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File: ■ Cocoa (*Theobroma cacao*)
■ Theobromine
■ High-density Lipoprotein (HDL) Cholesterol

HC 061331-475

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RE: Theobromine Is the Cocoa Component Responsible for Increasing High-density Lipoprotein (HDL) Cholesterol

Neufingerl N, Zebregs YEMP, Schuring EAH, Trautwein EA. Effect of cocoa and theobromine consumption on serum HDL-cholesterol concentrations: a randomized controlled trial. *Am J Clin Nutr*. June 2013;97(6):1201-1209.

Low serum high-density lipoprotein cholesterol (HDL-C) is an inverse risk factor for cardiovascular disease (CVD). Lowering low-density lipoprotein cholesterol (LDL-C) and increasing HDL-C are important factors in reducing CVD risk. Although some clinical studies have reported that cocoa (*Theobroma cacao*) increases HDL-C concentrations, others have not confirmed that benefit. The cardioprotective effects of cocoa are attributed mostly to its flavonoids; however, evidence on how those flavonoids affect lipid levels is lacking. Whether the flavonoids or theobromine, another bioactive component of cocoa, is responsible for increasing HDL-C concentrations is unclear. These authors conducted a multicenter, randomized, double-blind, placebo-controlled, parallel trial to investigate whether theobromine by itself or together with cocoa can increase HDL-C concentrations and if theobromine has any effect on blood pressure and heart rate.

The authors recruited subjects from the database of Eurofins Optimed Clinical Research centers in Grenoble and Lyon, France, who met the following inclusion criteria: 10-year risk of developing CVD of <10% based on the European low-risk chart; and healthy ranges of blood lipids, blood pressure, heart rate, blood glucose, and other biochemical and hematologic variables. Conducted between December 2010 and February 2011 at 2 sites in Grenoble and Lyon, France, the study began with a 2-week run-in period, followed by a 4-week intervention period.

Of the 152 healthy men and postmenopausal women aged 40 to 70 years who were recruited at baseline, 143 completed the intervention period and were included in the full analysis.

At baseline, the subjects were randomly assigned to 1 of the 4 following treatment groups to consume 1 of the following 200 mL test drinks daily:

- Cocoa intervention (CC group): 6 g of cocoa powder (Acticoa™; Barry Callebaut; France), naturally providing 150 mg of theobromine and 325 mg of flavonoids
- Theobromine intervention (TB group): 850 mg of pure theobromine (Fagron; The Netherlands)
- Theobromine and cocoa intervention (TB+CC group): 6 g of cocoa powder and 850 mg of added pure theobromine, providing a total of 1000 mg of theobromine and 325 mg of flavonoids
- Placebo group: No cocoa powder and no added theobromine

All drinks were manufactured by Unilever (Englewood Cliffs, New Jersey) Research and Development, and all contained approximately 80 kcal, 3 g of fat, 11 g of carbohydrates, and 3 g of protein per 200 mL drink. The subjects were instructed to consume the test drink 1 hour before breakfast. All drinks were consumed out of tinted bottles to maintain blinding. Throughout both the run-in and intervention periods, participants were instructed to exclude all chocolate and cocoa-containing products from their diet, as well as limit their consumption of caffeine-containing drinks to <4 servings per day, since caffeine is converted in the body into theobromine.

The subjects visited the study center on 2 consecutive days at baseline (the last day of the run-in period and the first day of the intervention period—visits 1 and 2) and again on 2 consecutive days at the end of the intervention period (the last day on which the test product was consumed and the following day—visits 3 and 4). On each of the 4 study visit days, fasting blood samples were drawn. Body weight was measured at baseline and on visit 4. In a subsample of the subjects (10 per treatment group), ambulatory blood pressure and heart rate were measured on visits 2 and 3. The authors report a 99.7% compliance rate.

From baseline to visit 3, plasma concentrations of theobromine increased 5-fold in the CC group, 17-fold in the TB group, and 19-fold in the TB+CC group. Plasma caffeine concentrations at baseline and at visit 3 were generally low in all groups, except in the TB+CC group, which saw a doubling of caffeine concentrations ($P<0.05$). "The doubling of plasma caffeine concentrations in the TB+CC group may be explained by the competition between caffeine and theobromine, which are both methylxanthines, for metabolic pathways," write the authors.

At 4 weeks, a significant effect on HDL-C concentrations was seen in the TB group but not in the CC group. In the TB group, HDL-C increased by 0.16 mmol/L (2.88 mg/dL) ($P<0.0001$) compared with baseline. LDL-C concentrations were significantly lower in the TB group ($P=0.0155$) compared with baseline, but not in the other groups. No significant interaction effects between the TB group and the CC group was noted for either of these variables.

The TB group experienced significantly increased apolipoprotein A1 ($P<0.0001$) and decreased apolipoprotein B ($P=0.0015$) concentrations compared with baseline. Apolipoprotein A1 and apolipoprotein B are the major apolipoproteins of HDL and LDL particles, respectively. The CC group experienced a small significant increase in apolipoprotein A1 ($P=0.0148$). No significant interaction effects between the TB group and the CC group on apolipoprotein A1 and apolipoprotein B were noted. No significant effects on total cholesterol or triacylglycerol concentrations were recorded.

In the subset of subjects, no significant effects were observed for either 24-hour systolic or diastolic blood pressure or 24-hour heart rate among the groups. Examining the hourly mean data, however, revealed that heart rate acutely increased by 10-15 beats per minute during the first few hours after consumption of the test product in the TB and TB+CC groups. This cardiac-stimulating effect, which is an undesirable side effect, has also been reported in previous studies with theobromine and other methylxanthines.[1,2]

Mild-to-moderate adverse effects (nausea, vomiting, headache, and diarrhea) were reported, mainly in the TB and TB+CC groups, and were resolved before the study's end. These contributed to the withdrawal of 8 subjects, 6 of which were in the TB+CC group.

Among the study's limitations, say the authors, is that they did not investigate possible physiologic mechanisms to explain how theobromine increases HDL-C. "Clearly, additional studies are required to address the effects of theobromine on possible biological targets to explore the underlying mechanisms of action for the increase in HDL cholesterol," they write.

According to the authors, their findings suggest that theobromine is the major active component in cocoa that is responsible for increasing HDL-C.

—Shari Henson

References

[1]Riksen NP, Smits P, Rongen GA. The cardiovascular effects of methylxanthines. In: Fredholm BB, ed. *Methylxanthines*. Heidelberg, Germany: Springer-Verlag Berlin; 2011:413-437.

[2]Smit HJ. Theobromine and the pharmacology of cocoa. In: Fredholm BB, ed. *Methylxanthines*. Heidelberg, Germany: Springer-Verlag Berlin; 2011:201-234.