Cocoa Flavonoids for Prevention of CVD: State of the Science

Written by Mary Mosley

Although it is long been suggested that antioxidants may have protective effects against cardiovascular disease (CVD), recent studies suggest that cardiovascular benefits are limited specifically to foods that are sources of polyphenol antioxidants, such as flavonoid-rich cocoa (FRC). The body of evidence for a beneficial effect with cocoa is building, but data from long-term randomized controlled trials with CVD endpoints such as death and myocardial infarction are required before recommending cocoa flavonoid intake for the prevention of CVD, stated Eric L. Ding, ScD, of Harvard School of Public Health, Boston, Massachusetts, USA.

Whereas an older meta-analysis found total flavonoid intake to be associated with lower risk of coronary heart disease (CHD) mortality in a 2006 study [Ding EL et al. *Nutr Metab (Lond)* 2006], higher quality studies in recent years have limited the benefits to cocoa flavonoids. A recent and comprehensive systematic review and meta-analysis of 24 RCTs with 1106 participants and a mean cocoa flavonoid dose of 500 mg daily showed that FRC was associated with improvement in multiple cardiovascular risk factors, including blood pressure (BP), lipids, insulin resistance, and flow-mediated dilation (FMD; Table 1) [Shrime MG et al. *J Nutr* 2011]. Total cholesterol, triglycerides, and

Table 1. Effect of Flavonoid-Rich Cocoa on Cardiovascular Risk Factors

Outcome	Number of Studies	Mean Cocoa Flavonoid Dose	Change (95% CI)	p Value
SBP (mm Hg)	20	496 (282)	− 1.63 (− 3.1, − 0.13)	.03
DBP (mm Hg)	19	441 (214)	− 0.97 (− 2.3, 0.35)	.15
Pulse (beats/minute)	12	397 (209)	1.07 (− 1.3, 3.5)	.39
Total cholesterol (mg/dL)	19	410 (199)	− 2.95 (− 6.9, 0.96)	.14
LDL cholesterol (mg/dL)	19	411 (229)	− 2.96 (− 5.8, − 0.17)	.04
HDL cholesterol (mg/dL)	18	430 (249)	1.77 (0.11, 3.4)	.04
Triglycerides (mg/dL)	18	379 (187)	− 3.16 (− 6.7, 0.36)	.08
C-reactive protein (mg/L)	5	429 (94)	− 0.03 (− 0.10, 0.03)	.31
BMI (kg/m^2)	11	596 (209)	0.10 (− 0.05, 0.25)	.20
FMD (%)	9	596 (300)	1.53 (0.67, 2.4)	.00
HOMA-IR	5	457 (286)	− 0.94 (− 1.3, − 0.59)	.00
QUICKI	4	796 (257)	0.01 (− 0.002, 0.03)	.08
ISI	3	492 (112)	4.95 (2.8, 7.1)	.00
Fasting glucose (mg/dL)	7	403 (252)	− 0.18 (− 2.1, 1.7)	.85

BMI=body mass index; DBP=diastolic blood pressure; FMD=flow-mediated dilation; HDL=high-density lipoprotein; HOMA-IR=homeostasis model assessment of insulin resistance; ISI=insulin sensitivity index; LDL=low-density lipoprotein; QUICKI=quantitative insulin sensitivity check index; SBP=systolic blood pressure.

Adapted from Shrime et al., *J Nutr* 2011.

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C-reactive protein were unchanged. Of note, there was a nonlinear dose response between FRC and FMD, with the maximum effect achieved with the 500-mg daily dose. This is the first meta-analysis to evaluate the effect of FRC on all CVD risk factors and a dose–response relationship, and its limitations include the trials being short term (2 to 18 weeks) and not having access to patient-level data, said Dr. Ding. In addition, another meta-analysis of cocoa flavonoids performed by researchers from Harvard also found benefits for lowering insulin and improving insulin resistance [Hooper L et al. *Am J Clin Nutr* 2008].

