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DISCLOSURES

None.

REFERENCES

1. Hausmann R, Kuppe C, Egger H, Schweda F, Knecht V, Elger M, Menzel S, Somers D, Braun G, Fuss A, Uhlig S, Kriz W, Tanner G, Floege J, Moeller MJ: Electrical forces determine glomerular permeability. *J Am Soc Nephrol* 21: 2053–2058, 2010
2. Thomson SC, Blantz RC: Biophysical basis of glomerular filtration. In: *The Kidney: Physiology and Pathophysiology*, 4th Ed., Edited by Alpern R, Hebert S, Elsevier/Academic Press, 2007, pp 565–588

See related article, "Electrical Forces Determine Glomerular Permeability," on pages 2053–2058.

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 the glomerular basement membrane (GBM), has been long believed to be the major determinant of albuminuria with podocyte foot process fusion being central.[2] 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,[3] use of vascular endothelial growth factor antibodies to induce glomerular endothelial injury,[4,5] and mutations of the laminin β3 gene[6] to result in macroalbuminuria without morphologic podocyte injury, although controversy remains.[2] 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 Fromter (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?"[15] 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

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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 correct. Facts are more important than faith when discrepancy exists, 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

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REFERENCES

1. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 20: 1069–1077, 2009
2. Ballermann BJ, Stan RV: Resolved: Capillary endothelium is a major contributor to the glomerular filtration barrier. *J Am Soc Nephrol* 18: 2432–2438, 2007
3. Singh A, Satchell SC, Neal CR, McKenzie EA, Tooke JE, Mathieson PW: Glomerular endothelial glycocalyx constitutes a barrier to protein permeability. *J Am Soc Nephrol* 18: 2885–2893, 2007
4. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, Richardson C, Kopp JB, Kabir MG, Backx PH, Gerber HP, Ferrara N, Barisoni L, Alpers CE, Quaggin SE: VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 358: 1129–1136, 2008
5. Sugimoto I, Takahashi Y: Evidence that the PsbK polypeptide is associated with the photosystem II core antenna complex CP43. *J Biol Chem* 278: 45004–45010, 2003
6. Hata D, Miyazaki M, Seto S, Kadota E, Muso E, Takasu K, Nakano A, Tamai K, Uitto J, Nagata M, Moriyama K, Miyazaki K: Nephrotic syndrome and aberrant expression of laminin isoforms in glomerular basement membranes for an infant with Herlitz junctional epidermolysis bullosa. *Pediatrics* 116: e601–e607, 2005
7. Farquhar MG: The glomerular basement membrane: Not gone, just forgotten. *J Clin Invest* 116: 2090–2093, 2006
8. Hamano Y, Grunkemeyer JA, Sudhakar A, Zeisberg M, Cosgrove D, Morello R, Lee B, Sugimoto H, Kalluri R: Determinants of vascular permeability in the kidney glomerulus. *J Biol Chem* 277: 31154–31162, 2002
9. Jarad G, Cunningham J, Shaw AS, Miner JH: Proteinuria precedes podocyte abnormalities in Lamb2−/− mice, implicating the glomerular basement membrane as an albumin barrier. *J Clin Invest* 116: 2272–2279, 2006
10. Kalluri R: Proteinuria with and without renal glomerular podocyte effacement. *J Am Soc Nephrol* 17: 2383–2389, 2006
11. Chen S, Wassenhove-McCarthy DJ, Yamaguchi Y, Holzman LB, van Kuppevelt TH, Jenniskens GJ, Wijnhoven TJ, Woods AC, McCarthy KJ: Loss of heparan sulfate glycosaminoglycan assembly in podocytes does not lead to proteinuria. *Kidney Int* 74: 289–299, 2008
12. Neal CR, Muston PR, Njegovan D, Verrill R, Harper SJ, Deen WM, Bates DO: Glomerular filtration into the subpodocyte space is highly restricted under physiological perfusion conditions. *Am J Physiol Renal Physiol* 293: F1787–F1798, 2007
13. Salmon AH, Toma I, Sipos A, Muston PR, Harper SJ, Bates DO, Neal CR, Peti-Peterdi J: Evidence for restriction of fluid and solute movement across the glomerular capillary wall by the subpodocyte space. *Am J Physiol Renal Physiol* 293: F1777–F1786, 2007
14. Gagliardini E, Conti S, Benigni A, Remuzzi G, Remuzzi A: Imaging of the porous ultrastructure of the glomerular epithelial filtration slit. *J Am Soc Nephrol* 21: 2081–2089, 2010
15. Comper WD, Haraldsson B, Deen WM: Resolved: Normal glomeruli filter nephrotic levels of albumin. *J Am Soc Nephrol* 19: 427–432, 2008
16. Amsellem S, Gburek J, Hamard G, Nielsen R, Willnow TE, Devuyst O, Nexo E, Verroust PJ, Christensen EI, Kozyraki R: Cubilin is essential for albumin reabsorption in the renal proximal tubule. *J Am Soc Nephrol* 21: 1859–1867, 2010
17. Gekle M, Volker K, Mildenberger S, Freudinger R, Shull GE, Wiemann M: NHE3 Na+/H+ exchanger supports proximal tubular protein reabsorption in vivo. *Am J Physiol Renal Physiol* 287: F469–F473, 2004
18. Menzel S, Kunter U, Kaldenbach M, Lanzmich R, Uhlig S, van Roeyen C, Rong S, Floege J, Moeller M: Transport of intact albumin from primary filtrate into the bloodstream *in vivo* [Abstract]. *J Am Soc Nephrol* 20: 62A, 2009
19. Rangel-Filho A, Sharma M, Datta YH, Moreno C, Roman RJ, Iwamoto Y, Provoost AP, Lazar J, Jacob HJ: RF-2 gene modulates proteinuria and albuminuria independently of changes in glomerular permeability in the fawn-hooded hypertensive rat. *J Am Soc Nephrol* 16: 852–856, 2005
20. Russo LM, Sandoval RM, McKee M, Osicka TM, Collins AB, Brown D, Molitoris BA, Comper WD: The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: Retrieval is disrupted in nephrotic states. *Kidney Int* 71: 504–513, 2007
21. Saleh MA, Boesen EI, Pollock JS, Savin VJ, Pollock DM: Endothelin-1 increases glomerular permeability and inflammation independent of blood pressure in the rat. *Hypertension* 56: 942–949, 2010
22. Sarav M, Wang Y, Hack BK, Chang A, Jensen M, Bao L, Quigg RJ:

