 significantly decreased, and β-carotene and LDL-particle size significantly increased only in the 15 mg/day group. Interestingly, the beneficial effect of lycopene supplementation on endothelial function (i.e., RH-PAT and sVCAM-1) were remarkable in subjects with relatively impaired endothelial cell function at initial level. Changes in RH-PAT index correlated with SOD activity (r=0.234, P=0.017) especially in the 15 mg lycopene/day group (r=0.485, P=0.003), lymphocyte DNA comet tail moment (r=-0.318, P=0.001), and hs-CRP (r=-0.238, P=0.011). In addition, changes in lycopene correlated with hs-CRP (r=-0.230, P=0.016) and SOD activity (r=0.205, P=0.037). CONCLUSION: An increase in serum lycopene after supplementation can reduce oxidative stress which may play a role in endothelial function	RCT

Disease: Endpoints of interest	First Author	Study Title and Complete Citation	Date	Abstract	Study Type
CVD: endothelial function	Stangl V	Lack of effects of tomato products on endothelial function in human subjects: results of a randomised, placebo-controlled cross-over study. Stangl V, Kuhn C, Hentschel S, Jochmann N, Jacob C, Böhm V, Fröhlich K, Müller L, Gericke C, Lorenz M. Br J Nutr. 2011 Jan;105(2):263-7. Epub 2010 Aug 24.	2011	Epidemiological studies suggest that consumption of tomato products reduces the risk of CVD via antioxidant, hypocholesterol- aemic and anti-inflammatory mechanisms. Although experimental data also describe beneficial effects on endothelial function, clinical data in human subjects are lacking. To test the hypothesis that tomato ingestion ameliorates endothelial function, we randomised healthy non-smoking postmenopausal women to consume a buttered roll with and without tomato purée (70 g) in a cross-over design. Endothelial-dependent flow-mediated dilation (FMD) and endothelial-independent nitro-mediated dilation of the brachial artery were assessed with high-resolution ultrasound (13 MHz linear array transducer). Acute (24 h) and long-term (7 d) effects were examined after daily consumption of the described meal. Nineteen volunteers completed the protocol and provided technically suitable ultrasound measurement data. Plasma lycopene levels increased from 0·30 (sem 0·04) (baseline) to 0·42 (sem 0·04) and to 0·74 (sem 0·06) μm after 24 h and 7 d, respectively, with tomato purée consumption. These data indicated an effective absorption of the tomato product. However, both acute and long-term tomato purée consumption had no effects on endothelium-dependent or -independent dilation of the brachial artery. In addition, we found no correlation between lycopene plasma levels and FMD. In conclusion, consumption of tomato products associated with a significant increase in plasma lycopene levels had no effects on endothelial function in healthy postmenopausal women.	RCT
CVD: oxidation lipids inflammation endothelial function	Burton-Freeman B	Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weight men and women. Burton-Freeman B, Talbot J, Park E, Krishnankutty S, Edirisinghe I. Mol Nutr Food Res. 2012 Apr;56(4):622-31. doi: 10.1002/mnfr.201100649. Epub 2012 Feb 14.	2012	SCOPE: This study was designed to evaluate the ability of tomato rich in lycopene to modify postprandial oxidative stress, inflammation, and endothelial function in healthy weight individuals. METHODS AND RESULTS: Twelve women and 13 men (mean age = 27 ± 8 years; mean body mass index= 22 ± 2) consumed high-fat meals known to induce postprandial oxidative stress on two separate occasions containing either processed tomato product or non-tomato alternative. Blood samples were collected at 0, 30, 60, 90, 120 min, then hourly until 360 min. Flow-mediated dilation (FMD) was performed at 0 and 210 min. Endpoints included changes in glucose, insulin, lipids, oxidized low-density lipoprotein (OxLDL), inflammatory cytokines, and FMD. Both meals induced increases in plasma glucose, insulin, and lipid concentrations ($p < 0.05$). A trend for higher triglycerides at >240 min was observed after the tomato meal ($p = 0.006$). Tomato significantly	RCT

				attenuated high-fat meal-induced LDL oxidation ($p < 0.05$) and rise in interleukin-6 ($p < 0.0001$), a proinflammatory cytokine and inflammation marker. CONCLUSION: The data indicate that consuming tomato products with a meal attenuates postprandial lipemia-induced oxidative stress and associated inflammatory response. The relevance of OxLDL and inflammation to vascular injury suggests a potentially important protective role of tomato in reducing cardiovascular disease risk. ClinicalTrials.gov Registration number - NCT00966550.	

