

EDITORIAL COMMENT

## Flavanol-Rich Cocoa

### A Promising New Dietary Intervention to Reduce Cardiovascular Risk in Type 2 Diabetes?\*

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Atherosclerotic cardiovascular disease represents the leading cause of the morbidity and mortality associated with type 2 diabetes (1). Well-established epidemiological data indicate that diabetic patients have a risk of incident myocardial infarction and stroke twice as high as that of the general population, with worse survival after their first event and subsequently increased mortality rates (2). Overall, approximately three-quarters of patients with type 2 diabetes mellitus will develop and possibly die of macrovascular disease, with a dramatic loss of life expectancy, quality of life, and impact on healthcare costs (3,4). Encouraging clinical trial evidence suggests that some of the available treatments for type 2 diabetes and an aggressive approach to risk factor reduction may decrease incident cardiovascular events and delay the onset of complications in diabetic patients (5). However, when compared with the general population, the excess risk conferred by diabetes has declined only marginally (6), partly because only a minority of diabetic patients achieves the recommended levels of control (3). Therefore, alternative approaches to the primary and secondary prevention of atherosclerosis in this population are highly needed.

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Given the impact of eating habits on cardiovascular disease and the epidemiological evidence of protective factors present in the diet of specific populations (7), significant emphasis has recently been placed on the identification of dietary elements exerting beneficial effects on the vasculature and on the elucidation of their molecular mechanism. The flavonoids, a ubiquitous class of plant-derived polyphenols, have been proposed as likely candidates, given the link between an increased dietary intake of

these phytochemicals and a reduction in cardiovascular events (8). The flavonoids comprise several distinct subclasses, which are present in different concentrations in various foods, including, but not limited to, red wine, black tea, onions, apples, and cocoa (9). While red wine and tea have attracted the initial focus of the scientific community, only in the last decade attention has been brought to the flavanol-rich cocoa. The interest in the effects of cocoa intake on the cardiovascular system was initially triggered by the observation that the indigenous Kuna Indians, a population living in an island off the coast of Panama, have a very low incidence of hypertension (10) and significantly lower death rates for ischemic heart disease, stroke, diabetes, and cancer when compared with the Kuna Indians living in urban Panama city (11). Among the potential factors underlying the differences between the 2 populations, dietary habits were found to be the most likely candidates. In particular, the high intake of home-prepared cocoa, extremely rich in flavanols, in the indigenous Kuna appeared to confer a relevant protective effect (9). Numerous subsequent investigations have also confirmed the inverse relation between dietary cocoa, blood pressure, and cardiovascular mortality in Western populations (12), and have laid the foundation for studies aimed at elucidating the underlying pathophysiological mechanisms. Given the role of the endothelium in hypertension and atherosclerosis, research efforts have focused on the acute and chronic effects of flavanol-rich cocoa on endothelial vasodilator function. After the initial report of strong peripheral nitric oxide (NO)-dependent vasodilation in healthy subjects (13), flavanol-rich cocoa has been shown to reverse endothelial dysfunction, measured as flow-mediated dilation (FMD) of the brachial artery, in smokers (14) and in hypertensive patients (15). Of note, in the latter population, dark chocolate also decreases low-density lipoprotein cholesterol, lowers blood pressure, and improves insulin sensitivity (15). Furthermore, in an intriguing study in heart transplant recipients, dark chocolate has been shown to improve endothelium-dependent responses in the coronary circulation and to decrease shear stress-induced platelet adhesion (16), suggesting that flavanols may directly affect atherothrombosis. However, whether similar beneficial actions are also present in patients with type 2 diabetes is unknown.

