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COMMENTARY

Chocolate for CV Health: What's the Evidence?

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For as long as I can remember, chocolate has been touted as a "no-no" for anyone trying to lose weight, or indeed for anyone simply trying to be health conscious. So what underlies the latest hype about chocolate's health benefits? Is there any truth to it?

My thoughts about chocolate and its ostensible preventive effects on cardiovascular disease (CVD) were reawakened by an intriguing announcement about a study being conducted by medical institutions and organizations of renown: the Brigham and Women's Hospital, the Fred Hutchinson Cancer Research Center, and the Women's Health Initiative. Started earlier this year, the 5-year, large-scale randomized controlled trial is testing the effect of a concentrated cocoa extract and multivitamin supplements in reducing the risks for CVD and cancer.

The Cocoa Supplement and Multivitamin Outcomes Study (COSMOS) will help determine whether concentrated cocoa extract can help reduce heart disease and stroke and whether commonly used multivitamin supplements can help reduce the risk for cancer, particularly in older women. It must be emphasized that the cocoa supplement to be studied is a highly concentrated extract of cocoa flavanols. This is not a study about eating chocolate!

How Did We Get Here?

A wide continuum of health benefits have been ascribed to chocolate; or, more specifically, flavanol-rich chocolate. I'd like to focus on the potential benefits in hypertension.

But first, it is important to differentiate between cacao, cocoa, and chocolate. The raw seeds obtained from the *Theobroma cacao* tree are referred to as cacao.[1] The seeds of the *T cacao* tree are rich in a subclass of polyphenol antioxidants known as flavonoids, specifically the flavanols catechin and epicatechin.[2] Once these seeds are processed by grinding or roasting them, the product becomes cocoa. Further processing and the addition of multiple other ingredients, including sugar and fat, result in the solid edible product we call chocolate.[3]

The medicinal use of cocoa has a long history dating back almost 500 years, when Hernán Cortés first encountered the drink in Mesoamerica.[4,5] Even before Cortés, Mayans and Aztecs took beans from the cacao tree and made a drink they called "xocoatl." Aztec Indian legend relates that cacao seeds were brought from Paradise, and that wisdom and power came from eating the fruit of the cacao tree.

More recently, the effects of plant flavanols on mammalian cells have attracted substantial interest, with investigative attention focused on the potential of these agents to modulate and even reverse CVD and cancer.[4] Several epidemiologic studies designed to examine a possible protective effect of flavanols in CVD have reported inverse associations—the more flavanols, the less disease.[5-13]

Increased oxidative stress and impaired nitric oxide bioavailability are the principal features of vascular dysfunction and can be detected as abnormal coronary vasomotion in response to diverse endothelium-dependent stimuli, including acetylcholine or the cold pressor test (CPT).[8,11] In patients with intact vascular function, both acetylcholine and CPT induce vasodilation. By contrast, patients with a dysfunctional endothelium have a paradoxic vasoconstriction, putting them at increased risk for cardiovascular events.[13] A landmark finding that untangled the importance of cocoa flavanols in CVD was the discovery that flavanols activated nitric oxide synthase in humans.

These considerations have focused attention on the potential salutary effects of plant flavanols. Epidemiologic studies have suggested a possible protective effect of flavanols in CVD.[11,12] Cocoa is the richest source of flavanols, although current processing of cocoa substantially reduces the flavanol content.

Studies in the Kuna Amerinds

An intriguing step toward delineating the potential effect of flavanols on cardiovascular health and disease derives from interesting studies conducted in the Kuna Indians (Amerinds).[13-15] The Kuna Amerinds of Panama are known to have low blood pressure levels and manifest only a negligible increase in blood pressure as they age.

This striking absence of hypertension was first documented by Kean almost 70 years ago.[13] Kean was a medical officer in the US Army, stationed in the Canal Zone in Panama where many Kuna Amerinds worked. Kean was intrigued by the low blood pressures of the Kuna. An obvious question was whether the absence of hypertension was attributable to protective genes or environmental factors. Twenty years ago, Hollenberg and colleagues[6,16] initiated a comprehensive study of the Kuna Amerinds that provided the link to our understanding of Kean's clinical observation.

A brief history of how the Kuna Amerinds settled on the San Blas Archipelago is worth retelling. The San Blas Islands are off the Caribbean coast of Panama. This archipelago has been home to the Kuna since the time of the Spanish Conquistadors. The Spanish Empire reached its peak of political and economic power under the Spanish Habsburgs during the 16th, 17th, and 18th centuries. During this period, the Spanish stole tons of gold and silver from the Inca Indians in what are now Chile and Peru, taking it to Spain. Because Chile and Peru are on the Pacific side of the Americas, and Spain is on the Atlantic side, the Kuna were coerced by the Spanish to carry the gold and silver over the Isthmus of Panama.

The death rate was very high among the Kuna, so some groups traversed the dense jungle and escaped to the San Blas Islands. Their diet there includes a significant intake of liquid cocoa made from local cacao, contributing about 1000 mg/day of flavanol. Consequently, the Kuna probably have the most flavanol-rich diet of any existing population.

Flavanols and Mortality

In 2007, Hollenberg and colleagues[17] from the University of Panama School of Medicine conducted an observational study to discern whether flavanol intake was associated with mortality. These investigators accessed the diagnosis on death certificates to compare cause-specific death rates from 2000 to 2004 in mainland Panama and in the San Blas islands, where only Kuna Amerinds live. Their hypothesis was that if high flavanol intake and consequent activation of the nitric oxide system were important in mediating the reduction in hypertension and cardiovascular events, the result would be a discernible reduction in the frequency of ischemic heart disease, stroke, diabetes, and cancer—all nitric oxide-sensitive processes.

