Just a spoonful of sugar helps the blood pressure go up

Expert Rev. Cardiovasc. Ther. 8(11), 1497–1499 (2010)

Stephanie Nguyen

Department of Pediatrics, University of California, Davis, CA, USA

Robert H Lustig

Author for correspondence: Department of Pediatrics, University of California, San Francisco, 513 Parnassus Ave, Box 0434, San Francisco, CA 94143-0434, USA
Tel.: +1 415 502 8672
Fax: +1 415 476 8214
rlustig@peds.ucsf.edu

"The US FDA recently announced plans to regulate salt consumption in an effort to curb this epidemic. But might they have missed something? Could it be our sugar intake as well?"

While thoroughly endearing, Mary Poppins isn't a doctor, and her medical advice is highly suspect. Hypertension, both as a primary phenomenon and as a component of the metabolic syndrome, has been increasing in prevalence over the last two decades [1,2]. Naturally, dietary indiscretion is the main culprit, but which dietary factor? The US FDA recently announced plans to regulate salt consumption in an effort to curb this epidemic [3]. But might they have missed something? Could it be our sugar intake as well?

"Naturally, dietary indiscretion is the main culprit, but which dietary factor?"

The US annual sugar intake is now 156 lbs per capita, or 22 teaspoons per day, which far exceeds recommendation guidelines [4,5]. Sugar-sweetened beverages (SSBs) are the main contributing factor, accounting for 33% of added sugar in the US diet. In recent years, fructose (50% of sucrose or 55% of high-fructose corn syrup) has come under scrutiny as a primary causative factor for hypertension.

How does fructose raise blood pressure? Fructose is thought to be a primary etiologic agent in the pathogenesis of obesity and metabolic syndrome, which secondarily raise blood pressure [6,7]. However, fructose may play a primary role in the pathogenesis of hypertension as well. Animal models demonstrate that a high-fructose diet leads to hypertension and renovascular damage [8]. Possible mechanisms include: enhancing the sympathetic nervous system [9], decreasing urinary sodium excretion [10], increasing sodium absorption in the gut [11], and in particular through uric acid production, which decreases levels of the intrinsic vasodilator nitric oxide [12]. Fructose is metabolized exclusively by the liver, which is the only organ with the requisite Glut5 transporter [13]. In the liver, fructose is immediately converted to fructose-1-phosphate by the enzyme fructokinase. This is an ATP-requiring reaction, depleting the hepatocyte of intracellular phosphate [14]. This leads to activation of the scavenger enzyme AMP deaminase-1, which converts the adenosine phosphate breakdown products (ADP, AMP and IMP) to uric acid [15]. Buildup of uric acid in the circulation inhibits endothelial nitric oxide synthase, resulting in decreased nitric oxide, our endogenous vascular smooth muscle relaxant, with resultant blood pressure elevation [16]. This pathway is clinically relevant as blockage of uric acid synthesis can lower blood pressure. In an experimental model of high fructose feeding for 2 weeks in adults, allopurinol prevented both uric acid and blood pressure elevation [17]. Furthermore, in a randomized, double-blind, placebo-controlled crossover trial, 30 hypertensive adolescents with serum uric acid higher than 6 mg/dl were given

Keywords: fructose • hypertension • metabolic syndrome • sugar • uric acid

EXPERT REVIEWS

 10.1586/ERC.10.120 ISSN 1477-9072

allopurinol, a xanthine oxidase inhibitor, to lower uric acid for 4 weeks [18]. Allopurinol lowered casual systolic blood pressure by 5 mmHg over placebo (p = 0.009). Along with lowering serum uric acid, allopurinol also lowered plasma renin activity and systemic vascular resistance index, both indicators of hypertension and vascular damage.

> "Others have found that sugar-sweetened beverage consumption correlates with blood pressure elevation in adolescents..."

Human data relating fructose consumption to uric acid and hypertension comprise cross-sectional, longitudinal and interventional studies. Multiple large cross-sectional studies in free-living populations with real-world dietary intake have demonstrated the association of SSB consumption with elevated serum uric acid [19–22]. In the largest study, Bomback *et al.* found that there were 12 and 31% increased odds of hyperuricemia when subjects consumed one soda/day and more than one soda/day, respectively. However, the authors did not find a statistically significant association using the same data set to look prospectively at the development of new cases of hyperuricemia. Others have found that SSB consumption correlates with blood pressure elevation in adolescents, although concurrent caffeine ingestion may have been a confounding risk factor [23]. When we examined SSB consumption with uric acid and blood pressure in adolescents using the US National Health and Nutrition Examination Survey (NHANES) database, we found that SSB consumption correlated with 0.18 mg/dl higher serum uric acid (p = 0.01) and 0.17 higher systolic blood pressure z-score (p = 0.03) after adjusting for multiple confounders such as BMI and dietary factors [22]. Furthermore, multiple cross-sectional studies have found that SSB consumption is associated with elevated blood pressure [22,24–28].

