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File: ■ Cocoa (*Theobroma cacao*, Malvaceae)
■ Hemodialysis
■ End-stage Renal Disease

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RE: Cocoa Flavanol Ingestion Improves Endothelial Function in Patients with End-stage Renal Disease

Rassaf T, Rammos C, Hendgen-Cotta UB, et al. Vasculoprotective effects of dietary cocoa flavanols in patients on hemodialysis: a double-blind, randomized, placebo-controlled trial. *Clin J Am Soc Nephrol*. 2016;11(1):108-118.

An increased risk for cardiovascular disease (CVD) is seen in patients with end-stage renal disease (ESRD). Flow-mediated vasodilation (FMD) of the brachial artery is a prognostic marker in patients with cardiovascular risk factors, established CVD, and ESRD. Microvascular changes in ESRD can contribute to the development of hypertension. In subjects without renal complications, a healthy diet rich in fruits and vegetables has been linked to a lower incidence of morbidity and mortality from CVD. Intervention studies have shown that cocoa (*Theobroma cacao*, Malvaceae) flavanols (CF) exert beneficial effects on blood pressure (BP) regulation and endothelial function. Few studies have investigated the benefit of flavanols on vascular dysfunction in patients with ESRD. These authors hypothesized that CF ingestion would improve chronic and hemodialysis (HD)-induced vascular dysfunction in patients with ESRD. They conducted a double-blind, randomized, placebo-controlled trial to assess the acute and long-term effects of CF ingestion on chronic and HD-induced vascular dysfunction in patients with ESRD.

Eligible patients were enrolled at the DaVita Renal Center, Düsseldorf, Germany, and were 18 years or older with ESRD, undergoing HD, and did not have a brachial artery fistula. The study included a baseline acute treatment study to determine the safety and efficacy of a singular CF intake and a chronic treatment study based on a parallel-group design. Of 95 patients screened, 57 were enrolled. In 2012, 11 patients were selected for the study's acute treatment phase; 1 patient was lost to follow-up, leaving 10 patients in the final analysis. Of those, 5 were unavailable for the chronic study because of hospitalization or change in dialysis center. In 2013, 52 patients were enrolled in the chronic treatment phase of the study; 3 patients were lost to follow-up, leaving 49 patients in the final analysis.

All selected patients were undergoing regular HD for renal disease, and some were suffering from other conditions, including hypertension (32%), diabetic nephropathy (23%), glomerulonephritis (19%), and polycystic kidney disease (18%).

The CF test materials were low-calorie, fruit-flavored beverage mixes supplied as agglomerated powders (Mars Symbioscience; Germantown, Maryland). CF and placebo powder sachets were closely matched for macronutrients, micronutrients, calories, theobromine, and caffeine. A CF sachet contained 450 mg total CF. The patients were instructed to dissolve the sachets in 150 mL water; they consumed 2 sachets in the acute study and daily in the chronic study. Dietary intake was assessed by interviews at baseline, during the study, and at a follow-up visit. The baseline acute crossover study, a trial, was conducted from October to November 2012. FMD measurements, plasma CF metabolites, and hemodynamics were obtained before the patients drank the test beverages and hourly for 4 hours. After a 1-week washout period, the patients returned to drink the alternate beverage.

FMD of the brachial artery was measured to assess endothelial function. Also measured were pulse-wave velocity, BP, epicatechin and related metabolites, nitrite and nitrate, and advanced glycation end-product carboxymethyl lysine. The inflammation marker hs-interleukin 6 and the oxidative stress marker oxidized low-density lipoprotein (OxLDL) also were assessed.

The authors report that acute CF ingestion improved conduit artery function, with enhanced FMD and a maximum response at 2 hours after CF intake compared with placebo ($P<0.001$). This finding corresponded to a 53% flavanol-induced FMD increase with no change in nitroglycerin-mediated vasodilation. The improved vascular function was associated with increased plasma CF metabolites. CF were well tolerated and did not affect plasma potassium or pH levels, BP, or heart rate.

The subsequent chronic treatment study was conducted from January to November 2013. The authors report improved macrovascular function in the 24 patients who ingested CF for 30 days. FMD increased 18% in the CF group compared with baseline ($P<0.001$), which was a significantly greater increase ($P<0.001$) compared with the placebo group ($n=25$).

After the chronic treatment trial, no significant effects were observed between groups in aortic stiffness, intima-media thickness, plasma nitrate and nitrite, serum markers of inflammation, myocardial ischemia, or other clinical parameters. In the CF group, 1 serious adverse effect (bleeding) and 3 adverse effects (angina, dizziness, and reflux) occurred. In the placebo group, 3 adverse effects (pruritus and dizziness twice) were reported.

To investigate the potential interaction and impact of CF on HD-induced acute vascular dysfunction, the authors performed measurements before, during, and after a single HD session. They found that a single CF ingestion alleviated HD-induced vascular dysfunction during and after HD compared with placebo ($P<0.001$) and was associated with reduced systolic BP during HD and reduced diastolic BP after HD.

Despite the studies' limitations noted by the authors (measuring only surrogate outcomes, inclusion of patients on maintenance HD, and not preselecting those with ESRD caused by other diseases in which CF might have had a different effect), they conclude that their results show "CF ingestion is well tolerated and improves endothelial functions in ESRD patients. CF mitigate chronic and HD-induced vascular dysfunction in ESRD" and may potentially "ameliorate vascular dysfunction in this high-risk population." Mars Symbioscience partially funded the study and provided the CF test products and analytical standards.

—Shari Henson

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