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EDITORIAL COMMENT

High-Fat Diets and Cardiovascular Disease

Are Nutritional Supplements Useful?*

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Over the past two decades, significant progress has been made in the treatment of acute and chronic cardiovascular disease. Although a large part of this success has been attributable to medical and technical advances, patient education concerning the importance of cardiovascular risk factors has been pivotal. Control of risk factors such as hypertension, smoking, and hypercholesterolemia has been successful because of patient education and medication development. Tempering some of these successes, however, is the growing epidemic of obesity in the U.S. According to the National Center for Health Statistics (1999), 61% of adults in the U.S. are overweight (body mass index [BMI] 25 to 29.9 kg/m^2), and 26% are obese (BMI $\geq$30 kg/m^2).

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Elevated BMI, particularly caused by abdominal or upper-body obesity, has been associated with diseases and metabolic abnormalities including hyperinsulinemia, insulin resistance, type 2 diabetes, hypertension, dyslipidemia, and coronary heart disease. Unfortunately, obesity has also become a growing problem in children and adolescents, with the prevalence of overweight children increasing from 5% to 11% over the past 30 years (1). Whereas useful medications have been developed to treat hypercholesterolemia, no such therapies are available to counteract the detrimental effects of saturated fats or high caloric intake on cardiovascular disease.

Dietary intake of specific nutrients has been suggested as a means of modifying the progression of cardiovascular disease. One such example is the proposed use of foods rich in select vitamins or flavonoids. Epidemiologic studies have reported an inverse relationship between the total dietary intake of plant flavonoids and the incidence of a cardiovascular disease (2,3). It has also been suggested that red wine consumption may reduce coronary disease (4,5). The source of this beneficial effect is believed to be flavonoids, polyphenol derivatives of diphenylpyrans that are found in plant but not animal food products. The skins, seeds, and stems from purple grapes are rich sources of these flavonoids. However, large, prospective trials evaluating diets rich in flavonoids are lacking and, at this time, benefit can only be inferred. Similarly, observational epidemiologic studies have associated intake of antioxidant vitamins with lower cardiovascular disease risk. Although increased endogenous antioxidant levels are associated with encouraging outcomes (6), recent studies have failed to demonstrate cardiovascular benefit from vitamin supplementation (7,8).

A proposed mechanism for the beneficial cardiovascular effects of flavonoids and vitamins is enhanced bioactivity of nitric oxide (NO), a potent vasodilator and platelet inhibitor. As most acute and chronic coronary syndromes are caused by attenuated vascular reactivity associated with platelet adhesion, aggregation, and thrombus formation in areas of ruptured atheromatous plaque (9,10), it has been suggested that select flavonoids may inhibit thrombosis and enhance vasodilation by a NO-dependent process (11–13). Reported mechanisms for the flavonoid- or vitamin-dependent increase in NO have included metabolism of reactive oxygen species, as well as regulation of endothelial NO synthase transcriptional or signaling pathways (14).

The role of the vascular endothelium, which mediates vasomotor tone through NO release, has been extensively characterized. Various methods have been utilized to assess the impact of therapeutic interventions on vascular tone. Common tests used for evaluating endothelial function include studies of flow-mediated coronary or brachial artery dilation. It is well established that cardiovascular disease and coronary risk factors including cholesterol level, male gender, family history, and age, are associated with impaired endothelium-dependent vasodilation in coronary arteries (15). Various dietary and nutritional interventions have been previously shown to alter coronary or peripheral vascular reactivity. However, although studies of impaired coronary vasoreactivity have been associated with increased clinical events (16,17), outcome studies demonstrating the clinical relevance of endothelial dysfunction in the brachial circulation are still needed (18). In addition, therapies including vitamin E (19) and estrogen (20) have been associated with enhanced NO-dependent flow-mediated vascular relaxation but have failed to demonstrate cardiovascular benefit in long-term prospective trials (8).

In the current issue of the *Journal*, Plotnick et al. (21) examine the effect of nutritional supplements on flow-mediated brachial artery vasoactivity after a high-fat meal. In this study, healthy subjects were randomized to four weeks of daily supplementation with a powdered fruit vegetable juice, a powdered juice and herbal/antioxidant supplement, or placebo. The subjects then consumed a high-calorie, high-fat meal containing 14 g of saturated fat and devoid of any fruits or vegetables, and flow-mediated brachial artery reactivity was measured. An important finding of this study was that the nutrient supplement did not

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need to be consumed with the high-fat meal, although how long the changes in flow-mediated reactivity persisted was not evaluated.

