

RISK FACTORS

Mechanistic insights into the cardiovascular benefits of a Mediterranean diet

Large-scale trials, such as the PREDIMED study, have shown that a Mediterranean diet can reduce the incidence of cardiovascular events, such as myocardial infarction and stroke, but the mechanism of benefit is uncertain. Two new trials published in *PLoS ONE* now provide some insights into how a diet enriched with fruit, vegetables, and olive oil might lower cardiovascular morbidity and mortality.

Joseph Cheriyan and colleagues from the University of Cambridge, UK were interested in the effects of lycopene, which is a potent antioxidant compound that gives tomatoes their red colour. According to Dr Cheriyan, “randomized trials of antioxidants using vitamin E have been disappointing with negative outcomes, but there is epidemiological evidence that lycopene levels are inversely correlated with the risk of cardiovascular disease”.

Therefore, in a double-blind trial, 36 patients with established cardiovascular disease and who were taking statins were randomly allocated to receive 7 mg per day of lycopene or a matched placebo for 2 months. In a parallel group, 36 healthy volunteers were similarly randomly allocated to receive lycopene or placebo. Participants were advised to make no changes to their regular diet or medications.

The investigators measured endothelium-dependent vasodilatation, endothelium-independent vasodilatation, and basal nitric oxide synthase activity using venous plethysmography and intra-arterial infusion of acetylcholine, sodium nitroprusside, or NG-monomethyl-L-arginine, respectively. “Endothelial function measured using forearm blood flow,” says Dr Cheryian, “has been shown to prospectively predict outcomes in otherwise healthy older adults and is regarded as the gold-standard technique in the field.”

The results of the trial were presented at the British Cardiovascular Society Annual

Conference in June 2014. In the patients with cardiovascular disease, endothelium-dependent vasodilatation increased by 53% with lycopene compared with placebo ($P=0.03$). No changes were detected in endothelium-independent vasodilatation or basal nitric oxide responses with lycopene compared with placebo in these patients. Similarly, no differences were found in any of the three primary outcomes with lycopene or placebo in the healthy individuals.

A *post-hoc* analysis showed that, in the patients with cardiovascular disease, endothelium-dependent vasodilatation was lower than in healthy volunteers at enrolment into the study (30% lower; $P=0.008$). After lycopene treatment, endothelial function was restored to a level similar to that of healthy individuals at baseline (2% lower; $P=0.85$).

These data indicate that cardiovascular disease is associated with endothelial dysfunction despite optimal secondary prevention medication (statins, for example, are known to improve endothelial function). Oral supplementation with lycopene might further improve endothelial function, but the researchers emphasize that “supplementing one component of [the Mediterranean] diet may not necessarily replace the benefits of a complex mixture of interacting nutrients as part of a healthy diet”.

In the other study, investigators assessed the effects of a Mediterranean diet on inflammatory biomarkers associated with atherosclerosis and plaque vulnerability in a subgroup of the PREDIMED study cohort. A total of 164 individuals at high risk of cardiovascular disease were randomly allocated to receive a Mediterranean diet supplemented with extra-virgin olive oil (50 ml per day), a Mediterranean diet supplemented with nuts (30 g per day), or a low-fat diet.

After 1 year, individuals eating a Mediterranean diet supplemented with

olive oil or nuts had significantly larger reductions in systolic (6 mmHg) and diastolic (3 mmHg) blood pressures and LDL-cholesterol level (8–10%) than those eating a low-fat diet. Levels of C-reactive protein and IL-6 (biomarkers of inflammation associated with atherosclerotic plaque instability) were decreased with either form of Mediterranean diet compared with a low-fat diet. Similarly, levels of soluble intercellular adhesion molecule 1 and P-selectin were decreased with the Mediterranean diets compared with the low-fat diet.

Rosa Casas, lead author on the trial publication, concludes that “in addition to improving classic cardiovascular risk factors (blood pressure and serum cholesterol concentrations), the Mediterranean diet also has long-term anti-inflammatory effects by reducing [the levels of] several inflammatory molecules, such as adhesion molecules, interleukins, and metalloproteinases, [which are] related to atheroma plaque formation and instability”. The investigators suggest that “a nonpharmacological intervention (such as a Mediterranean diet) can reduce the incidence of cardiovascular disease in a similar way to taking statins, but without the potential adverse effects and at a lower cost”.

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Original articles Gajendragadkar, P. R. *et al.* Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. *PLoS ONE* 9, e99070 (2014) | Casas, R. *et al.* The effects of the Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. *PLoS ONE* 9, e100084 (2014)

