


No concept in kidney physiology raises as much interest and debate as albuminuria. All agree that the glomerular capillary wall is a highly selective barrier that restricts the passage of plasma proteins—thus its moniker the “glomerular filtration barrier” (GFB). Albumin is the most abundant plasma protein, and significant albuminuria is considered “selective glomerular proteinuria,” in contrast to the low molecular weight proteinuria that is classically linked to tubular abnormalities. Although most attention has been focused on GFB abnormalities as being responsible for albuminuria, Comper et al.1 continue to present evidence for a tubular origin, with the latest appearing in this issue of JASN.2 The view they advocate is in stark disagreement with long-accepted dogma of kidney physiology and pathophysiology, but if these investigators are correct, then there would be a major shift in the way proteinuric kidney diseases are viewed and, most important, treated.

Inherent in the hypothesis of a tubular origin for proteinuria is the claim that albumin’s glomerular sieving coefficient (GSC) is high, at 0.02 to 0.04. This means that 2 to 4% of the albumin molecules subjected to the GFB cross into the glomerular filtrate. This estimate is approximately 50 times higher than the widely accepted GSC of approximately 0.0006.3 The difference between these values is staggering; if the higher value is correct, then it means that in normal rats (GFR of 2 ml/min), 2 to 4 g/d albumin would be filtered, as opposed to only approximately 66 mg/d with the historically accepted GSC. When scaled to humans (GFR of 120 ml/min), 150 to 300 g/d albumin would be filtered; this level of albumin (essentially all of the albumin in the bloodstream) would obviously have to be reclaimed by a very efficient mechanism in the tubules to explain the lack of nephrotic-range albuminuria and negative nitrogen balance in healthy individuals. Indeed, Comper and colleagues4 hypothesize that such a mechanism exists, and that albuminuria is caused primarily by defects in tubular uptake of intact albumin rather than by increased leakiness of the GFB. A corollary of the hypothesis is that albumin is not tubulotoxic, at least under normal conditions.

In this issue of JASN, Russo et al.3 use two-photon microscopy in living rats to study the early diabetic kidney’s handling of fluorescent Alexa568-conjugated rat albumin. Their data are in agreement with their previous results and support their hypothesis. By comparing the fluorescence signals in Bowman’s space with those inside the glomerular capillary, they calculate the GSC of Alexa568-albumin to be 0.034, which is not changed in proteinuric diabetic animals. Filtered fluorescent albumin is rapidly taken up by proximal tubule cells (PTCs) in the normal kidney, but, in proteinuric animals, the retrieval pathway is impaired, resulting first in increased peptiduria and eventually in frank albuminuria. Glycemic control in diabetic animals prevents albuminuria by protecting the retrieval pathway in PTCs. Furthermore, the GSC of a 69-kD fluorescent dextran tracer, calculated to be 0.025, was comparable to that of the fluorescent albumin. The half-life of albumin, however, was longer, and only al-

**Albuminuria, Wherefore Art Thou?**

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doi: 10.1681/ASN.2009010075

Published online ahead of print. Publication date available at www.jasn.org.

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bumin was able to bind to the brush border of PTCs. The latter suggests that the two molecules are processed differently after filtration, consistent with resorption of intact albumin (but not dextran) by PTCs.

The authors’ high GSC hypothesis has met with intense criticism, and interested readers are encouraged to consult relevant publications, commentaries, and responses for details. It is notable that the data of Comper and colleagues have been criticized for potential artifacts as a result of low signal-to-noise ratios in their two-photon analyses of fluorescent albumin levels in plasma and ultrafiltrate in living rats, yet their calculated GSC for FITC-dextran agrees with that determined by Rippe and colleagues,

providing a sense of validity to their state-of-the-art two-photon method; however, whether fluorescently labeled albumin is a true surrogate for native albumin may be questionable. Although the authors assume that labeling albumin with Alexa568 does not change its physical characteristics, little is known about the ability of Alexa568-albumin to associate with plasma lipids and fatty acids, which may affect its effective molecular radius, shape, deformability, and interactions with the GFB, and is the elapsed time between bolus injection and detection of fluorescence long enough for such associations to occur? In any event, regardless of whether the calculated GSC of 0.034 is applicable to native albumin, an important message of the article is that the GSCs of both Alexa568-albumin and FITC-dextran remain the same (respectively) in normal and proteinuric diabetic rats, suggesting that tubular dysfunction is in fact responsible for the increased albumin excretion in early diabetic nephropathy. This is by no means a novel concept, but the direct visualization of quantitative differences in the extent of association of filtered Alexa568-albumin with the PTC brush border by the two-photon method provides a powerful demonstration.

Another important criticism of the hypothesis of the tubular origin of albuminuria is the lack of a convincing demonstration of the high-efficiency albumin retrieval mechanism that would be required to prevent nephrotic syndrome. The hypothesis is effectively disproved if PTCs are not able to absorb huge quantities of albumin from the tubular lumen and then transport it intact to the circulation. So where is the smoking gun? One plausible reason that Park and Maack did not find evidence for this mechanism in their classic studies has already been presented, but why is fluorescent albumin confined primarily to the apical pole of PTCs in the two-photon movies and micrographs, where it continues to accumulate at the later time points, if it must be returned to the circulation through the basal aspects of these cells? Explanations that have been provided are that the process of transcellular albumin transport is too rapid, the vesicles involved are too small to be visualized, and the mechanism responsible has yet to be fully characterized. Another possible explanation for the data, if one accepts the high GSC, is that the large filtered load is resorbed but in the form of difficult-to-detect degradation peptides rather than as intact albumin; this would, however, require the plasma albumin half-life to be on the order of hours rather than weeks.

As evident at a 2008 American Society of Nephrology Annual Meeting symposium devoted to this topic, the controversy surrounding the notion of a high GSC coupled with a high tubular albumin resorption capacity has evolved into an emotionally charged debate. It seems that a satisfactory resolution may require even more sophisticated techniques and experimental approaches that will provide the proverbial “slam dunk” to end the controversy with indisputable data. As glomerular biologists, we eagerly await a satisfactory mechanistic explanation for how the increasing number of podocyte gene mutations responsible for albuminuria in patients and in animal models can be reconciled with the concept of a tubular origin for proteinuria.

ACKNOWLEDGMENTS

Our research has been supported by grants from the National Institutes of Health (R01DK078314 and R21DK074613 to J.H.M. and P30DK079333 to G.J.), by an Established Investigator Award from the American Heart Association (J.H.M.), and by an Alaska Kidney Foundation-American Society of Nephrology Research grant (G.J.).

DISCLOSURES

None.

REFERENCES

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 featuring tubulointerstitial inflammation with kidney model associated with an inflammatory response in the renal cortex. Extending this work, Cirillo et al. previously reported that high-fructose diets accelerated the progression of CKD in the rodent remnant kidney model 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,