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FILE: ▪ Chocolate (*Theobroma cacao*)
▪ Vascular Function
▪ Coronary Artery Disease

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RE: Effects of Flavanol-Rich Cocoa on Vascular Function in Patients with Coronary Artery Disease

Farouque HMO, Leung M, Hope SA, et al. Acute and chronic effects of flavanol-rich cocoa on vascular function in subjects with coronary artery disease: a randomized double-blind placebo-controlled study. *Clin Sci.* 2006;111:71–80.

Evidence from population-based studies suggests that a high dietary intake of flavonoids may reduce the risk of cardiovascular disease. Although the mechanism responsible for this supposed benefit is unclear, antioxidant and antiplatelet activities and immunoregulatory properties of flavonoids, as well as beneficial effects on the epithelium, may all play a contributory role. Chocolate and cocoa (*Theobroma cacao*) have very high flavonoid contents and appear to contribute importantly to the total dietary intake of flavonoids. The main flavonoids found in cocoa are catechin and epicatechin. The objective of this study was to investigate the effects of flavanol-rich cocoa on non-invasive and invasive measurements of vascular and endothelial function in patients with chronic ischemic heart disease.

A randomized, double-blind, placebo-controlled study was conducted in 40 patients (10 women and 30 men) with a mean age of ≈61 years and angiographically documented coronary artery disease. The location of the study is not given. The subjects were randomly assigned to receive either a flavanol-rich chocolate bar and cocoa beverage (Mars, Inc. Hackettstown, NJ) daily (444 mg of flavanols and ≈107 mg of epicatechin monomer daily) or a matching placebo (19.6 mg of flavanols and ≈4.7 mg of epicatechin monomer daily) for 6 weeks. Flow-mediated dilation (FMD) of the brachial artery and systemic arterial compliance (SAC) were measured at baseline, 90 minutes after consumption of the first beverage, and at 3 and 6 weeks of the study. The responses of soluble cellular adhesion molecules and of forearm blood flow (FBF) to infusions of 3–30 μg of acetylcholine chloride (ACh)/minute and of 0.3–3 μg of sodium nitroprusside (SNP)/minute, forearm ischemia, and isotonic forearm exercise were evaluated at baseline and at 6 weeks. Biomarkers of endothelial function [soluble intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin] were also evaluated at baseline and at 6 weeks. Differences with a P value < 0.05 were considered significant.

No significant differences in FMD, SAC, or FBF were observed between groups at baseline. Neither FMD nor SAC changed significantly, acutely or chronically, in either group. No significant differences in the cell adhesion molecules or in FBF responses to ischemia, exercise, SNP, or ACh were observed in the flavanol group between baseline and 6 weeks. ICAM-1 and E-selectin did not differ significantly between the 2 treatment groups at baseline or at 6 weeks. VCAM-1 concentrations were significantly lower in the placebo group than in the flavanol group at baseline, but did not change significantly after treatment with flavanols for 6 weeks.

Several well-established measures of vascular endothelial function were investigated in response to flavanol consumption for 6 weeks. The results indicated that the treatment was safe but that the consumption of flavanol-rich cocoa did not improve endothelial vascular function or SAC in patients with coronary artery disease. This finding is in contrast with that of Heiss et al,[1] in which a benefit on vascular function was observed after a flavanol intake comparable to and in a sample size similar to that of the present study. However,the subjects in that study were on average 20 years younger than those who participated in this later study; the younger subjects also had fewer conventional cardiovascular risk factors. It is possible that the number of cardiovascular disease risk factors and severity of disease were too great for flavanol to exert a positive effect over the time frame of the present study. The authors recommend that "short- and long-term studies of younger subjects with single identifiable untreated cardiovascular [disease] risk factors should be the subject of future investigation."

Most notable in the Heiss acute study was an increase in brachial artery FMD [from 3.4 to 6.3% ($P<0.001$)] "which was associated with surrogate evidence of increased NO bioactivity" from ingestion of cocoa rich in flavanols (176mg), whereas ingestion of cocoa low in flavanols (<10mg) effected no change in FMD. The authors of the present study find "intriguing" the neutral effect of flavanol-rich cocoa on endothelial function, in the light of earlier clinical studies with short-term (2 week) consumption of purple grape juice[2] and short-and long-term (4 week) black tea consumption,[3] both producing significant improvement of brachial artery FMD in patients with CAD.

No significant effect on either systolic or diastolic blood pressure, on mean arterial pressure or heart rate was noted. It is suggested that the use of concomitant vasoactive medication for treatment of hypertension and ischemic heart disease in the study population may have offset any potential antihypertensive effect of flavanol-rich cocoa.

Finally, these researchers point out that "the lack of improvement on tests of vascular function with flavanol-rich cocoa does not signify a neutral impact on clinical vascular end points. Large and longer-term studies will be required to address such clinical questions."

—Brenda Milot, ELS

References

[1]Heiss C, Dejam A, Kleinbongard P, Schewe T, Sies H, Kelm M. Vascular effects of cocoa rich in flavan-3-ols. *JAMA*. 2003;290:1030–1031.

[2] Stein J, H., Keevil J. G., Wiebe D.A., Aeschlimann S. and Folts J.D. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary aratery disease. *Circulation*, 1999; 100:1050-1055.

[3] Duffy S.J., Keaney Jr, J.F., Holbrook M. et al. Short-and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. *Circulation* 2001;104: 151-156.

The American Botanical Council has chosen not to reprint the original article.