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File: ■ Cocoa (*Theobroma cacao*)
■ Vascular Function
■ Flavanols
■ Type 2 Diabetes

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RE: Consumption of Flavanol-Containing Cocoa Reverses Vascular Dysfunction in Diabetic Patients

Balzer J, Rassaf T, Heiss C, et al. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients: a double-masked, randomized, controlled trial. *J Am Coll Cardiol.* 2008;51(22):2141-2149.

The prevalence of type 2 diabetes mellitus is increasing worldwide and is accompanied by an increasing risk of cardiovascular disease and mortality. Prescription medications are often used extensively in an attempt to prevent and/or treat complications of type 2 diabetes; however, they are often inadequate. Observational studies have shown that lifestyle modification (e.g., increased physical activity, weight loss, and dietary changes) can prevent diabetes and its associated complications. Epidemiologic studies have recently shown an inverse correlation between flavanol consumption and mortality from cardiovascular disease and the incidence of diabetes. Flavanols are predominantly found in fruit, vegetables, tea (*Camellia sinensis*), red wine (*Vitis vinifera*), and especially cocoa (*Theobroma cacao*). The results of dietary intervention trials have shown beneficial effects of flavanols on low-density-lipoprotein (LDL) oxidation, platelet aggregation, insulin sensitivity, endothelial function, and blood pressure. The objective of the present study was to investigate the feasibility and efficacy of a dietary intervention with flavanols from cocoa on improving vascular function in diabetic patients.

Men and women aged 50-80 years on hypoglycemic medication with a history of stably treated type 2 diabetes for at least 5 years were screened for eligibility. Ten patients were enrolled in a feasibility study, and 41 patients were enrolled in an efficacy study. Both studies had a randomized, double-masked design. In the feasibility study, the subjects consumed a single cocoa drink providing 75 mg (control), 371 mg (medium content), or 963 mg (high content) flavanols on 3 separate occasions (crossover design). Flow-mediated dilation (FMD), a measure of endothelial function, was measured an hour

before and 1, 2, 3, 4, and 6 hours after ingestion of the cocoa drink. Blood samples were collected 2 hours after ingestion for the measurement of plasma flavanol concentrations. In the efficacy study, the subjects consumed 3 doses daily of either 321 mg flavanols (treatment group; 963 g/day total) or 25 mg of flavanols (control group; 75 mg/day total) for 30 days. FMD, blood pressure, heart rate, clinical variables, and plasma flavanol metabolites were measured at baseline and again on the same day 2 hours after ingestion of the day's first amount of cocoa on days 0, 8, and 30. The cocoa drinks were prepared from a dry cocoa beverage mix (made using CocoaPro® cocoa powder; Mars Inc.; Hackettstown, New Jersey), and all of the cocoa drinks were similar in other macro- and micro-nutrient, caloric and alkaloid content, taste, and appearance. The primary outcome measure was endothelial function, which was determined on the basis of FMD of the brachial artery. Secondary outcome measures included changes in plasma flavanol metabolites 2 hours after ingestion of cocoa, blood pressure, and fasting plasma glucose, plasma lipid, and glycated hemoglobin concentrations.

In the feasibility study, the mean FMD of the study population was $3.8 \pm 0.3\%$. A dose-dependent increase in FMD was observed after consumption of 371 and 963 mg flavanols, but not after ingestion of 75 mg flavanols (control). The highest FMD ($5.5 \pm 0.4\%$; $P < 0.001$ compared with baseline) occurred 2 hours after ingestion of the highest flavanol intake (963 mg). Plasma flavanols and FMD increased significantly in all of the subjects who ingested 963 mg flavanols. In the efficacy study, fasting FMD in the treatment group increased significantly from $3.3 \pm 1.1\%$ at baseline to $4.1 \pm 1.1\%$ on day 8 ($P < 0.001$) and to $4.3 \pm 1.2\%$ on day 30 ($P < 0.0001$). Significant acute-on-chronic increases (increases after consumption of the day's first amount) in FMD after flavanols ingested continued throughout the duration of the study ($P < 0.0001$). Plasma flavanol metabolites did not increase significantly in the control group but did increase significantly in the treatment group, from 1473.2 ± 670.9 nmol/L at baseline to 2177.7 ± 995.1 nmol/L ($P = 0.0027$) on day 30. No significant changes in blood pressure or in fasting plasma glucose and plasma lipid concentrations were observed in either the treatment or the control group on day 30, except for a significant decrease ($P = 0.0063$) in the LDL concentration in the treatment group. Glycated hemoglobin on day 30 was significantly lower than that at baseline in both the treatment ($P = 0.0480$) and control ($P = 0.0038$) groups.

The authors conclude that their study "clearly establishes improvements of endothelial function after regular consumption of flavanol-containing cocoa in patients with type 2 diabetes." Flavanol consumption was well tolerated with no evidence of tachyphylaxia (desensitization to the treatment). The findings indicate the therapeutic potential of flavanols for helping reduce the risk of cardiovascular disease in type 2 diabetics on medication.

—Brenda Milot, *ELS*

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