During the past two decades, we have witnessed a global epidemic in metabolic syndrome. It is estimated that one fourth of the adult population has the syndrome, and the increasing prevalence is largely attributed to a parallel rise in the prevalence of obesity. Data from the recent National Health and Nutrition Examination Survey (NHANES) show the prevalence of obesity (body mass index ≥30) was 33.3% among adult men and 35.3% among adult women in 2005 through 2006. Metabolic syndrome and obesity are also increasing at an alarming rate among children and adolescents, which of course are a cause of serious concern because obese children invariably grow into obese adults.

Metabolic syndrome is a cluster of several cardiovascular risk factors that include glucose intolerance, central obesity, dyslipidemia, and hypertension. The public health impact of this syndrome is weighty, given it is a primary risk factor for cardiovascular disease, obstructive sleep apnea, and type 2 diabetes. This current plight is further underscored by increasing prevalence is largely attributed to a parallel rise in the prevalence of obesity. Data from the recent National Health and Nutrition Examination Survey (NHANES) show the prevalence of obesity (body mass index ≥30) was 33.3% among adult men and 35.3% among adult women in 2005 through 2006. Metabolic syndrome and obesity are also increasing at an alarming rate among children and adolescents, which of course are a cause of serious concern because obese children invariably grow into obese adults.

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The Not-so-Sweet Side of Fructose

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Does fructose itself have direct adverse effects on the renal tubular cells to cause kidney injury? In this issue of JASN, Cirillo et al. investigate the potential direct effects of fructose on human proximal tubular epithelial cells. The same group previously reported that high-fructose diets accelerate the progression of CKD in the rodent remnant kidney model associated with an inflammatory response in the kidney featuring tubulointerstitial inflammation with monocye-macrophage infiltration and increased expression of monocyte chemotactic protein 1 (MCP-1) in the renal cortex. Extending this work, Cirillo et al. demonstrate that fructose treatment induces a proinflammatory response in human proximal tubular epithelial cells (HK-2) with stimulation of MCP-1 and reactive oxygen species, through a ketohexokinase-dependent mechanism. Moreover, fructose treatment increases intracellular uric acid,
and uric acid in turn induces MCP-1 production, which may be a mechanism by which uric acid accelerates renal disease. This study is significant for several reasons. First, it establishes a potential role for direct and detrimental effects of fructose on proximal tubular epithelial cells. It also takes us a step toward unraveling the mechanism that may be a causal link between high fructose intake and metabolic syndrome and the development of renal disease. Moreover, this study extends previous reports of fructose-induced inflammatory state in the kidney that may contribute to the progression of CKD.

Indeed, there is a significant body of evidence that links chronic inflammation to obesity and metabolic syndrome in patients with CKD. Data from the NHANES III cohort showed an association of metabolic syndrome with inflammation in CKD, and the presence of the metabolic syndrome is associated with greater odds for inflammation for various levels of creatinine clearance. Increased expression of inflammatory cytokines as well as genes associated with insulin resistance and lipid metabolism are observed in glomeruli of patients with obesity-related glomerulopathy compared with gender- and age-matched glomeruli of control donor kidneys. Given that a hallmark of the metabolic syndrome is insulin resistance and insulin exerts anti-inflammatory effects, resistance to its action may explain, at least in part, why obesity/metabolic syndrome is a pro-inflammatory state. The findings reported by Cirillo et al. propose a plausible mechanism of ketohexokinase-dependent metabolism of fructose in the proximal tubule stimulating MCP-1 and oxidative stress to induce an inflammatory response in the kidney. What remains unanswered is whether this represents a unique pathway for inflammation in the proximal tubule. The authors previously reported that fructose also directly stimulates endothelial inflammatory processes by upregulating the proinflammatory mediator intercellular adhesion molecule-1; therefore, it seems likely that additional inflammatory pathways are involved as well and should be investigated in future studies.