The first supplement utilized in this study contained a combination of a multiple fruit and vegetable concentrates. Because of this mix of concentrates, it is unclear if these findings would be similar using other related nutrient preparations or foods. Because the active components of this supplement were not identified, and the compounds were not monitored either directly or utilizing surrogate biomarkers, it cannot be assumed that subsequent preparations of this or similar supplements will retain their vasoactive properties. Also, because the herbal extract was not tested alone, it is impossible to know if it has any beneficial effects when used in isolation. The only conclusion that can be drawn is that this extract did not lead to any significant additive effects when given with the juice concentrate powder. Whereas the fruit and vegetable concentrate appeared to be of benefit, the addition of the vitamin supplement appeared to have no additional effect on brachial function and led to an increase in total and low-density lipoprotein cholesterol as compared with the juice concentrate alone. Interestingly, a recent large prospective trial suggested that vitamin supplements negated the atherosclerotic attenuating effects of lipid-lowering drugs (22). In this study, treatment with antioxidants alone lowered the high-density lipoprotein $(HDL)_2$ level, and antioxidant therapy blunted the rise in HDL_2 seen with the lipid-altering treatment.

The mechanism for the finding of enhanced brachial reactivity after phytonutritional supplementation is not known. Although the authors demonstrate increased plasma levels of nitrate/nitrite, this does not provide enough information to determine whether the increase in NO is due to enhanced vascular release or increased bioavailability. Several findings argue against the plasma nitrate/nitrite levels as reflecting the total body NO production. These include the lack of correlation between plasma nitrate/nitrite levels and change in NO-dependent vasodilation. Also, arginine was present in the vitamin/antioxidant supplement and did not alter the nitrate/nitrite levels. Although plasma nitrate/nitrite content changed with supplementation, these levels depend upon diet and, as discussed in the study, dietary protein was not regulated, making these levels unreliable. Further complicating this measurement is the nitrite reportedly contained in the juice extract. Because of these limitations, it cannot be assumed that total NO or NO synthase activity increased in the subjects on the supplements. Although the vascular changes may be due to a direct antioxidant effect, this cannot be definitely concluded as other reactive oxygen species or antioxidants were not measured. In addition, many vitamins and phytonutrients have been shown to have nonantioxidant mechanisms for altering vascular function, including effects on signaling pathways (14). Alpha-tocopherol, as well as purple grape juice and other flavonoids, have been shown to influence vascular NO by a protein kinase C (PKC)-dependent mechanism (23,24). Reactive oxygen species may also cause activation through regulation of PKC (25); therefore, antioxidant metabolism of reactive oxygen species by phytonutrients may influence signaling activity and, potentially, vascular NO release.

In summary, the study by Plotnick et al. (21) presents intriguing data concerning a potential mechanism for the beneficial effects of flavonoid supplementation and adds to the growing information available demonstrating that substances rich in flavonoids enhance brachial function. Although these findings are notable, they are not broadly clinically relevant until tested prospectively with longer-term clinical end points. Thus, the current findings should not lead to the general recommendation of phytonutrients for the modification of cardiovascular disease; nor should these findings suggest that the clearly established diseases associated with high-fat or high-calorie diets can be offset by the use of nutritional supplements. Although these findings beckon us to draw broader implications, even if proven true in larger studies, it is doubtful that this will lead to a recommendation of high-calorie, high-fat diets. Perhaps these findings could be interpreted in a more limited manner—i.e., does the intake of a fatty meal lead to detrimental vascular effects that can be acutely treated? If validated in subjects with cardiovascular disease, would such studies lead to the use of nutritional supplementation with the occasional high-fat meal or should we just be recommending a salad with the steak dinner?

Thus, this study does not suggest that a phytonutrient or vitamin supplement is the solution for high-fat, low-fiber, low-nutrient diets but instead reinforces the positive effects of nutrient-rich fruits and vegetables. Validation of the potentially broader implication of these results, namely that intake of specific fresh fruits and vegetables is beneficial to cardiovascular health and can balance the potentially detrimental effects of the fat intake in our diet, would be of significant interest.

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