Renal FcRn reclaims albumin but facilitates elimination of IgG. *J Am Soc Nephrol* 20: 1941–1952, 2009
23. Verhulst A, D'Haese PC, De Broe ME: Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol* 15: 2249–2257, 2004
24. Yao B, Singh AB, Zhang M-Z, Harris RC: A novel mouse model of AKI with targeted injury of proximal tubule cells [Abstract]. *J Am Soc Nephrol* 20: 733A, 2009
25. Kuhn TS: *The Structure of Scientific Revolutions,* Chicago, University of Chicago Press, 1996

See related article, "Imaging of the Porous Ultrastructure of the Glomerular Epithelial Filtration Slit," on pages 2081–2089.

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.[1] The rate of rise in plasma sodium concentration (P_{Na}) in patients with chronic hyponatremia should be $<$8 mmol/L per d[2] and even lower in patients at higher risk for ODS: Those with alcoholism, cirrhosis, malnutrition, or hypokalemia.[3]

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.[4] A rapid increase in P_{Na} 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.[5] Microglial activation seems to contribute to this process.[6]

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Minocycline, a tetracycline derivative, has been shown to have protective effects in experimental models of central nervous system injury, including demyelinating damage.[7] 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.[8,9] 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.*,[9] 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.[9] Notwithstanding, minocycline-treated rats had much better survival in the study by Suzuki *et al.*[8] 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.*[9] 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.[10]

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 P_{Na} 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,[11] 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.[12] Therefore, five sixths (83%) of the GFR is reabsorbed in PCT, a value that is close to the estimate from lithium clearance in hu-