The potential importance of the findings by Cirillo et al. to humans remains to be established. Their findings provide a mechanistic insight into understanding the renal consequences of high-fructose intake and raise concern regarding the short- and long-term effects of fructose and its risk in humans. Clearly, further human studies are needed before we can determine whether the findings are due truly to causal relationship of high fructose intake with metabolic syndrome and CKD or there are yet-unmeasured factors, such as lifestyle and other confounders. There is an urgent need to determine whether policy recommendations regarding sugary soda and high-fructose consumption should be implemented in the strongest terms. Tackling this issue will be a major challenge ahead, given the enormous public health implications posed by the worldwide epidemic of metabolic syndrome, especially in children and adolescents who will grow into adulthood, before it becomes a tsunami of CKD that cannot be prevented.

DISCLOSURES
None.

REFERENCES
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The extent of injury to the tubulointerstitial compartment has been recognized for several decades as closely linked to declining renal function in glomerular diseases. In addition to secondary inflammatory injury and ischemia as mechanisms of injury in the tubulointerstitium downstream from diseased glomeruli, proteinuria itself is now recognized as a pathogenic factor and an independent risk factor for the progression of kidney disease.1–3 Reduction of proteinuria is a therapeutic goal and an independent risk factor for the progression of chronic kidney disease.4 Current strategies to reduce proteinuria are largely focused on treatment of the underlying glomerular disease and by alteration of glomerular hemodynamics and filtration. With improved understanding of basic mechanisms of proteinuria-induced injury, however, more refined and proximate strategies based on molecular pathogenesis of proteinuria-induced tubulointerstitial injury may be possible.

The damaging effects of proteinuria on the renal tubulointerstitial compartment involve a variety of mechanisms.5 These include tubular cell toxicity, when the lysosomal capacity to degrade proteins reabsorbed in excess by the tubules is overwhelmed, the downstream exposure to chemoines in tubular fluid, or the expression of surface neo-antigens and adhesion molecules with proinflammatory action. In addition, tubular epithelial cells respond to exposure to filtered serum proteins, as to other forms of injury, by undergoing epithelial-to-mesenchymal transition (EMT), with reduction of epithelial phenotype and functions and induction of increased cell motility and matrix production. Transition toward a mesenchymal phenotype has been demonstrated in epithelial and endothelial cells by in vitro as well as in vivo studies and is recognized as an important contributor to the development of fibrosis,6 not only in the kidney but also in lung and liver. The mechanisms involved in proteinuria-induced EMT in renal tubular cells have not been clearly identified.5

As an important component of innate immunity, the complement system is activated in proteinuric states. Tang et al.7 in this issue of JASN examine the clinical and experimental evidence that complement activation plays a role in tubulointerstitial injury and dysfunction during proteinuria. Existing data suggest roles for both the membrane attack complex, C5b-9, and the anaphylotoxin C5a in injury and dysfunction in proteinuric states. There is also recent evidence that C3- or C6-deficient mice have reduced EMT in models of proteinuria.

The elegant studies by Tang et al.7 provide a new focus on another complement activation product, the anaphylotoxin C3a, and its role in altering proximal tubular epithelial cell (PTEC) phenotype in vitro and presumptively in vivo. The HKC-8 in vitro cell system is capable of activating complement and undergoing EMT on exposure to serum C3a but not C5b-9. An antagonist of the C3a receptor expressed on the cells inhibits the effect and blocks an increase in the mRNA encoding collagen I. The antagonist also blocks EMT and collagen I-induced by exposure to serum. Extending these observations in vivo in an adriamycin model of proteinuria, C3a receptor null mice develop less albuminuria, lower mortality, and less severe renal failure compared with wild-type mice. C3aR null mice also have less glomerular injury and less severe tubulointerstitial disease, as measured by tubular diameter/cell height ratio and interstitial volume, with less interstitial collagen and fewer myofibroblasts and macrophages.

Although in vitro evidence of C3aR-mediated injury induced by proteinuria in human renal proximal tubular cells reported by Tang et al.7 is compelling, it is difficult to define the role of complement and C3a directly at the level of the tubular epithelium in the in vivo studies, because glomeru-