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Disease: Endpoints of interest	**First Author**	**Study Title and Complete Citation**	**Date**	**Abstract**	**Study Type**
CVD: lipids inflammation BP insulin resistance endothelial function	Thies F	Effect of a tomato-rich diet on markers of cardiovascular disease risk in moderately overweight, disease-free, middle-aged adults: a randomized controlled trial. Thies F, Masson LF, Rudd A, Vaughan N, Tsang C, Brittenden J, Simpson WG, Duthie S, Horgan GW, Duthie G. Am J Clin Nutr. 2012 May;95(5):1013-22. doi: 10.3945/ajcn.111.026286. Epub 2012 Apr 4.	2012	BACKGROUND: Cardiovascular disease (CVD) is a major cause of mortality in the United Kingdom. Epidemiologic studies suggest that consumption of tomato-based foods may lower CVD risk. Such potential benefits have been ascribed in part to high concentrations of lycopene in the tomatoes. However, these findings have not yet been validated by comprehensive intervention trials. OBJECTIVE: The aim of this study was to conduct a single-blind, randomized controlled intervention trial with healthy middle-aged volunteers to assess whether the consumption of tomato-based foods affects recognized biomarkers of CVD risk. DESIGN: After a 4-wk run-in period with a low-tomato diet, 225 volunteers (94 men and 131 women) aged 40-65 y were randomly assigned into 1 of 3 dietary intervention groups and asked to consume a control diet (low in tomato-based foods), a high-tomato-based diet, or a control diet supplemented with lycopene capsules (10 mg/d) for 12 wk. Blood samples were collected at baseline, at 6 wk, and after the intervention and were analyzed for carotenoid and lipid profiles and inflammatory markers. blood pressure, weight, and arterial stiffness were also measured. Dietary intake was also determined during the intervention. RESULTS: None	RCT

				of the systemic markers (inflammatory markers, markers of insulin resistance and sensitivity) changed significantly after the dietary intervention. Moreover, lipid concentrations and arterial stiffness were also unaffected by the interventions. CONCLUSION: These data indicate that a relatively high daily consumption of tomato-based products (equivalent to 32-50 mg lycopene/d) or lycopene supplements (10 mg/d) is ineffective at reducing conventional CVD risk markers in moderately overweight, healthy, middle-aged individuals. This trial was registered at isrctn.org as ISRCTN34203810.	
CVD: oxidation endothelial function	Xanplanteris P	Tomato paste supplementation improves endothelial dynamics and reduces plasma total oxidative status in healthy subjects. Xaplanteris P, Vlachopoulos C, Pietri P, Terentes- Printzios D, Kardara D, Alexopoulos N, Aznaouridis K, Miliou A, Stefanadis C. Nutr Res. 2012 May;32(5):390-4. doi: 10.1016/j.nutres.2012.03.011. Epub 2012 May 15.	2012	Consumption of tomato products is linked to beneficial outcomes through antioxidant and anti-inflammatory mechanisms. The aim of this study was to determine whether a 14-day period of tomato paste supplementation would improve endothelial function. Nineteen volunteers (mean age, 39 ± 13 years; 8 men/11 women) were studied in a randomized (exposure sequence), single- blind (operator), crossover design. The study consisted of a supplementation arm (70 g tomato paste containing 33.3 mg of lycopene) and a control arm, during which no tomato paste was added to their regular diet. Volunteers maintained their regular diet during study arms. Two-week washout periods preceded each arm. Flow-mediated dilatation (FMD) measured by brachial artery ultrasonography was used as an estimate of endothelial function at day 1 (acute response) and day 15 (midterm response). Plasma lipid peroxides were measured with a photometric enzyme-linked immunosorbent assay as an index of total oxidative status. Tomato supplementation led to an overall FMD increase compared with the control period (P = .047 for repeated-measures 3 × 2 analysis of variance). At day 1, FMD was not significantly increased (P = .329). By day 15, tomato supplementation resulted in an increase in FMD by 3.3% ± 1.4% , whereas at the control arm, FMD declined by -0.5% ± 0.6% (P = .03);	RCT

				magnitudes of change are absolute FMD values. Total oxidative status decreased at the end of the supplementation period compared with baseline values (P = .038). Daily tomato paste consumption exerts a beneficial midterm but not short-term effect on endothelial function. Further studies are warranted to explore the effects of tomato paste on endothelial dilation in different age groups and comorbidities.	