The investigators reported that in mainland Panama, CVD was the leading cause of death (83.4/100,000), followed by cancer (68.4). By contrast, the rates among island-dwelling Kuna were dramatically lower (9.2 for CVD and 4.4 for cancer). Similarly, deaths due to diabetes were much more common in the mainland (24.1/100,000) than in the San Blas islands (6.6).

The investigators suggested that these comparatively lower risk levels among Kuna in the San Blas might be related to their very high flavanol intake and sustained nitric oxide synthesis activation. However, because this was an observational study and because many risk factors can affect hypertension, the study did not provide definitive evidence of a link.

Cocoa Flavanols, Nitric Oxide, and Cardiovascular Health

In 2000, Karim and colleagues[18] documented the influence of cocoa flavanols on endothelial function in the rabbit aorta. Subsequently, Fisher and colleagues[6] extended that observation to healthy human subjects, finding that 4 days of flavanol-rich cocoa ingestion induced "striking" vasodilation. These investigators used a cocoa "dose" that was calculated from studies of the Kuna to provide about 900 mg of epicatechin per day. Because the cocoa-induced vasodilator response was reversed completely by arginine analogs that are known to block nitric oxide synthesis, such as L-NAME, the authors concluded that nitric oxide constituted the major, if not the sole, determinant of the vasodilator response. The study also showed that treatment with flavanol-poor cocoa did not induce the vasodilator response, thereby indicating that flavanols were the major determinant of the vasodilator response.

Finally, urine samples from Kuna living on the islands and those on the mainland demonstrated a statistically significant correlation between the chronic consumption of cocoa flavanols and elevated urinary excretion of nitric oxide metabolites. In concert, these observations demonstrate that, in humans, the ingestion of the flavanol epicatechin is linked, at least in part, to the vascular effects observed after the consumption of flavanol-rich cocoa.[19]

Chocolate, Cocoa, and Blood Pressure

Determining the role of chocolate in hypertension seems like it should be as simple as feeding people chocolate and measuring their blood pressures, but several relevant variables must be considered. What is being administered, chocolate or cocoa? What is the flavanol content of the cocoa (or chocolate), and what dose is employed? Are study participants young or old, hypertensive or normotensive? For how long is the cocoa or chocolate administered? What is the control? Whereas Hollenberg[17] and Fisher[6] used flavanol-poor cocoa as controls, other investigators have administered sham chewing or white chocolate to those in the control arm, resulting in a lack of double-blind administration and a confounding of the placebo effect.

Perhaps because of the many differences in study design, the effect of cocoa on blood pressure remains incompletely defined. Fisher and colleagues[6] found no relationship between blood pressure and a high dose of unambiguously flavanol-rich cocoa in normotensive healthy subjects studied for less than a week. By contrast, a meta-analysis found that both cocoa and chocolate induced a drop in systolic and diastolic blood pressures in elderly patients with hypertension.[12] Likewise, Taubert and colleagues[9] demonstrated a significant reduction in blood pressure with as little as one square of chocolate a day in patients with high-normal or mild hypertension. In the Zutphen Elderly Study, cocoa intake was inversely related to blood pressure in 470 elderly men.[20]

The Antioxidant Properties of Dark Chocolate

Dark chocolate contains high levels of the flavanols that exert antioxidant properties, and emerging evidence suggests a potential benefit of a variety of flavanol-rich foods and beverages on cardiovascular events. In a double-blind, randomized, placebo-controlled clinical trial in patients with congestive heart failure, Flammer and colleagues[21] compared the effect of commercially available flavanol-rich chocolate with cocoa-liquor-free control chocolate on endothelial and platelet function. They demonstrated that flavanol-rich chocolate acutely improves vascular function and inhibits platelet function in patients with congestive heart failure.

Ding and colleagues[22] have reviewed the range of potential mechanisms through which flavanols and cocoa exert benefits on cardiovascular health. The proposed mechanisms include activation of nitric oxide and antioxidant, anti-inflammatory, and antiplatelet effects, which in turn may improve endothelial function, lipid levels, blood pressure, and insulin resistance.

Where Does That Leave Us?

In light of studies suggesting that flavanol-rich chocolate may confer cardiovascular benefits, should we consider cocoa to be a cardiovascular nutraceutical? To the contrary, important caveats are in order. During the conventional chocolate manufacturing process from fresh cocoa seeds to the final product, the concentration of flavanols is markedly reduced.[23]

Moreover, the term "dark chocolate" is misleading; nothing about the color of the chocolate indicates the flavanol content. For example, the process of adding alkali-potash to cocoa nibs ("dutching") enhances the taste, texture, and appearance of the cocoa, eliminating the bitterness along with most of the active flavanols.[24] Alkalization also results in a darkening of the cocoa, producing a very dark chocolate that is essentially devoid of flavanols.

Fermentation and roasting also have a detrimental impact on the flavanol content of foods. In addition, the concentration of flavanols may depend on the origin of the raw cocoa.[25] Milk chocolate has the lowest flavanol content compared with cocoa powder and dark chocolate.[26]

Finally, the high caloric load of commercially available chocolate (about 500 kcal/100 g) may cause weight gain, which is itself a risk factor for hypertension, dyslipidemia, and diabetes.

The experimental road to delineating the putative benefits of flavanol-rich chocolate is challenging, albeit potentially rewarding. Many lines of evidence suggest that flavanol-rich chocolate may confer cardiovascular benefits, including lowering blood pressure, improving insulin sensitivity, and possibly lowering the risk for congestive heart failure.[27]

While we await the results of the COSMOS study, my recommendation is to rely on exercise and the DASH diet to enhance cardiovascular health. If you are a "chocoholic," it is fine to eat dark chocolate, but at present solely for enjoyment—not yet on the pretense that we are indulging for medicinal benefits.

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