Eating, vascular biology, and atherosclerosis: a lot to chew on

Robert A. Vogel*

Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, 22 South Greene Street, Room S3B06, Baltimore, MD 21201, USA

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This editorial refers to 'Diet and inflammation: a link to metabolic and cardiovascular diseases'† by K. Esposito et al., on page 15

Coronary risk factors, such as hypercholesterolaemia and hypertension, are primary causes of atherosclerosis, at least partly due to their adverse impact on vascular biology. Impaired vascular biological states, such as endothelial dysfunction and inflammation, however may be independently atherogenic. Three examples that suggest that vascular indexes need to be considered independent of risk factors are anti-inflammatory effects of statins, hormone replacement therapy (HRT), and post-prandial endothelial dysfunction and inflammation. The REVERSAL and PROVE IT-TIMI 22 trials demonstrated that changes in LDL cholesterol and C-reactive protein independently correlated with coronary atherosclerosis progression and coronary heart events.1,2 On-treatment C-reactive protein was as predictive of subsequent coronary events as was LDL cholesterol. Prior to the recent HRT trials, many clinicians routinely recommended HRT to post-menopausal women to lower their cardiovascular risk. This was not unreasonable because HRT increases HDL cholesterol and decreases LDL cholesterol and lipoprotein(a). At the same time, HRT increases inflammation (e.g. C-reactive protein) and coagulation, two key atherogenic factors.3 Estrogen and HRT improve endothelial function, but this improvement disappears within a few months for as yet unclear reasons. In light of these lipid-independent vascular biological effects, it is not surprising that the recent HRT trials did not find beneficial effects on cardiovascular risk.

Esposito et al. review dietary effects on endothelial function and inflammation.4 In summary, both high-fat and high-sugar diets and single meals reduce endothelial-dependent vasodilation and increase inflammatory markers, such as C-reactive protein, interleukin-6, interleukin-8, interleukin-18, and tumour necrosis factor-α. The vascular effects of a high-fat meal last longer than those of a high-sugar meal, but the addition of a large sugar load to a high-fat meal increases the magnitude of the effects. A single high-fat meal also increases circulating microparticles, another index of endothelial dysfunction, activates coagulation factor VII, and impairs vascular compliance. Several studies have shown that post-prandial vascular biological impairment is greater in subjects with diabetes mellitus.

Considerable evidence suggests that high-fat and high-sugar meals induce vascular dysfunction through increases in oxidative stress. Reactive oxygen species are increased following a high-fat meal, especially in diabetic subjects, and increased nitric oxide inactivation has been demonstrated. The addition of direct (e.g. vitamins C and E) and indirect (e.g. folic acid) antioxidants to single meals reduces post-prandial endothelial dysfunction. Increased oxidative stress reduces the activity of the redox sensitive enzyme, dimethylarginine dimethylaminohydrolase, increasing levels of asymmetric dimethylarginine (ADMA), which competes with L-arginine for nitric oxide synthase substrate availability. Post-prandial oxidative stress increases the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, at least partly due to increases in nuclear factor κB, a pro-inflammatory nuclear regulator.

Dietary implications

Testing the vascular effects of single meals has greatly accelerated our understanding of dietary influences on atherosclerosis. The initial single-meal trial compared the effects of a typical American fast food and a low-fat meal.5 This and subsequent studies have taught us much about diet and vascular biology. In general, endothelium-dependent vasodilation is reduced to the greatest extent by saturated fatty acids, especially of the long-chain variety. The oxidation of cooking oil, which occurs during its reuse, also increases its adverse effect. At the other end of the saturation spectrum, highly unsaturated omega-3 fatty acids, such as decosahexaenoic acid (six double bonds), found in fish oil, do not impair endothelial function when ingested in a single meal and improve endothelial function when given chronically. Concordant with these observations is the finding that fatty acids inhibit inflammatory markers proportional to how many double bonds they contain. This would suggest dietary superiority for highly unsaturated fatty acids over monounsaturated oleic acid,
found in olives. Polyunsaturated fatty acids also reduce triglycerides more than monounsaturated fatty acids, although their ingestion results in lower HDL cholesterol levels. Polyunsaturated fatty acid HDL lowering does not necessarily increase cardiovascular risk because it appears to be due to increases in the SR-B1 receptor, an important component of reverse cholesterol transport. Despite having only three double bonds, plant-derived α-linolenic acid also appears to be a cardioprotective. Increased α-linolenic acid intake has recently been shown to be associated with reduced carotid artery intima-media thickness and lower long-term cardiovascular risk.

Foods given together may have different vascular effects than the sum of the individual components. Antioxidant-rich foods, such as fruits, vegetables, red wine, and red wine-based ingredients (e.g. balsamic vinegar), ingested with high-fat foods reduce subsequent vascular impairment.6,7 Given chronically, Mediterranean style diets following several of these principles have been shown to improve endothelium-mediated vasodilation and reduce inflammatory markers. These vascular findings may explain the dramatic results of the Lyon Diet Heart and Indo-Mediterranean Diet Heart studies, in which Mediterranean style diets reduced all-cause and coronary heart disease mortality to half.2,8 The lack of effect on lipoproteins and subject weight in the Lyon study strongly suggests that the direct vascular biological impact was predominately responsible for the experimental diet’s efficacy.

Drug effects

In addition to antioxidant foods and vitamins, several drug classes have been shown to reduce the vascular impairment caused by high-fat and high-sugar meals, including statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB). There are likely several mechanisms involved in this beneficial effect. Statins increase hepatic apo B/E receptor density, leading to faster clearance of post-prandial remnant-like lipoproteins. Along with free fatty acids, the latter is associated with endothelial dysfunction. ACE-inhibitors and ARBs reduce oxidative stress through reduced NADPH oxidase activity. It is as yet unclear whether improved post-prandial vascular biology is responsible for a significant part of the proven antiatherogenic effects of statins, ACE-inhibitors, and ARBs.

Clinical use of post-prandial measurements

Considerable evidence suggests that fasting lipoprotein measurements is not optimal for estimating cardiovascular risk, if for no other reason that westernized man rarely fasts for the recommended 12-h period. Patients with coronary heart disease have more pronounced post-prandial hypertriglyceridaemia, which in the majority of vascular biological studies is associated with greater endothelial dysfunction and inflammation. It is not clear, however, how to standardize post-prandial lipoprotein measurements and what would be their clinical implications.

Should we measure post-prandial vascular indexes to determine individual patient coronary risk and to make dietary recommendations? Our laboratory is currently studying genetic polymorphisms and post-prandial vascular biology in 1000 members of a genetically close population. As has been found before, preliminary analysis of this ongoing study shows that individuals have very varied vascular response to the same high-fat meal. Some individuals experience negligible changes, whereas others totally lose their endothelium-mediated vasodilatation. To determine the atherogenic implications of post-prandial vascular biology, individual changes will be correlated with carotid intima-media thickness. Esposito et al. have nicely summarized the intricate connection between diet and vascular biology. It now remains to be demonstrated whether these observations have important prognostic and therapeutic implications. This field is one of several areas examining the independent importance of vascular biology.

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References