Dietary fructose and the metabolic syndrome
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Introduction
Fructose consumption has increased dramatically over the past several decades [1], and with it the incidence of the metabolic syndrome. The metabolic syndrome is a constellation of pathologies including obesity, insulin resistance, dyslipidemia, and hypertension [2]. Fructose has been shown to be involved in the progression to metabolic syndrome, through dysregulation of many molecular signaling factors [3]. This review focuses on the mechanisms whereby fructose advances the components of the metabolic syndrome, including the effect of dietary fructose on plasma uric acid, advanced glycation end products (AGEs), inflammation, and alterations in metabolic hormones.

Evidence for fructose contribution to metabolic syndrome
There is a growing body of evidence in both animal models and human studies suggesting that high dietary intake of fructose is an important nutritional factor in the development of metabolic syndrome and its associated complications. Animal model experiments have clearly demonstrated this connection; fructose feeding in rats causes hypertension and hyperinsulinemia [4], and in hamsters it causes insulin resistance, hypertriglyceridemia, hepatic very-low-density lipoprotein over-production, obesity, and hyperglycemia [5,6]. Human studies also demonstrate fructose’s ability to change metabolic hormonal response, possibly contributing to decreased satiety.

Recent findings
Recent animal studies have confirmed the link between fructose feeding and increased plasma uric acid, a potentially causative factor in metabolic syndrome. Advanced glycation end products are also implicated because of their direct protein modifications and indirect effects on inflammation and oxidative stress. Human studies have demonstrated fructose’s ability to change metabolic hormonal response, possibly contributing to decreased satiety.

Summary
There is much evidence from both animal models and human studies supporting the notion that fructose is a highly lipogenic nutrient that, when consumed in high quantities, contributes to tissue insulin insensitivity, metabolic defects, and the development of a prediabetic state. Recently evidence has helped to decipher the mechanisms involved in these metabolic changes.

Keywords
fructose, hyperuricemia, insulin resistance, metabolic syndrome, oxidative stress
Although the detrimental effects of fructose have been well established, the mechanisms whereby this happens are only now being discovered. Several proposed mechanisms are discussed below.

**Dietary fructose and inflammation**

Studies conducted in recent years have found that dietary fructose causes inflammation, which is implicated in progression to the metabolic syndrome [1,13]. Fructose may be responsible for enhancing the production of tumor necrosis factor (TNF)-α and activation of c-Jun amino-terminal kinase (JNK), which are key mediators of the inflammatory pathway [1,3,14]. Fructose has been shown to activate the inflammatory mediator STAT-3 (signal transducer and activator of transcription-3) in rats [15**], accompanied by an increase in nuclear factor-κB, which is a key component of another inflammatory cascade. In addition to these changes, that study also showed a decrease in the activity of peroxisome proliferator-activated receptor-α, causing a decrease in fatty acid oxidation and an increase in lipid accumulation. In addition, TNF-α, a potent proinflammatory cytokine that is increased by dietary fructose in animal models [1,14], has been shown to induce intestinal insulin resistance and lipoprotein production in the hamster model [16**]. Although thus far observed only in animal studies, this discovery highlights the important link between inflammation and development of the metabolic syndrome, while further uncovering the importance of the intestine in the progression of fructose-induced metabolic disturbances.

Interestingly, although fructose does induce inflammation, it may have the ability to reduce liver damage caused by inflammation [17]. Experiments have shown that fructose minimizes TNF-receptor 1-mediated hepatic steatosis and necrosis in mice because of fructose’s ATP-depleting properties [17].

Previous studies formed a consensus that high fructose feeding directly causes hypertension [13,18**,19**,20], and this may be mediated by inflammation. Experiments have shown that plasma insulin and the free radical hydrogen peroxide were increased in rats fed high (60%) fructose [18**]. More importantly, the animals exhibited increased systolic blood pressure and increased expression of angiotensin 1 in both heart and aortic tissue, as well as increased expression of aortic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-4 and vascular cell adhesion molecule-1, indicating increased oxidative stress and inflammation, respectively. These changes were all reversed by treatment with captopril, an angiotensin-converting enzyme inhibitor. Its effectiveness in reducing fructose-mediated hypertension and associated gene fluctuations implicates the renin–angiotensin system in the fructose effect. Further experimentation has demonstrated that fructose added to a diet high in salt significantly affects mortality in rats [19**], as compared with different macronutrient diet compositions. After 90 days of 70% fructose and 6% NaCl administration only 15% of the rats survived, as compared with 70% of rats fed complex carbohydrate plus salt. These findings indicate that fructose has a very profound effect on inflammation and hypertension, and this effect can be complicated further by combination with other dietary components.