The longitudinal data in natural history studies relating fructose to hypertension have been somewhat more confusing. Studies from the Framingham and Framingham Offspring Study did not find a statistically significant risk for the development of hypertension with increasing SSB consumption [26]. In the larger Nurses Health Study, the authors found that SSBs and diet sodas both increased the risk for the development of hypertension [28]. When other authors included the Nurses Health Study with data from the Health Professionals Follow-up Study, they found that percent fructose consumption was not associated with the development of hypertension [29].

Finally, there are the interventional data: fructose feeding in adults has also been found to yield inconsistent results. Perez-Pozo *et al.* found a marked increase in both uric acid and blood pressure after 2 weeks of high-fructose feeding [17], while Stanhope *et al.* found no effect of high-fructose feeding on blood pressure after 10 weeks [30]. Furthermore, when subjects with hypertension owing to intrinsic renal disease were given high-fructose diets for 6 weeks, blood pressure did not increase significantly [31]. Currently, the best prospective epidemiologic evidence that reducing SSB consumption can lower blood pressure is from the PREMIER study, an 18-month randomized controlled behavioral trial to reduce blood pressure in 810 normotensive and hypertensive adults [32]. Three points can be taken from this study. First, a reduction of SSB consumption by one serving per day decreased systolic blood pressure by 1.8 mmHg and diastolic blood pressure by 1.1 mmHg. After adjusting for weight loss during the trial, reducing SSB consumption by one serving per day reduced systolic blood pressure by 0.7 mmHg and diastolic blood pressure by 0.4 mmHg. Clearly, the effect size was much smaller, but these results do show that reducing SSB consumption can lower blood pressure independently of its effect on weight. Second, there was a significant dose–response relationship between SSB consumption and blood pressure. Those with the greatest reduction of SSB consumption had the biggest benefit; a mean reduction of systolic blood pressure of 7.2 ± 4.3, 8.0 ± 4.3 and 9.5 ± 4.3 mmHg across tertiles (p < 0.001). For those who were hypertensive, there was a reduction in the proportion of participants who were hypertensive by 17, 18.5 and 23.5% (p < 0.001) across the tertiles of SSB consumption. Finally, reduction in blood pressure occurred in those who were normotensive as well as hypertensive, which argues for benefit to the general population. While most of the benefit may occur due to weight loss, there does appear to be an independent effect that sugar itself contributes to blood pressure. In the larger context, for the general normotensive adult population, a 2-mmHg reduction of systolic blood pressure would lower mortality from stroke by 10% and from ischemic heart disease by 7% [33].

> "Currently, the best prospective epidemiologic evidence that reducing sugar-sweetened beverage consumption can lower blood pressure is from the PREMIER study..."

The current overconsumption of fructose and its potential for cardiovascular pathology, including hypertension on its own and within the constellation of the metabolic syndrome, has led the American Heart Association to issue a 2009 scientific statement remanding the USA to cut its added sugar consumption by two-thirds, from 22 teaspoons/day to six teaspoons/day for women and nine teaspoons/day for men [34]. Given that fructose is not an essential nutrient, and the global increases in obesity, Type 2 diabetes and metabolic syndrome, this is a timely and accurate prescription.

In conclusion, if Mary Poppins hadn't supplied the spoonful of sugar, maybe her charges wouldn't have needed the medicine in the first place.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 303(20), 2043–2050 (2010).

2 Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care* 27(10), 2444–2449 (2004).

3 Mitka M. IOM recommends Federal regulation over the salt content of certain foods. *JAMA* 303(22), 2238–2240 (2010).

4 US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for Americans, 2005 (6th Edition)*. US Government Printing Office, Washington, DC, USA (2005).

5 Marriott BP, Olsho L, Hadden L, Connor P. Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003–2006. *Crit. Rev. Food Sci. Nutr.* 50(3), 228–258 (2010).

