COMMENT

Diet, the endothelium and atherosclerosis

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ABSTRACT

Dietary factors have been implicated in the difference in the risk of cardiovascular disease observed between populations. However, clinical trials and mechanistic studies of dietary modification are difficult to undertake, and the data set on dietary intervention for cardiovascular disease is now much smaller than that for pharmacological interventions. Moreover, the precise mechanism by which dietary modification might alter the risk of cardiovascular disease is uncertain. In this issue of Clinical Science, Ambring and co-workers investigate the effect of a Mediterranean-inspired diet on endothelial function and lipid fractions.

Atherosclerosis develops following prolonged exposure of the vascular wall to elevated levels of cholesterol, blood glucose, blood pressure and also to products of the inflammatory response. These risk factors appear to exert a graded increase in risk without evidence of a threshold and, thus, all members of a population are at risk from these exposures to a greater or lesser degree. Dysfunction of the vascular endothelium, manifest as a decreased availability of vasodilator, antithrombotic and anti-inflammatory mediators, such as NO (nitric oxide), appears to be central to the initiation, progression and complications of atherosclerosis [1]. Endothelial dysfunction is present in subjects with exposure to these risk factors, being evident in advance of clinically apparent disease, and the degree of dysfunction is predictive of later vascular events. Common mechanisms may underlie endothelial dysfunction from risk factor exposures and these include an increased generation of oxygen radicals and a functional deficiency of tetrahydrobiopterin, both of which may act finally to reduce NO availability.

A Western diet high in saturated fat, simple sugars and salt and low in fibre, fish oils and antioxidants has been associated with an increased risk of atherosclerosis, an effect which is likely to be mediated through elevations in orthodox risk factors and possibly also through pro-inflammatory, pro-oxidant and prothrombotic mechanisms. Populations from Southern Europe, who consume a Mediterranean-style diet low in saturated fat, rich in oleic acid and antioxidants, have a lower incidence of cardiovascular disease as do populations, such as the Greenland Inuit, who consume diets rich in ω-3 polyunsaturated fatty acids derived from oily fish [2]. Based on these observations and the findings from prospective observational studies, components of these diets have, sensibly, been the focus of many dietary guidelines. The manufacture of nutriceuticals and therapeutic foods (such as margarines containing oleic acid or plant-derived sterol esters that lower cholesterol) is also a burgeoning industry. Despite this, the evidence base of high-quality randomized controlled trials of dietary interventions to reduce cardiovascular events, either in the primary or secondary prevention setting, is much smaller than that for pharmacological interventions, such as statin drugs.

One reason for this discrepancy is that dietary interventions are difficult to evaluate in the experimental setting of clinical trials or mechanistic studies. They are complex interventions whose individual components vary depending on the diet studied. Their uptake also requires a high degree of commitment from trial participants, and off-protocol uptake of a healthier diet by those assigned the control intervention may lead to an artificial diminution of treatment effect. In this issue of Clinical Science, Ambring and co-workers [3] make a valiant attempt to evaluate the effect over 4 weeks of a Mediterranean-inspired diet which, in comparison with an ordinary Swedish diet, contained twice the amount of fibre, 4–9 times more antioxidants, three times the

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amount of polyunsaturated and ω-3 fatty acids, and which was additionally supplemented with sterol esters given as an ingredient in margarine. Using a randomized crossover design with a 4-week washout period, subjects were found to achieve decreases in total and LDL (low-density lipoprotein)-cholesterol, triacylglycerols (triglycerides) and apo B (apolipoprotein B) of approx. 20 % after 4 weeks of a Mediterranean diet, but these favourable lipid changes were not associated with improvements in endothelial function in resistance vessels assessed by forearm venous occlusion plethysmography, the primary end-point of the study. There were also no changes in indices of oxidant stress, arterial distensibility or fibrinolytic capacity and, of note, no increase in HDL (high-density lipoprotein)-cholesterol. The absence of a carry-over effect on plasma lipids between the arms of the study suggests such dietary interventions need to be maintained to sustain the changes in lipid profile.

As the authors discuss [3], the failure to detect an improvement in endothelial function in this study could reflect a lack of adequate statistical power, the relatively short duration of the dietary intervention or the fact that the subjects studied were young and had a reasonable baseline risk factor profile. In subjects at higher risk, including healthy elderly men and women [4], patients with diabetes or hypercholesterolaemia [5,6] and patients recovering from recent myocardial infarction [7], Mediterranean-style diets for between 6 weeks to 12 months were associated with improvements in endothelial function.

The effects on lipid profile noted by Ambring and co-workers [3] are also of interest. Although similar changes have been documented in some other trials of Mediterranean diet [8], they have not been seen in all [9–11]. Indeed, a small number of clinical trials with hard end-points have provided evidence of a protective effect of Mediterranean diet in the secondary prevention setting, despite the absence of major lipid changes [9–11]. Further trials, with a larger sample size, would clarify the effect of the Mediterranean diet on plasma lipid fractions, allow a more reliable assessment of the size of any protective effect in terms of cardiovascular events and allow an assessment of whether any benefits are mediated through or independent of lipid changes.

Pharmacological therapies to lower blood pressure or cholesterol, or to achieve an antiplatelet activity have been notably successful in both high-risk primary and secondary prevention settings. In clinical practice, these therapies are targeted towards those at highest risk of cardiovascular events, as the absolute benefit in such individuals is greater, and the risk-benefit ratio for therapies with a finite rate of adverse effects, such as aspirin, is more favourable. Nevertheless, the majority of clinical cardiovascular events occur in individuals in mid-to-late life with average levels of these risk factors, because such individuals form the bulk of the population. Dietary and lifestyle modification of risk factors in this group would seem an attractive alternative to pharmacological therapies, but the implementation of these changes on a population scale would have large socio-political consequences. The alternative approach, that of risk factor modification for all beyond a certain age by pharmacological means, using a ‘polypill’ that combines several evidence-based therapies [12], has excited some and appalled others.

REFERENCES