**Dietary fructose and hyperuricemia**

High plasma uric acid levels have long been recognized to be associated with aspects of the metabolic syndrome, including obesity, hypertension, and cardiovascular disease [21]. Fructose has the unique ability, compared with other dietary sugars, to raise plasma uric acid levels [21,22]. Plasma uric acid levels are also independently associated with metabolic syndrome, indicating that the two are somehow linked [23*,24*,25–29]. Plasma uric acid is associated not only with increased body weight but also and specifically with visceral fat accumulation [24*]. Induction of hyperuricemia in rats causes several aspects of the metabolic syndrome, including hypertriglyceridemia, hyperglycemia, and hypertension [22]. A study of 5000 humans showed a strong correlation between fructose intake and hyperuricemia [30*]. In addition, fructose-fed rats treated with the uric acid-lowering agent allopurinol exhibited improved in the metabolic syndrome [31]. These data support hyperuricemia as a causative factor in metabolic syndrome progression.

Now that uric acid has been established as being strongly correlated to the metabolic syndrome, how might it exert this effect? As mentioned earlier, one popular theory is that uric acid reduces plasma levels of the vasodilator nitric oxide. Sustained decrease of nitric oxide eventually causes hypertension, which is an essential feature of the metabolic syndrome [22]. In addition, nitric oxide may play a role in escalating hyperinsulinemia. Normally, insulin increases endothelial nitric oxide bioavailability, dilating blood vessels and enabling glucose to reach skeletal muscle easily [21,22]. When nitric oxide secretion is impaired, glucose uptake is reduced and more insulin is secreted to compensate [21,22].

A recent study [32] showed that uric acid increases oxidative stress in adipose tissue indirectly, via activation of NADPH oxidase, leading to a decrease in total nitric oxide concentration [33**]. Reactive oxygen species produced by NADPH oxidase caused increased lipid oxidation and increased activation of the mitogen-activated protein kinases p38 and extracellular signal-regulated kinase-1/2. This study provides further evidence
for the association between uric acid, oxidative stress, and inflammation, leading to metabolic syndrome.

Increased plasma uric acid is also a risk factor for renal disease [21]. Hyperuricemia was found to worsen renal disease in rats, and is an independent risk factor for renal disease in humans [21]. Dietary fructose has been connected to increased plasma uric acid, which is associated with renal disease. Recently, in order to verify the conclusion that dietary fructose directly causes renal dysfunction, rats were fed 60% fructose and developed hypertension, hyperuricemia, and hypertriglyceridemia [34**]. The rats also developed kidney problems including hypertrophy, glomerular hypertension, and reduced glomerular flow. These results are similar to previous observations on rats with induced hyperuricemia, indicating that fructose may be exerting its effects on the kidney via increased plasma uric acid. A second study [35] showed that a 60% fructose diet accelerated kidney disease in rats with surgically induced chronic kidney disease. This effect may be mediated by hyperuricemia or by other components of the metabolic syndrome, including inflammation or hyperinsulinemia.

Thus far few studies have directly investigated the use of uric acid-lowering drugs such as allopurinol to treat the metabolic syndrome or its associated pathologies. As mentioned above, one study showed that allopurinol improves the metabolic syndrome in rats [31], but other results indicate that allopurinol administered to humans had no effect on glucose tolerance, plasma insulin levels, triglycerides, cholesterol, or glucose [36]. Future work is necessary to determine whether plasma uric acid is a worthwhile pharmacologic target.

**Dietary fructose and advanced glycation end products**

Commonly associated with hyperglycemia, AGEs are produced by a nonenzymatic reaction between sugars and protein or lipids [37*]. Slowly metabolized proteins such as collagen and elastin are most vulnerable to this reaction because of their increased exposure time [38*]. The formation of AGEs has both direct and indirect effects associated with the metabolic syndrome. Directly, AGEs decrease the solubility of collagen and elastin [39], contributing to atherosclerosis. Indirectly, AGEs contribute to inflammation and oxidative stress, which also contribute to progression of the metabolic syndrome.

Although AGE formation is correlated with hyperglycemia, fructose produces 10 times more AGEs than does glucose [37*,40]. Although the effects of AGEs have been under investigation for many years, the role of fructose is only now being uncovered. Pentosidine, a common AGE, has been correlated with the severity of complications in diabetes mellitus [37*]. Fructose consumption has been found experimentally to cause a significant increase in pentosidine in aorta and skin tissue of several different strains of rats [38*].

AGE formation is not only detrimental because of the direct effect of AGEs on protein integrity, but also because of their downstream effects. AGEs interact with a receptor [receptor for AGE (RAGE)], which mediates inflammatory pathways. Dietary fructose-mediated generation of AGE and activation of RAGE is yet another way in which fructose can induce inflammation, contributing to the metabolic syndrome. The soluble form of RAGE is correlated with inflammatory biomarkers in plasma of type II diabetic patients [41*] and in certain populations of nondiabetic individuals [42]. Although soluble RAGE has the potential to sequester AGEs in the plasma, the in-vivo findings of positive correlation with coronary artery disease [43] indicate that soluble RAGE may be an indicator of cell-bound RAGE levels.

In addition to directly reacting with protein to create AGEs, fructose can create AGEs indirectly through its intermediates. Methylglyoxal is an intermediate of fructose metabolism, produced during glycolysis [44**]. Fructose feeding in rats causes an increase in serum and tissue methylglyoxal, which in turn is associated with increased insulin resistance and plasma triglycerides [45]. This effect is reduced by co-administration with N-acetyl cysteine, a methylglyoxal scavenger. This strongly implicates methylglyoxal in the pathogenesis of the insulin resistance and triglyceride dysregulation. Methylglyoxal might therefore exert its effects by the formation of both AGEs and reactive oxygen species.

