

Uric Acid, the Metabolic Syndrome, and Renal Disease

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Metabolic syndrome, characterized by truncal obesity, hypertriglyceridemia, elevated BP, and insulin resistance, is recognized increasingly as a major risk factor for kidney disease and also is a common feature of patients who are on dialysis. One feature that is common to patients with metabolic syndrome is an elevated uric acid. Although often considered to be secondary to hyperinsulinemia, recent evidence supports a primary role for uric acid in mediating this syndrome. Specifically, fructose, which rapidly can cause metabolic syndrome in rats, also raises uric acid, and lowering uric acid in fructose-fed rats prevents features of the metabolic syndrome. Uric acid also can accelerate renal disease in experimental animals and epidemiologically is associated with progressive renal disease in humans. It is proposed that fructose- and purine-rich foods that have in common the raising of uric acid may have a role in the epidemic of metabolic syndrome and renal disease that is occurring throughout the world.

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The metabolic syndrome is defined as a syndrome of truncal obesity, insulin resistance, elevated BP, hypertriglyceridemia, and hyperuricemia (Table 1) (1–4). The prevalence of metabolic syndrome has been increasing at an alarming rate throughout the world. In the United States, the current prevalence is estimated to be 27% (29% in women and 25.2% in men) (5); in Europe, it is 15.7% in men and 14.2% in women (6); and in China it is 13.7% (9.8% in men and 17.8% in women) (7).

The presence of metabolic syndrome is strongly associated with the development of diabetes (8), hypertension (9), cardiovascular disease (10), and all-cause mortality (11). However, recent studies have emphasized that metabolic syndrome also is both associated with and a risk for the development of chronic kidney disease (CKD). For example, in a recent study, the metabolic syndrome was found to be strongly correlated with CKD (defined as GFR <60 ml/min) and microalbuminuria, and the risk increased progressively with the number of criteria constituting the syndrome (12). In another study of Native Americans without diabetes, a positive relationship was identified between microalbuminuria and features of the metabolic syndrome (13).

The mechanism(s) by which metabolic syndrome might accelerate renal disease remains unclear. One possibility relates to the presence of obesity itself. Obesity has been found to be an independent risk factor for CKD (12,14), and treating obesity might stabilize renal function (15) or reverse early hemodynamic abnormalities and glomerular dysfunction (16). Obesity has been associated with a type of focal segmental glomerulosclerosis (FSGS) called “obesity-related glomerulopathy” (17).

Hall *et al.* (18) proposed that lipid deposition in the inner medulla increases intrarenal pressure, leading to decreased tubular flow, which results in increased sodium reabsorption in Henle loop, volume expansion, and the development of systemic hypertension. Obesity also increases the risk factor for diabetes and hypertension and has been shown to lead to glomerular hypertension and hyperfiltration (18). The metabolic syndrome also is associated with the release of inflammatory cytokines and the presence of endothelial dysfunction and oxidative stress (19), all which could contribute to the development of glomerulosclerosis. Insulin resistance also may have a direct role in the pathogenesis of renal injury, as a consequence of stimulating the sympathetic nervous system and the renin-angiotensin-aldosterone system (20). Dyslipidemia, which is a feature of the metabolic syndrome, may induce toxic and inflammatory tubulointerstitial injury (21). Finally, the metabolic syndrome is also associated with an elevated serum uric acid, which has also been implicated in renal disease (see below). The rise in metabolic syndrome indirectly may be a major contributor to the general rise in renal disease that has been observed throughout the world in the past few decades.

Uric Acid, Fructose Intake, and Metabolic Syndrome

In the past few years, there has been increasing evidence that hyperuricemia may be a true cardiovascular and renal risk factor (reviewed in reference [22]). Hyperuricemia predicts the development of hypertension (23), metabolic syndrome (23), diabetes (24), stroke (25), and cardiovascular events (25). Epidemiologic studies also have found that hyperuricemia is an independent risk factor for renal dysfunction in the normal population (26) and in patients with hypertension (27), diabetes (28), and CKD (29). Mild hyperuricemia in normal rats induces systemic hypertension, renal vasoconstriction, glomerular hypertension and hypertrophy, and tubulointerstitial injury inde-

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Table 1. Definition of metabolic syndrome by WHO, NCEP ATP III, and IDF^a

WHO Definition (2)	NCEP ATP III Definition (3)	IDF Definition (4)
Insulin resistance identified by type 2 diabetes or impaired fasting glucose or impaired glucose tolerance or insulin resistance (by insulin clamp) plus two or more of the following: BMI >30 kg/m ² and/or waist:hip ratio >0.9 (male) and >0.85 (female) Triglycerides ≥150 mg/dl BP ≥140/90 mmHg and/or antihypertensive drugs HDL cholesterol <35 (male) and <39 (female) Microalbuminuria (albumin excretion rate ≥20 μg/min) or albumin:creatinine ratio ≥30 mg/g	Metabolic syndrome is defined by three or more of the following risk factors: Waist circumference >88 cm (women) and >102 cm (men) Triglycerides ≥150 mg/dl HDL cholesterol <40 (male) and <50 (female) BP ≥130/85 mmHg Fasting glucose level ≥110 mg/dl	Central obesity (waist circumference, ethnicity specific) plus two or more of the following: Triglycerides ≥150 mg/dl or treatment for this abnormality HDL cholesterol <40 (male) and <50 (female) or specific treatment BP ≥130/85 mmHg or pharmacologic treatment

^aIDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization.

pendent of intrarenal crystal formation (30–32). Hyperuricemia also has been found to accelerate renal disease in the remnant kidney model (33) and to accelerate experimental cyclosporine nephropathy (34). The main pathophysiologic mechanism by which uric acid causes these conditions involves an inhibition of endothelial nitric oxide bioavailability (35), activation of the renin angiotensin system (30), and direct actions on endothelial cells and vascular smooth muscle cells (36). The importance of these pathways is suggested by a recent prospective study in which lowering uric acid in individuals with hyperuricemia and renal dysfunction was associated with improved BP control and slower progression of renal disease (37).

Recently, uric acid also was found to have a causal role in the metabolic syndrome that was induced experimentally by fructose (38). Fructose rapidly raises uric acid as a consequence of activation of fructokinase with ATP consumption, intracellular phosphate depletion, and stimulation of AMP deaminase (39). Lowering uric acid in fructose-fed rats ameliorates much of the metabolic syndrome, including a reduction in BP, serum triglycerides, hyperinsulinemia, and weight gain (38). The rise in uric acid after fructose ingestion likely has a significant role in inducing insulin resistance *via* its effect to lower nitric oxide (35) and also possibly by a direct effect of uric acid on the adipocytes (Sautin *et al.*, submitted).

In turn, fructose intake correlates well with the recent rise in the epidemic of metabolic syndrome, diabetes, hypertension, and kidney disease (40). Fructose constitutes 50% of table sugar and also is a major component in high-fructose corn syrup, which is used in the United States as a sweetener. Intake of fructose has increased markedly in the past few decades and correlates with the rising rates of metabolic syndrome. This

leads to the hypothesis that fructose intake may be a novel mediator of the epidemic of renal disease. Future studies are planned to determine whether fructose intake may be increased in patients with progressive renal disease, particularly those with features of metabolic syndrome. The possibility that fructose may cause similar hemodynamic changes in the kidneys as uric acid also will be investigated, as well as studies to determine whether fructose can accelerate renal disease in experimental animals. A better understanding of the role of fructose and uric acid in the pathogenesis of the renal disease might make a major contribution to our understanding of the underlying mechanisms of the current epidemic.

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