Disease: Endpoints of interest	**First Author**	**Study Title and Complete Citation**	**Date**	**Abstract**	**Study Type**
CVD: endotelial function	Gajendragadkar PR	Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. Gajendragadkar PR, Hubsch A, Mäki-Petäjä KM, Serg M, Wilkinson IB, Cheriyan J. PLoS One. 2014 Jun 9;9(6):e99070. doi: 10.1371/journal.pone.0099070. eCollection 2014.	2014	AIMS: The mechanisms by which a 'Mediterranean diet' reduces cardiovascular disease (CVD) burden remain poorly understood. Lycopene is a potent antioxidant found in such diets with evidence suggesting beneficial effects. We wished to investigate the effects of lycopene on the vasculature in CVD patients and separately, in healthy volunteers (HV). METHODS AND RESULTS: We randomised 36 statin treated CVD patients and 36 healthy volunteers in a 2:1 treatment allocation ratio to either 7 mg lycopene or placebo daily for 2 months in a double-blind trial. Forearm responses to intra-arterial infusions of acetylcholine (endothelium-dependent vasodilatation; EDV), sodium nitroprusside (endothelium-independent vasodilatation; EIDV), and NG-monomethyl-L-arginine (basal nitric oxide (NO) synthase activity) were measured using venous plethysmography. A range of vascular and biochemical secondary endpoints were also explored. EDV in CVD patients post- lycopene improved by 53% (95% CI: +9% to +93% , P=0.03 vs. placebo) without changes to EIDV, or basal NO responses. HVs did not show changes in EDV after lycopene treatment. blood pressure, arterial stiffness, lipids and hsCRP levels were unchanged for lycopene vs. placebo treatment groups in the CVD arm as well as the HV arm. At baseline, CVD patients had	RCT

				impaired EDV compared with HV (30% lower; 95% CI: -45% to -10% , P=0.008), despite lower LDL cholesterol (1.2 mmol/L lower, 95% CI: -1.6 to -0.9 mmol/L, P<0.001). Post-therapy EDV responses for lycopene-treated CVD patients were similar to HVs at baseline (2% lower, 95% CI: -30% to +30% , P=0.85), also suggesting lycopene improved endothelial function. CONCLUSIONS: Lycopene supplementation improves endothelial function in CVD patients on optimal secondary prevention, but not in HVs. ClinicalTrials.gov NCT01100385	
CVD: IMT	Zou ZY	Effects of lutein and lycopene on carotid intima-media thickness in Chinese subjects with subclinical atherosclerosis: a randomised, double-blind, placebo- controlled trial. Zou ZY, Xu XR, Lin XM, Zhang HB, Xiao X, Ouyang L, Huang YM, Wang X, Liu YQ. Br J Nutr. 2014 Feb;111(3):474-80. doi: 10.1017/S0007114513002730. Epub 2013 Sep 19.	2014	The aim of the present study was to evaluate the effects of lutein and lycopene supplementation on carotid artery intima-media thickness (CAIMT) in subjects with subclinical atherosclerosis. A total of 144 subjects aged 45-68 years were recruited from local communities. All the subjects were randomly assigned to receive 20 mg lutein/d (n 48), 20 mg lutein/d+20 mg lycopene/d (n 48) or placebo (n 48) for 12 months. CAIMT was measured using Doppler ultrasonography at baseline and after 12 months, and serum lutein and lycopene concentrations were determined using HPLC. Serum lutein concentrations increased significantly from 0·34 to 1·96 μmol/l in the lutein group (P< 0·001) and from 0·35 to 1·66 μmol/l in the combination group (P< 0·001). Similarly, serum lycopene concentrations increased significantly from 0·18 to 0·71 μmol/l in the combination group at month 12 (P< 0·001), whereas no significant change was observed in the placebo group. The mean values of CAIMT decreased significantly by 0·035 mm (P= 0·042) and 0·073 mm (P< 0·001) in the lutein and combination groups at month 12, respectively. The change in CAIMT was inversely associated with the increase in serum lutein concentrations (P< 0·05) in both the active treatment groups and with that in serum lycopene concentrations (β = - 0·342, P= 0·031) in the combination group. Lutein and lycopene supplementation significantly increased the serum concentrations of lutein and lycopene with a decrease in CAIMT being associated with both concentrations. In addition, the combination of lutein and lycopene supplementation was more effective than lutein alone for protection against the development of CAIMT in Chinese subjects with subclinical atherosclerosis, and further studies are	RCT

				needed to confirm whether synergistic effects of lutein and lycopene exist.	