In an attempt to curb fructose-induced AGE accumulation, several groups have investigated potential treatment strategies. A compound called LR-90 is effective in reducing AGE accumulation and AGE/protein cross-linking in diabetic rats [45]. In addition, a number of recent studies have found that natural products, including garlic, green tea, and red nut sedge (Cyperus rotundus) effective in preventing AGE accumulation [40,46–48].

**Hormonal response to dietary fructose**

Hormone dysregulation is of primary importance in the progression of metabolic syndrome and has been well studied in some respects; fructose has been shown to cause hormonal disturbances and changes in insulin sensitivity in a number of animal models [1]. Fructose, unlike other sugars, does not elicit a surge in insulin after ingestion. This may be because the pancreas lacks the fructose transporter GLUT5 [2] or because fructose does not stimulate gastric inhibitory peptide release, which stimulates insulin secretion [49]. Fructose also does not...
elicit a surge in leptin, a hormone that indicates satiety, in the way that glucose does [2]. Fructose has, however, been shown to increase fasting plasma leptin concentrations [15**, 50], possibly an indication of leptin resistance.

A recent study investigating the simple issue of the effect of a sustained high fructose diet on plasma parameters in humans [51**] found that white adult men maintained on a diet including 18% fructose for 4 weeks experienced a 36% rise in total plasma triglycerides, a 72% rise in very-low-density lipoprotein triglycerides, and a 48% rise in leptin. There was no effect on plasma insulin or glucose, body weight, or insulin sensitivity.

Fructose’s effect on adiponectin, a hormone-like peptide that is inversely related to body mass index and body fat [52], is currently unclear. Adiponectin mRNA levels were found to be low in fructose-fed rats and were increased after administration of the peroxisome proliferator-activated receptor-γ agonist rosiglitazone [53**]. When plasma adiponectin levels were measured directly in another study, however, fructose feeding in rats caused an increase in the peptide [54*]. Similarly, fructose feeding in cynomolgus monkeys caused an elevation in adiponectin [55*], reaffirming this finding. The increased circulating adiponectin seen with fructose feeding might be a sign of adiponectin resistance, because these animals did not exhibit any of the beneficial effects typically associated with adiponectin, including increased insulin sensitivity and low blood pressure [14].

Human studies, however, are ambiguous in their results concerning fructose feeding and hormonal response. Many studies have found no difference between fructose and sucrose [56*] or between fructose and glucose [57] in their effects on appetite, leptin, or insulin levels in normal-weight individuals. This highlights the need for further human studies to elucidate the hormonal disturbances elicited by dietary fructose consumption.

**Conclusion**

High dietary fructose consumption is increasingly being recognized as a causative factor in the development of components of the metabolic syndrome, including dyslipidemia, insulin resistance, and hypertension. Recent advances have uncovered some of the physiologic and molecular mechanisms and have implicated hyperuricemia, inflammation, AGEs, and oxidative stress in these fructose-induced metabolic defects (Fig. 1).

A better understanding of the dietary and environmental factors that underlie the current epidemic of the metabolic syndrome is critical to curbing the rise in the number of insulin-resistant, obese, and diabetic populations worldwide. Recent studies continue to highlight the key role played by fructose as an important lipogenic and diabetogenic nutrient, contributing to this growing epidemic.

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- **of outstanding interest**

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 256–257).

In this study, fructose feeding diminishes insulin's ability to inhibit lipoprotein secretion from the intestine, suggesting fructose-induced insulin resistance in that organ. This paper also uncovers that enhanced activation of the extracellular signal-regulated kinase pathway may be involved in intestinal insulin resistance.


The combination of dietary fructose and cholesterol causes impaired cardiac insulin signaling. This novel report demonstrates that fructose’s effects on insulin signaling are not limited to classic insulin-sensitive tissues.


This comprehensive review explains the link between AGEs and vascular damage. These authors reconcile the reputation of uric acid as an antioxidant with its observed pro-oxidation effects in vivo. They discover the role of NADPH in regulating this relationship.


This study demonstrates the dose-dependent effect of dietary fructose on blood pressure and kidney function. This link between dietary fructose and renal health helps to clarify the effect of fructose in more aspects of the metabolic syndrome.


This paper provides further evidence that dietary fructose contributes directly to diseased states, including that of the kidney.


This comprehensive review explains the link between AGEs and vascular damage. The review is especially helpful in explaining proposed molecular mechanisms of the association.


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This paper shows the association between soluble RAGE and inflammation. This important link clears a path for further studies to explain the mechanism of this association.


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Because methyl glyoxal can induce oxidative stress and inflammation, this finding has important implications in the development of the metabolic syndrome.


Fructose feeding causes increases in plasma very-low-density lipoprotein but does not cause lipid accumulation in adipose tissue. The lack of effect on insulin signaling is interesting and requires further examination.