6 Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. *J. Am. Diet Assoc.* 110(9), 1307–1321 (2010).

7 Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat. Rev. Gastroenterol. Hepatol.* 7(5), 251–264 (2010).

8 Sanchez-Lozada LG, Tapia E, Jimenez A *et al.* Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. *Am. J. Physiol. Renal Physiol.* 292, F423–F429 (2006).

9 Brito JO, Ponciano K, Figueroa D *et al.* Parasympathetic dysfunction is associated with insulin resistance in fructose-fed female rats. *Braz. J. Med. Biol. Res.* 41(9), 804–808 (2008).

10 Rebello T, Hodges RE, Smith JL. Short-term effects of various sugars on antinatriuresis and blood pressure changes in normotensive young men. *Am. J. Clin. Nutr.* 38(1), 84–94 (1983).

11 Singh AK, Amlal H, Haas PJ *et al.* Fructose-induced hypertension: essential role of chloride and fructose absorbing transporters PAT1 and Glut5. *Kidney Int.* 74(4), 438–447 (2008).

12 Feig DI, Mazzali M, Kang DH *et al.* Serum uric acid: a risk factor and a target for treatment? *J. Am. Soc. Nephrol.* 17(4 Suppl. 2), S69–S73 (2006).

13 Drouard V, Ferraris RP. Regulation of the fructose transporter Glut5 in health and disease. *Am. J. Physiol. Endocrinol. Metab.* 295, E227–E237 (2008).

14 Fiaschi E, Baggio B, Favaro S *et al.* Fructose-induced hyperuricemia in essential hypertension. *Metabolism* 26, 1219–1223 (1977).

15 Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. *Kidney Int.* 73, 489–496 (2008).

16 Nakagawa T, Tuttle KR, Short R, Johnson RJ. Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. *Nat. Clin. Pract. Nephrol.* 1(2), 80–86 (2006).

17 Perez-Pozo SE, Schold J, Nakagawa T *et al.* Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int. J. Obes. (Lond.)* 34(3), 454–461 (2010).

18 Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 300(8), 924–932 (2008).

19 Bomback AS, Derebail VK, Shoham DA *et al.* Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. *Kidney Int.* 77(7), 609–616 (2010).

20 Choi JW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 59(1), 109–116 (2008).

21 Gao X, Qi L, Qiao N *et al.* Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension* 50(2), 306–312 (2007).

22 Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J. Pediatr.* 154(6), 807–813 (2009).

23 Savoca MR, Evans CD, Wilson ME, Harshfield GA, Ludwig DA. The association of caffeinated beverages with blood pressure in adolescents. *Arch. Ped. Adolesc. Med.* 158(5), 473–477 (2004).

24 Bremer AA, Auinger P, Byrd RS. Relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999–2004 National Health and Nutrition Examination Survey. *Arch. Pediatr. Adolesc. Med.* 163(4), 328–335 (2009).

25 Denova-Gutierrez E, Talavera JO, Huitron-Bravo G, Mendez-Hernandez P, Salmeron J. Sweetened beverage consumption and increased risk of metabolic syndrome in Mexican adults. *Public Health Nutr.* 13(6), 835–842 (2010).

26 Dhingra R, Sullivan L, Jacques PF *et al.* Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 116(5), 480–488 (2007).

27 Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J. Am. Soc. Nephrol.* 21(9), 1543–1549 (2010).

28 Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA* 294(18), 2330–2335 (2005).

29 Forman JP, Choi H, Curhan GC. Fructose and vitamin C intake do not influence risk for developing hypertension. *J. Am. Soc. Nephrol.* 20(4), 863–871 (2009).

30 Stanhope KL, Schwarz JM, Keim NL *et al.* Consuming fructose-, not glucose-sweetened beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J. Clin. Invest.* 119, 1322–1334 (2009).

31 Van der Schaaf MR, Koomans HA, Joles JA. Dietary sucrose does not increase twenty-four-hour ambulatory blood pressure in patients with either essential hypertension or polycystic kidney disease. *J. Hypertens.* 17(3), 453–454 (1999).

32 Chen L, Caballero B, Mitchell DC *et al.* Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. *Circulation* 121(22), 2398–2406 (2010).

33 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360(9349), 1903–1913 (2002).

34 Johnson RK, Appel LJ, Brands M *et al.* Dietary sugars intake and cardiovascular health. A scientific statement from the American Heart Association *Circulation* 120, 1011–1020 (2009).