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**Dietary Fructose and Elevated Levels of Blood Pressure**

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Hypertension is a multifactorial disease in which both genetic and environmental factors play a role in the slope of changing

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BP with increasing age.¹ Most health care providers and patients alike are aware of the relationship between increasing dietary salt and BP. There is also evidence this relationship may be modified by increasing dietary potassium consumption.²³ Moreover, more recent data indicate an increasing ratio between vegetable and animal protein in the diet may reduce the risk for development of incident hypertension.⁴

The article by Jalal et al.⁵ in this issue of JASN adds to a growing body of literature indicating that increasing amounts of dietary fructose, whether in the foods we eat or in sugar-sweetened beverages, associates with higher levels of BP in adults without a history of hypertension. The authors conducted a cross-sectional analysis collected from the National Health and Nutrition Examination Survey (NHANES) between 2003 and 2006 involving more than 4500 adults without a history of hypertension. After adjusting for demographics; comorbidities; physical activity; total kilocalorie intake; and dietary confounders such as total carbohydrate, alcohol, salt, and potassium intake, they note that increased daily fructose intake (>74 g) independently and significantly associates with greater odds for elevated levels of BP. Dietary fructose >74 g/d associates with a 30% higher risk for a BP >140/90 mmHg. This dietary fructose intake corresponds to an equivalent of approximately 2½ sugar-sweetened beverages each day.

There is substantial additional evidence supporting a relationship between sugar-sweetened beverages and elevated BP. Recently, Chen et al.⁶ performed a prospective analysis of 810 adults who participated in an 18-month behavioral intervention trial and noted that at baseline, the mean sugar-sweetened beverage intake was 0.9 ± 1.0 per day. They used a mixed-effects model to estimate the changes in BP in response to changes in sugar-sweetened beverage consumption after controlling for potential confounders. A reduction of just one sugar-sweetened beverage per day was associated with a statistically significant 1.8/1.1-mmHg reduction in BP during a period of 18 months, even after adjustment for weight change during the same period.

Another cross-sectional study like the work of Jalal et al.⁵ demonstrated a positive association between sugar-sweetened beverages and the risk for hypertension. Data from the Nurses Health Study indicated a strong positive association between cola beverage intake and hypertension risk.⁷ Similarly, an analysis of data from the Framingham Offspring study⁸ noted the consumption of soft drinks, both regular and diet soda combined, associates with an increased, although not statistically significant, risk for higher levels of BP. Earlier cross-sectional findings from NHANES, similar to the database used by Jalal et al.⁵ but from 1999 to 2004, demonstrated that among adolescents from the United States, there is a positive association between sugar-sweetened beverage consumption and BP.⁹ Thus, the observations by Jalal et al.⁵ are in complete concert with previously published findings.

The mechanism by which increased dietary fructose increases BP is uncertain.⁵ Some investigators suggested that if sugar-sweetened beverages are the primary source of fructose, then the co-ingestion of caffeine may boost BP¹⁰,¹¹; however, tolerance to caffeine-induced BP changes often builds up, which limits enthusiasm for thinking caffeine may be the culprit. Experimental studies in animals also demonstrated a variety of dietary sugars including glucose, fructose, and sucrose can induce hypertension.¹²–¹⁴ This has led some investigators to believe sugar perhaps may enhance activity of the sympathetic nervous system.¹⁵ Others have also thought that increased ingestion of dietary sugar reduces sodium excretion, creating a salt-sensitive state with higher levels of BP in the face of increasing dietary salt.¹⁶ Johnson and colleagues¹⁷,¹⁸ also suggested that increasing fructose consumption raises BP by increasing serum uric acid, which could have direct vascular effects to limit endothelial nitric oxide production or activate the renin-angiotensin system.

Whatever the mechanism, these observations have important public health implications. Although dietary fructose and sugar-sweetened beverages are linked in part to the obesity epidemic,¹⁹ many of the observations of these studies demonstrate effects on BP independent of kilocalorie intake and weight gain. If modest reductions in sugar-sweetened beverage consumption on the order of one to two per day could reduce daily fructose consumption to <74 g, then this could conceivably result in a 3- to 4-mmHg decrease in systolic BP. Not only might this reduce incidence and mortality from stroke and coronary heart disease by measurable levels, but it also may delay prehypertension and incident hypertension. This change in pattern of diet may be more feasible than radically reducing dietary salt consumption or altering the ratio of vegetable to animal protein in the diet.

Although the mechanism to explain the relationship between dietary fructose and sugar-sweetened beverages and elevated levels of BP remains unknown, what is clear is that modifying their intake may have profound effects on the future risks for cardiovascular disease in our aging population that is already struggling with an epidemic of obesity.

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DISCLOSURES

None.

REFERENCES

Two centuries after its discovery, digitalis remains perennially controversial, even as it is largely supplanted by newer, safer drugs. For atrial fibrillation, β blockers and calcium channel blockers offer better rate control than digoxin; for congestive heart failure (CHF), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, β blockers, and aldosterone antagonists have a proven survival advantage. Consensus guidelines have become increasingly cautious: In 2005, the American Heart Association/American College of Cardiology Heart Failure guidelines downgraded digoxin from a class I recommendation (in 2001) to class IIa; the 2009 update added special cautions about dosing and levels. Overall use has declined from approximately 80% of patients with systolic heart failure to 30%, yet no less a scientist and statesman than Eugene Braunwald recently urged a large National Institutes of Health–sponsored trial of low-dosage digoxin for acute CHF.

The basic clinical facts about digoxin for nondialysis patients come from two venerable randomized trials. In the Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial of 178 patients,4 withdrawal of digoxin from patients who had an ejection fraction of ≤35% and were tolerating the drug well (an important caveat—these were survivors already) carried a 5.9-fold relative risk of death or heart failure, and no survival benefit or detriment: Reduced rates of heart failure admission and death from pump failure were neutralized by increased rates of other cardiovascular death, presumably from arrhythmias. Subsequent analyses of this and other studies suggested that serum levels of digoxin <1.0 ng/dl are sufficient for inotropic benefit, whereas lethal arrhythmias occur predominantly at levels >1.0 ng/dl.

For nephrologists, the role of digoxin in hemodialysis patients would seem less controversial. The narrow therapeutic window, long half-life, and the potential for lethal arrhythmias of the drug—especially in the context of hypokalemia—are