See corresponding article on pages 203 and 348.

Flavonoid consumption and cardiometabolic health: Potential benefits due to foods, supplements, or biomarkers?

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Higher intake of fruit and vegetables, nuts, and whole grains has each been prospectively associated with lower morbidity and mortality of cardiometabolic diseases (CMDs) in adults (1–4). These consistent observations from high-quality and large prospective cohorts strongly implicate that substances rich in plant foods may confer important cardiometabolic benefits. Yet, it remains a matter of debate which specific micronutrients, minerals, phytochemicals, and/or bioactive components of these plant foods may be responsible for cardiometabolic protection (5). Polyphenols such as flavonoids have been shown to have antioxidant, anti-inflammatory, and antithrombotic properties and may improve vascular endothelial function, insulin secretion, and action, as well as lower blood pressure (6). To date, mechanistic studies have come from animal experiments and small, short-term clinical studies that have not evaluated the clinical relevance of any effects attributed to flavonoids.

In this issue of the *American Journal of Clinical Nutrition*, 2 independent research groups report complementary novel findings that further implicate the roles of flavonoid-rich foods to changes in biomarkers and improvements in carotid intima-media thickness (cIMT) or stroke risk. First, in the population-based Guangzhou Nutrition and Health Study (GNHS) of 2572 men and women aged 40–75 y followed for 8.8 y, Zuo et al. (7) measured isoflavone biomarkers, including daidzein, genistein, equol, and total isoflavones, at 2 time points (baseline and year 3) and prospectively related these markers to the progression of cIMT measured at baseline, year 3, and year 9. Whether measured in serum or urine, baseline concentrations of total and individual isoflavones were each directly and inversely associated with subsequent changes in common carotid artery-cIMT. Most interestingly, Zuo et al. (7) also observed that the inverse associations of serum equol with changes in CCA-cIMT were mediated by increased sex hormone binding globulin (SHBG) and decreased systolic blood pressure, suggesting that isoflavones may have direct and favorable effects on hormonal and hemodynamic components of CMD.

To date, many individual polyphenols have been identified in biological samples, and serum concentrations of these biomarkers are typically known to have large within-person variations, representing numerous interactive forces in the absorption, distribution, metabolism, and excretion processes. This raises many questions for future evaluation. First, how sensitive and specific are these biomarkers to specific dietary intake? Are there other dietary, lifestyle, or clinical determinants that may confound the relations of interest? It seems highly probable that the inverse relations between isoflavones and cIMT observed were simply due to greater intake of plant-based foods (e.g., soy intake and dietary fiber) and their effects on serum LDL, as soy products containing isoflavones are known to lower serum total cholesterol and LDL cholesterol (8, 9). Zuo et al. (7) did adjust for the intake of soy protein in their models and showed that the associations remained. Moreover, there were no significant differences in intake of soy protein according to cIMT. Indeed, these differences in cIMT by serum isoflavone concentrations are consistent with findings from a recent meta-analysis indicating a reduction of cardiometabolic risk markers beyond LDL cholesterol associated with greater intake of another type of flavonoids, cocoa flavanols (6), including 0.11 mmol/L (95% CI: −0.24, 0.01, $P = 0.08$) in plasma glucose, 2.51 uIU/mL (95% CI: −3.80, −1.22, $P < 0.001$) in plasma insulin, 0.78 points (95% CI: −1.13, −0.43, $P < 0.001$) in HOMA-IR, and an increase of 1.97 points (95% CI: −0.15, 4.08, $P = 0.07$) in insulin sensitivity index.

Most interestingly, Zuo et al. (7) also reported that serum and urine concentrations of equol—a non-steroidal estrogen—were directly related to cIMT and that the relations were mediated by SHBG concentrations among GNHS participants. Equol is produced from the isoflavone daidzein by colonic microflora, which has been shown to have large interindividual variations, and those who consume greater amounts of plant foods and

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Abbreviations used: cIMT, carotid intima-media thickness; CMD, cardiometabolic disease; COSMOS, Cocoa Supplement and Multivitamin Outcomes Study; CVD, cardiovascular disease; GNHS, Guangzhou Nutrition and Health Study; SHBG, sex hormone binding globulin.

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dietary fiber are more likely to be equol producers (10–12). The prevalence of equol producers is ∼25% in GNHS participants, with some notable differences by sex. The novel findings reported by Zuo et al. (7) indicate that equol concentrations may have significant long-term effects on vascular function and clinically meaningful CMD in Chinese men and women. Future research should investigate isoflavones and their biological intermediaries as measures for interactions (gene-diet-microbiota), rather than simply as an "objective" measure for intake of isoflavone-rich foods.

In another report from a prospective cohort of 55,169 Danish adults followed for 21 y, Parmenter et al. (13) examined the association of dietary flavonoid intake with the risk of ischemic stroke. Flavonoid intake was estimated using a semiquantitative FFQ at baseline. Compared with participants in the lowest quintile of total flavonoid intake (median of 174 mg/d), those with total flavonoid intake >395 mg/d (the upper 3 quintiles) had an apparent 10% lower risk of ischemic stroke, although additional adjustment for dietary factors attenuated the effect. Interestingly, spline analyses indicate a potential nonlinear, L-shaped relation in which total flavonoid intake >395 mg/d did not appear to confer further benefit. Parmenter et al. (13) also examined the patterns of ischemic stroke risk for individual flavonoid components that generally paralleled the findings for total flavonoids with a possible exception for a modestly greater magnitude of risk reduction for flavanol oligo + polymers. Overall, this is a high-quality, large prospective cohort of Danish adults with long-term follow-up and negligible loss to follow-up. Similar inverse relations between intake of flavonoids and risk of peripheral artery disease hospitalizations have recently been observed in the same cohort of Danish men and women (14).

Taken together, the findings from these 2 prospective studies add to the suggestive evidence that increased intake of flavonoid-rich foods may lower the risk of cardiometabolic disease, although these articles also highlight a challenge presented by the vast heterogenous and diverse nature of phenolic subclasses and food sources. Moreover, these 2 original reports reflect different perspectives in this research domain, with Zuo et al. (7) focused more on mechanism through isoflavone biomarkers and cIMT, whereas Parmenter et al. (13) emphasized the overall effect of dietary total flavonoids and subclasses on the clinical outcome of ischemic stroke. What should be the next step? To date, there remains a lack of large randomized controlled trials that directly and definitively evaluate the long-term effect of intake of flavanols (either through diet or supplements) on the risk of CMDs, including stroke or relevant measures of glucose homeostasis.

Optimally, both real-world observational studies and controlled-intervention trials should connect intake of flavanols to corresponding changes in biomarkers and changes in both short-term intermediate outcomes and longer-term clinical outcomes. The Cocoa Supplement and Multivitamin Outcomes Study (COSMOS), a large-scale, long-term randomized clinical trial testing a cocoa extract supplement on cardiovascular disease (CVD) in 21,444 older US adults (15, 16), recently completed its intervention phase and will contribute important data on the effect of cocoa flavanols on CVD along with an understanding of the role of associated biomarkers and intermediate CMD outcomes as supported by a meta-analysis on cocoa flavanols on cardiometabolic risk markers (6). Yet, the COSMOS trial represents a focused page within the overall flavonoid story, no different from these 2 informative original reports of prospective analyses in the *American Journal of Clinical Nutrition*. Whether via observational studies or intervention trials, future work on flavonoids must place its findings with precision in the context of both the specific components of flavonoids tested and their connections with specific health outcomes to inform healthy dietary practices.

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