

## Review Article

# The Impact of Fructose on Renal Function and Blood Pressure

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Fructose is a sugar present in sucrose, high-fructose corn syrup, honey, and fruits. Fructose intake has increased markedly in the last two centuries, primarily due to increased intake of added sugars. Increasing evidence suggests that the excessive intake of fructose may induce fatty liver, insulin resistance, dyslipidemia, hypertension, and kidney disease. These studies suggest that excessive intake of fructose might have an etiologic role in the epidemic of obesity, diabetes, and cardiorenal disease.

## 1. Introduction

Fructose is a monosaccharide that is widely available in natural food sources such as fruits and honey. However, in most countries the main source of fructose is from sucrose, a disaccharide composed of equal portions of fructose and glucose. In the United States another major source of fructose is high-fructose corn syrup (HFCS), which is a commercial liquid product consisting of fructose and glucose in varying proportions, but which in soft drinks is usually 55% fructose and 45% glucose.

Fructose intake has increased markedly over the last 2 centuries, primarily due to the increasing intake of sucrose and HFCS [1–3]. In particular, the introduction of HFCS in the 1970s resulted in an accelerated intake of added sugars in the USA, in part because HFCS was inexpensive and could be easily mixed in with processed foods [4]. It has been suggested that the increase in added sugars worldwide may partially explain the marked increase in frequency of overweight and obese humans and may explain the rising frequency of metabolic syndrome, diabetes, hypertension, and cardiovascular diseases (coronary artery disease, congestive heart failure, stroke, and chronic kidney disease) [1–3].

Fructose is absorbed into the intestine enterocyte by the Glut-5 specific transporter. While some fructose is metabolized in the small intestinal wall, much of it is passed via

the portal vein to the liver, with perhaps 20 to 30% escaping into the systemic circulation [5, 6]. Within the hepatocyte, fructose is phosphorylated to fructose-1-phosphate by fructokinase. Because this reaction has no negative feedback system, if sufficient fructose is present, intracellular phosphate and ATP depletion can transiently occur. This results in the generation of AMP which is metabolized by AMP deaminase to inosine monophosphate and eventually to uric acid [5]. The transient ATP depletion has some similarities to ischemia and can result in arrest of protein synthesis with the induction of oxidative stress and inflammation [7–9].

Circulating fructose is taken up by a variety of cell types, including endothelial cells, but also is excreted into the urine where it is absorbed via the Glut-5 transporter into the S3 segment of the proximal tubule. This cell also expresses fructokinase; as such, the metabolism of fructose by this proximal tubular cell can also lead to local oxidative stress and inflammation [8, 10].

## 2. Biological Effects of Fructose

**2.1. Liver Effects: Fatty Liver and Glycogen Accumulation.** Fructose is known to stimulate fat accumulation in the liver by both increasing synthesis and blocking fat oxidation [11, 12]. These effects are independent of energy intake [12–14]. Perhaps not surprisingly, clinical studies have linked

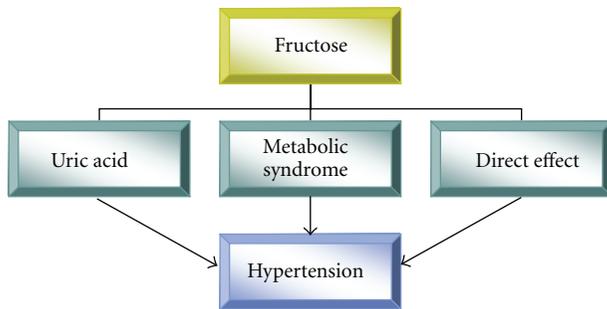


FIGURE 1: Proposed pathogenesis of fructose-induced hypertension.

the intake of excessive fructose with the development of nonalcoholic fatty liver disease in humans, and the amount of fructose ingested correlates with the risk for progression to cirrhosis [15, 16].

Fructose is also known to stimulate glycogen accumulation in the liver [17, 18], which primarily appears to be due to inhibiting glycogenolysis due to inhibition of glycogen phosphorylase [19].

