Yet Another Advance in Understanding Albuminuria?

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Although the clinical relevance of proteinuria, especially albuminuria, has been well documented in chronic kidney disease,1 the quantitative mechanistic significance of different barrier components to albuminuria remains an area of considerable excitement and debate. The glomerular filtration barrier (GFB), formed by fenestrated endothelia with their glycocalyx, podocytes with their interdigitated foot processes and slit diaphragms, the subpodocyte space, and their glycocalyx, podocytes with their interdigitated foot processes have been long believed to be the major determinant of albuminuria.2,3 Multiple genetic, molecular, and morphologic lines of evidence implicate the podocyte and its slit diaphragm as playing a central role in the GFB. However, changing concepts regarding the mechanistic relevance and clinical importance of each of these individual components of the GFB have been advancing at a rapid rate.

The glycocalyx of glomerular endothelial cells has been shown by enzymatic degradation,4 use of vascular endothelial growth factor antibodies to induce glomerular endothelial injury,5,6 and mutations of the laminin B3 gene7 to result in macroalbuminuria without morphologic podocyte injury, although controversy remains.8 Basement membrane charge properties and their molecular constituents have also been reexamined and deleted, respectively, in attempts to understand further their importance. Clearly, laminin β2 mutants and null mice for either laminin β2 or the α3 chain of type IV collagen demonstrate the potential role of the GBM in albuminuria.7–10 In addition, the glomerular endothelial cell and GBM may be able to compensate for changes in the podocyte that lead to foot process fusion and loss of the heparin sulfate glycosaminoglycan and anionic charge.11 The recent discovery of a subpodocyte space has added another dimension to the GFB, although its role in protein filtration remains unknown.12,13

On this background, is it little wonder that a talented investigative team, with considerable experience in the area, used a new technological advancement in scanning electron microscopy in this issue of JASN to produce data that bring into question long-held beliefs regarding the structure and function of the podocyte slit diaphragm.14 They describe the existence of heterogeneous ellipsoidal and circular pores, located in the central region of the slit diaphragm, log normally distributed with a mean diameter far greater than envisioned previously. This was accomplished with careful attention to potential fixation, imaging, and quantitative analysis artifacts, although high-pressure freezing would have been the preferred tissue preparation.

Like many scientific advances challenging previously held beliefs, it is likely to be initially refuted vigorously, which is a healthy and required part of the scientific evaluation process. Pore sizes were quantified and compared between Munich Wistar Frontter (MWF) rats, known to develop albuminuria with age and develop focal glomerular sclerosis, and Wistar rats that do not develop albuminuria. The mean pore sizes of both strains were similar, but MWF rats had a small increase in the very largest pores, which the authors propose to be the mechanism of albuminuria. However, in both rat strains, unique images with high resolution and state-of-the-art quantitative morphometric analysis revealed pore sizes that beg the question, “Is albumin filtered across the glomerulus under normal physiologic conditions in levels previously deemed unrealistic by many investigators in the field?” This is especially true given the accumulating evidence from a number of studies using genetic, biochemical, imaging, and molecular approaches and indicating an important role for proximal tubule epithelial cells in albumin reabsorption and reclamation.16–24

The present data could easily be interpreted to substantiate further the role of the proximal tubule under physiologic and pathologic conditions in minimizing albuminuria. The authors invoke endothelial and GBM barriers in
series with the podocyte pores to explain the lack of albuminuria under physiologic conditions. However, why do these same glomerular proximal barriers not prevent albuminuria in the MWF rats? This conclusion seems inconsistent with the data. How can they have it both ways?

Questions will also arise regarding the rat strains used for comparisons. Is it appropriate to compare very old MWF rats that have reduced GFR with Wistar rats (age unknown) that have normal serum creatinine? Would more appropriate, insightful, and confirmatory data have been obtained from young MWF rats without proteinuria? This comparison would have allowed the investigators to evaluate pore numbers and size as albuminuria progressed with age and before foot process fusion and decreases in GFR occurred. Do the large pores increase in size and/or number with increasing albuminuria?