In this issue of the *Journal*, Balzer et al. (17) address this lack of knowledge by reporting the results of a study on the acute and chronic effects of flavanol-containing cocoa intake on the vascular function of treated type 2 diabetic patients between ages 50 and 80 years. The primary outcome measures were changes in FMD of the brachial artery, a well-established noninvasive technique to assess NO-dependent endothelial function. The secondary outcomes included changes of the plasma concentration of free flavanols (epicatechin, catechin), and their respective conjugated flavanol metabolites, measured by high-pressure liquid chromatography. To overcome several of the limitations of previous investigations, the authors first

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conducted a *feasibility study* on 10 patients to determine the appropriate dosing, assess safety and tolerability, and measure the effect size of the intervention in order to calculate the appropriate sample size of the subsequent *efficacy study*. The *efficacy study* was undertaken using a randomized, double-masked, parallel-group design and included 44 patients randomly allocated to a treatment group (321 mg of flavanols per dose; 3 doses per day) or a control group (25 mg of flavanols per dose; 3 doses per day). Each group ingested a single dose of either treatment or control 3 times a day over a period of 30 days. The authors assessed the acute effects, 2 h after ingestion of the control or the cocoa drink, and the long-term effects, on days 8 and 30.

The authors report that, in the *feasibility study* population, acute ingestion of the medium and high dose of flavanols caused dose-dependent increases in plasma flavanol metabolite levels and improved FMD by 44% ( $p < 0.001$ ). Importantly, endothelium-independent nitroglycerin-mediated dilation was not affected by any of the dietary interventions. In the *efficacy study*, fasting plasma levels of flavanol metabolites increased by 46% on day 8 ( $p < 0.01$ ) and by 48% on day 30 ( $p < 0.01$ ). The daily consumption of flavanol-containing cocoa by patients assigned to the treatment group resulted in consistent increases in baseline FMD. The acute effects on FMD in the treatment group were of similar effect size at study entry and after 8 and 30 days of regular cocoa intake. In accordance with the finding of the *feasibility study*, nitroglycerin-mediated dilation was similar between the 2 groups and was not affected by the dietary interventions.

The results of this study answer several important questions. First, does the ingestion of flavanols result in a dose-dependent and predictable increase in the plasma levels of long-standing diabetic patients? Previous investigations have shown that nutrients in the diet may not reach physiological levels in subjects with diabetes (18), possibly secondary to abnormal gastrointestinal function (19). Therefore, a lack of effect of a dietary intervention would not necessarily be secondary to a lack of pharmacodynamic activity. The data reported in this investigation indicate that flavanol intake in diabetic patients results in plasma levels consistent with those observed in nondiabetic subjects (14,15), suggesting that absorption of flavanols is not a limiting factor in this population and that flavanol clearance is not increased. Second, are the vascular effects biologically relevant and sustained over time? The patient population of this study had baseline FMD values that were lower than the reference values measured in the same laboratory. After the acute ingestion of a flavanol-rich cocoa drink, FMD values were normalized, indicating temporary reversal of endothelial dysfunction. Of note, in the treatment group, baseline FMD increased steadily and the magnitude of the acute effect was maintained over time, suggesting a lack of significant desensitization or tolerance. Importantly, the vascular responses to nitroglycerin administration were not affected by any of the interventions and remained constant over time, confirming the hypothesis that the changes in

vascular function are secondary to the effects of treatment on endothelial function and NO bioavailability.

In summary, this elegant investigation addresses many of the reservations raised toward previous studies. The *feasibility study* allowed the authors to determine the dose and the appropriate sample size for the efficacy trial. Participants were carefully selected and represented a typical diabetic population. The cocoa drinks were standardized and matched for caloric, nutritional, caffeine, and theobromine content and had similar taste. The results of the *efficacy study* clearly showed sustained effects of high flavanol cocoa intake on vascular function over a period of 30 days.

These findings expand previous observations to patients with type 2 diabetes and represent a further step in our understanding of the vascular effects of flavanol-rich cocoa. However, although endothelial function has been shown to predict future cardiovascular events (20), randomized, large scale clinical trials assessing relevant clinical outcomes are necessary before any recommendations are made regarding dietary supplementation with flavanol-rich cocoa.

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