**2.2. Insulin Resistance and Islet Dysfunction.** Fructose intake has been shown to induce insulin resistance in rats [20, 21]; fructose can also induce insulin resistance in humans [22]. The proposed mechanisms are complex but may include a consequence of hepatic lipid deposition, with diacylglycerol accumulation leading to activation of protein kinase [22, 23] or via the hepatic stimulation of PGC-1 $\beta$  [24]. Some of the effects may also be due to fructose-induced hyperuricemia with effects on endothelial and adipocyte function [14, 25]. However, the lowering of uric acid with allopurinol did not prevent the development of insulin resistance in subjects administered large doses (200 g/d for two weeks) of fructose [26].

Fructose intake may also accelerate the development of type 2 diabetes in rats, possibly by accelerating islet dysfunction via induction of mild islet inflammation and oxidative stress [12, 27]. One study suggests that this might be due in part to the effects of systemic uric acid that increase in response to fructose (or sucrose) ingestion [12].

Fructose may also stimulate the production of advanced glycation end products (AGEs) that have been shown to be toxic in diabetes [28]. Indeed, chronic fructose ingestion has been associated with the accelerated formation of cataracts in diabetic rats [29].

Intake of sugary soft drinks has also been associated with the development of obesity and diabetes. [30, 31] Indeed, a recent meta-analysis by Malik et al. found a strong independent relationship between the intake of sugar-containing soft drinks with the subsequent development of diabetes [32].

**2.3. Obesity.** Fructose does not acutely stimulate leptin or insulin release and hence may not trigger normal satiety responses [33]. In addition, added sugars such as sucrose have been found to trigger dopamine responses in the ventral and dorsal striatum, which chronically may lead to downregulation of the D2 receptors and sugar bingeing [34].

Fructose intake can also induce a central leptin resistance in rats, leading to increased food intake and the development of visceral obesity [35]. Interestingly, rats on a high-fructose diet may not show an increase in overall body weight unless it is associated with diets high in fat [36].

**2.4. Hypertension and Vascular Effects.** Fructose intake from added sugars is also associated with elevated blood pressure in humans [37], and diets low in added sugar have been reported to lower blood pressure [38]. Furthermore, the acute ingestion of fructose (60 g) can increase systolic blood pressure in humans, and this is not seen in subjects given the same dose as glucose [39]. In addition, in one study, overweight men were administered 200 g fructose daily for two weeks and sustained a significant increase in ambulatory blood pressure [26].

Studies in experimental animals have confirmed that fructose can raise blood pressure. Interestingly, the increase in blood pressure in response to fructose is better observed by tail cuff measurement as opposed to intra-aortic telemetry [40, 41]. However, blood pressure rises in response to sucrose or fructose diet by telemetry during the first hours of feeding [12, 42].

The mechanism of hypertension in response to fructose is complex but appears to be mediated by increased sodium absorption in the intestine, by inhibition of systemic endothelial function, and by stimulation of the sympathetic nervous system [14, 43, 44] (Figure 1). In addition, some of the effect of fructose to increase blood pressure may be the consequence of fructose-induced increases in intracellular and serum uric acid. First, fructose-induced hypertension in rats is largely ameliorated by lowering uric acid levels [40]. Second, in one study in overweight men, the rise in ambulatory blood pressure in response to 200 g of oral fructose per day for two weeks was blocked in those subjects concomitantly administered allopurinol [26].

**2.5. Kidney Disease.** Fructose and sucrose are also known to induce renal hypertrophy and tubulointerstitial disease in rats [10, 45, 46]. The mechanism may involve two central pathways (Figure 2). First, the rise in uric acid in response to uric acid may cause an afferent arteriopathy resulting in glomerular hypertension [40]. Second, fructose may also be filtered into the urine where it is taken up in the S3 segment of the proximal tubule, leading to local intracellular generation of uric acid with oxidative stress and local inflammation [8].