The Zutphen Elderly Study, a prospective cohort study of 470 men in the Netherlands who were followed for 15 years, was among the high-quality studies that showed an association between cocoa intake and reductions in CVD and total mortality [Buijsse B et al. *Arch Intern Med* 2006]. Subject who had the highest amount of cocoa intake were associated with reduced risk of CV death (adjusted relative risk, 0.50; 95% CI, 0.32 to 0.78; p = .004) and all-cause death at 15 years (adjusted relative risk, 0.53; 95% CI, 0.39 to 0.72; p < .001) as compared to subjects with the least amount of ingestion.

A systematic review and meta-analysis of 7 nonrandomized studies showed that higher versus lower levels of chocolate consumption were associated with a reduced risk of any CVD (relative risk, 0.63; 95% CI, 0.44 to 0.90) [Buitrago-Lopez A et al. *BMJ* 2011]. Further evidence for an association between chocolate consumption and reduction in stroke came from the Cohort of Swedish Men study of 37,103 men that found a 17% relative risk reduction in the highest (62.9 g/week) versus the lowest (0 g) quartiles of consumption [Larsson S et al. *Neurology* 2012] and a meta-analysis of 5 studies that showed a relative risk reduction of 0.81 for stroke (95% CI, 0.73 to 0.90) [Larsson S et al. *Neurology* 2012].

The evidence of benefit with FRC and chocolate from preclinical, prospective cohort, and short-term clinical studies to prevent CVD has provided the framework for long-term RCTs with hard CVD endpoints. Planning is underway for the Cocoa Supplement and Multivitamins Outcomes Study [COSMOS], led by researchers from Brigham and Women's Hospital and Harvard Medical School, that will begin in 2015 and enroll 18,000 men and women who are free of CVD to determine the effect of high-quality cocoa flavanol supplementation (750 mg daily) and also a multivitamin in a double-blind, placebo-controlled, 2×2 factorial study.

HMO Effective Against Rotavirus Diarrhea in Experimental Studies

Written by Mary Mosley

Rotavirus infection is reduced by breastfeeding in the first year of life (Panda S et al. *Epidemiol Infect* 2014). Human milk oligosaccharides (HMO) are thought to contribute to this protection, in part by binding to some rotavirus strains and interrupting virus binding to host cell glycoconjugate receptors.

The burden of rotavirus infection is significant. In 2008, based on global surveillance by the World Health Organization, rotavirus was estimated to cause 25 million outpatient visits, >2 million hospitalizations [http://www.who.int/biologicals/areas/vaccines/rotavirus/background/en/], and >453,000 deaths in children aged <5 years [http://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/]. The greatest disease burden is in developing countries where the availability of rotavirus vaccines is limited and also seems to be less effective [Patel MM et al. *Pediatr Infect Dis J* 2011].

Sharon M. Donovan, PhD, RD, University of Illinois, Urbana, Illinois, USA, reviewed work by her group that tested the hypothesis that HMO, particularly those forms containing sialic acid, would decrease rotavirus infectivity by reducing binding and modulating gut microflora.

In a set of experiments to screen for rotavirus inhibitory activity *in vitro*, they found that sialyllactose-containing HMO and HMO isolated from preterm human milk (iHMO) inhibited infectivity and binding of sialic acid-dependent rotavirus at those concentrations present in human milk [Hester SN et al. *Br J Nutr* 2013]. They also found dose-dependent effects for binding and infectivity, which were more effective at a lower concentrations with 6'-sialyllactose than with 3'-sialyllactose; the groups believes that this distinction may be related to differences in the structures of the cellular binding sites. Dr. Donovan stated these results support sialic acid-dependent rotavirus binding by sialic acid-containing HMO as a primary mechanism of action.

Next, they studied the ability of HMO to inhibit rotavirus activity *in situ* using a piglet model. They showed that both sialic acid-containing HMO and a neutral HMO (lacto-N-neotetraose, LNnT) decreased rotavirus infectivity in isolated loops of intestine [Hester SN et al. *Br J Nutr* 2013], suggesting other possible mechanisms for the effect of HMO. Dr. Donovan noted that this study was also important for establishing a model that will allow for the screening of different HMO fractions, such as neutral and acidic, in order to determine which are most