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Just a spoonful of sugar helps the blood pressure go up

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“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

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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, Bombback *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.

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