In summary, previously held concepts in the complex process of glomerular albumin filtration are being challenged both across the glomerulus and downstream of the glomerulus on the basis of biochemical, molecular, genetic, and methodologic advances. Each of these challenges is met by skepticism, often severe in nature. These investigators are to be congratulated for pushing science forward because far too many reviews have indicated why the past must be forgotten. Facts are more important than faith when discrepancies exist, and they serve to move the field forward. Undoubtedly, this study will lead to additional studies and the area will be further refined. Discovery is advanced by technological advances and thinking outside the existing box.²⁵

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DISCLOSURES

None.

REFERENCES

22. Sarav M, Wang Y, Hack BK, Chang A, Jensen M, Bao L, Quigg RJ:
Managing Overly Rapid Correction of Chronic Hyponatremia: An Ounce of Prevention or a Pound of Cure?

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Rapid correction of chronic hyponatremia may lead to osmotic demyelination syndrome (ODS) and devastating neurologic sequelae. The rate of rise in plasma sodium concentration (PNa) in patients with chronic hyponatremia should be <8 mmol/L per d and even lower in patients at higher risk for ODS: Those with alcoholism, cirrhosis, malnutrition, or hypokalemia. The pathophysiology of ODS is poorly understood. The brain loses organic osmolytes rapidly to adapt to hyponatremia but reclaims them slowly in response to its correction. A rapid increase in PNa shrinks cerebral vascular endothelial cells, which opens the blood–brain barrier, allowing lymphocytes, complement, and cytokines to enter the brain, damage oligodendrocytes, and cause demyelination. Microglial activation seems to contribute to this process.

Minocycline, a tetracycline derivative, has been shown to have protective effects in experimental models of central nervous system injury, including demyelinating damage. In this issue of JASN, two studies examine the role of minocycline in prevention of ODS caused by rapid correction of chronic hyponatremia in rats. Data are mostly from experiments in which minocycline was started at the time of or several hours before correction of hyponatremia. In the study by Gankam et al., a large dose of minocycline was used. The administration of minocycline is associated with a marked reduction in the incidence and severity of neurologic symptoms; nevertheless, 48% of these rats died. Notwithstanding, minocycline-treated rats had much better survival in the study by Suzuki et al. Although the administration of minocycline is associated with less activation of microglia and diminished release of inflammatory cytokines, rats still develop some demyelinating brain lesions. Gankam et al. also studied a group of rats in which minocycline was started 18 hours after rapid correction of hyponatremia; six of 13 rats died. In a recent study by the same group, in which hyponatremia was re-induced after rapid correction of chronic hyponatremia, only one of 16 rats died.

Although both studies provide interesting insights into the role of microglial activation in ODS, the data provided do not argue strongly for a role for minocycline in the prevention of ODS in clinical practice should inadvertent rapid correction of chronic hyponatremia occur. The critical issue in the management of chronic hyponatremia is to prevent rapid correction. A rapid rise in PNa is almost always due to a water diuresis, which happens when vasopressin action suddenly ceases, such as with volume repletion in patients with intravascular volume depletion, cortisol replacement in patients with Addison disease, resolution of nonosmotic stimuli for vasopressin release such as nausea or pain, or if distal delivery of filtrate increases. This last aspect of the pathophysiology of chronic hyponatremia and its correction needs emphasis. An important point is that chronic hyponatremia can develop in the absence of vasopressin action.

In the absence of vasopressin, the maximum urine volume is the volume of filtrate delivered to the distal nephron, which is the GFR minus the volume reabsorbed in the proximal convoluted tubule (PCT). Although it was thought that approximately 66% of the GFR is reabsorbed in the PCT, we now think it is greater. Recent data suggest that the thin descending limb of the loop of Henle of the majority of nephrons lacks aquaporin 1 and therefore the entire loop of Henle of these nephrons is most likely water impermeable. Hence, a better estimate of the fraction of filtrate reabsorbed in PCT (including pars recta) is obtained from micropuncture studies of the distal convoluted tubule in rats using the tubular fluid–plasma inulin concentrations ratio. The lowest measured value is 6. Therefore, five sixths (83%) of the GFR is reabsorbed in PCT, a value that is close to the estimate from lithium clearance in hu-