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 \( \geq 30 \)) 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 recent emerging evidence that metabolic syndrome is also associated with albuminuria and increasing incidence of chronic kidney disease (CKD). Moreover, this relationship persists even after exclusion of individuals with diabetes.

Thus, metabolic syndrome is an independent risk factor for the development of CKD, in the absence of diabetes, and independent of hypertension.

So what is behind this epidemic? Although there are likely many contributing factors, including a shift in diet to “junk food” with excessive caloric intake coupled with a propensity toward a sedentary lifestyle, an increase in fructose intake is also implicated. Nelson, most aptly remarked that we have “morphed insidiously into a fructose nation.” Fructose is sugar that is found naturally in fruits and is also commonly used as an industrial sweetener. During the past 30 yr in the United States, there has been a marked increase in daily intake of fructose largely as a result of the introduction and widespread use of high-fructose corn syrup to sweeten beverages; however, we are beginning to recognize the not-so-sweet side of fructose. Epidemiologic and experimental studies link high fructose consumption with the development of metabolic syndrome, insulin-resistant diabetes, and more recently kidney disease. Results from the NHANES (1999 through 2004) showed that sugary soda consumption was associated with albuminuria. Recent reports also showed that fructose consumption is associated with an increased risk for kidney stones and gout. These studies suggested a link among soda consumption, high-fructose corn syrup, and CKD.

What might be the mechanism by which fructose consumption increases the risk for CKD? The story underlying fructose-induced metabolic syndrome and CKD is just beginning to emerge. Studies led by Johnson and colleagues demonstrated that a high-fructose diet induces features of metabolic syndrome, including hyperinsulinemia, hypertriglyceridemia, hypertension, and weight gain, as well as glomerular hypertension and hyperuricemia in rats. Several plausible mechanisms related to consequences of metabolic syndrome have been proposed, including insulin resistance, lipotoxicity, oxidative stress, endothelial dysfunction, and hemodynamic alterations. Furthermore, fructose-induced hyperuricemia likely has a pathogenic role.

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 monocyte-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 proinflammatory 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

18. Gersch MS, Mu W, Cirillo P, Reungsu S, Zhang L, Roncal C, Sautin YY, Johnson RJ, Nakagawa T: Fructose, but not dextrose, accelerates the
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 now a major therapeutic goal in reducing risk for renal progression. \(^4\) 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 tubulo-interstitial 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 chemokines 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 \textit{in vitro} as well as \textit{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 \textit{et al.} \(^7\) in this issue of \textit{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 \textit{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 \textit{in vitro} and presumptively \textit{in vivo}. The HKC-8 \textit{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 \textit{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 \textit{in vitro} evidence of C3aR-mediated injury induced by proteinuria in human renal proximal tubular cells reported by Tang \textit{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 \textit{in vivo} studies, because glomeru-