The administration of fructose to rats with reduced renal function (the remnant kidney model) can accelerate the progression of renal disease, resulting in worse proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis [47]. Fructose intake also impairs calcium absorption and reduces 25-OH Vitamin D and 1,25-dihydroxy Vitamin D levels in this model [48]. Furthermore, the intake of sugary soft drinks in humans is associated with increased prevalence of albuminuria [49]. Our group has also recently administered a low-fructose diet to subjects with stable chronic kidney disease for a period of 6 weeks. While we observed no effect on renal function during the period of the study, we did

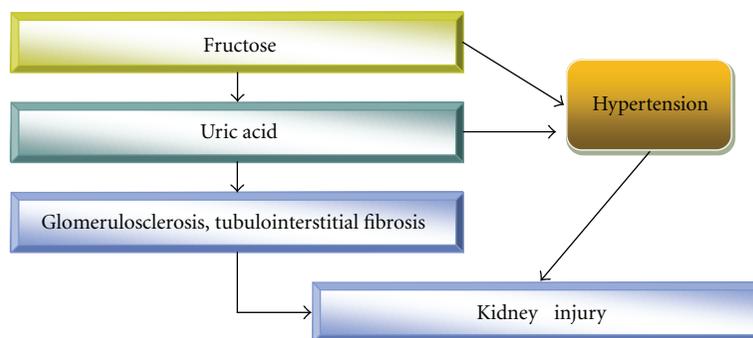


FIGURE 2: Mechanisms of kidney dysfunction in fructose-induced hypertension.

observe a reduction in inflammatory markers and a fall in blood pressure in subjects with the “dipper” physiology (i.e., those subjects whose blood pressure spontaneously falls at night during sleep) [49]. Clearly further studies are needed to determine if limiting added sugars may benefit subjects with kidney disease.

**2.6. Role of Natural Fruits.** While much work has focused on fructose as driving obesity, insulin resistance, and cardiorenal disease, not all fructose sources may be the same. Thus, natural fruits also are rich in antioxidants, ascorbate, polyphenols, potassium, and fiber that may counter the effects of fructose [13, 50]. Indeed, Forman et al. [51] reported that fructose intake did not correlate with elevated blood pressure in a population in which much of the fructose intake was from fruit, whereas Jalal et al. [37] found a strong association of fructose intake with blood pressure when the fructose content from natural fruits was excluded.

**2.7. Caveats.** While there is increasing evidence for a role for fructose as a contributory factor to obesity and metabolic syndrome, most of the data has relied on epidemiological studies, experimental models, and cell culture. In contrast, studies in which fructose or sucrose is administered to subjects have shown variable effects on metabolic parameters. In general, few metabolic effects are observed with fructose when it is given to young, healthy, and lean subjects [52–54]. This contrasts with studies in overweight/obese or insulin-resistant subjects in which metabolic effects from fructose or sucrose are commonly observed [22, 26, 55–58]. One potential explanation may relate to the absorption of fructose, which is known to increase with fructose exposure [59, 60]. Fructose effects are also potentiated by glucose [61, 62], and most studies have only examined fructose alone. Most studies also show, both in animals and humans, that the effects of fructose are greater on postprandial lipids, fatty liver, and insulin resistance rather than on weight gain per se. Indeed, the effects of fructose may be more on inducing leptin resistance, and it may require the addition of high-fat diet to show the weight gain [35]. More studies are necessary before firm conclusions can be made. Nevertheless, the evidence that excessive intake of fructose may have multiple adverse effects on human health seems to be mounting.

### 3. Conclusions

There are likely multiple mechanisms driving the current epidemic of obesity, diabetes, and cardiorenal disease. Recent studies suggest that excessive fructose intake may be one of the causes. Future studies should investigate the effect of reducing fructose intake or blocking the metabolic effects of fructose as a means for preventing or treating these important diseases.

### Disclosure

Dr. R. J. Johnson and Dr. T. Nakagawa have several patent applications on blocking the metabolic effects of fructose as a means to prevent or treat components of the metabolic syndrome. Dr Johnson also has a lay book, *The Sugar Fix* (Rodale, 2008).

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