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Response to the Letter to the Editor Entitled "Integrating Tissue Proteomics and Urinary Analysis to Capture Dynamic Podocyte Injury"

The Author Replies: We thank Angeletti *et al.*[1] for their compliments. Our study, demonstrated marked loss in podocyte proteins in kidney biopsies of adult patients with minimal change disease (MCD) and primary and secondary focal segmental glomerulosclerosis compared with membranous nephropathy (MN).[2] However, though cluster analysis demonstrated tight clustering of proteins in both MCD and primary and secondary focal segmental glomerulosclerosis, there were large variations in MN, suggesting significant protein depletion in some cases. We speculate that in MCD and primary focal segmental glomerulosclerosis, circulating permeability factor(s) and/or antibody are so toxic to the podocyte that they cause an abrupt and massive disruption in multiple proteins simultaneously, whereas in MN, a more selective and delayed injury occurs. Indeed, Lahme *et al.*[3] shows that in MN, autoantibodies trigger the formation of antigen-autoantibody aggregates on podocyte foot processes, that bud off as stalked vesicles, which are then released into the urine, carrying with them podocyte proteins. Considering that this process targets a specific antigen and requires time to markedly impact the total amount of podocyte protein, it support the idea that differences between MN and other podocytopathies may reflect not only distinct mechanisms, but also different dynamics of podocyte injury.[1] Interpretation of proteomic data from kidney biopsies cannot be taken in isolation but in the context of other parameters (e.g., proteinuria, serum albumin, and estimated glomerular filtration rate). Because patients with MCD and primary focal segmental glomerulosclerosis have an abrupt clinical presentation (we strictly selected patients at similar levels of proteinuria), their clinical or proteomic profiles can be closely corelated. Urinary podocyte-derived extracellular vesicles are increased in relapsing MCD than in patients with MCD in remission[4]; however, how they compare with nephrotic patients with MN, or if they are modified by changes in estimated glomerular filtration rate, degree of glomerulosclerosis, etc., requires further investigation. This highlights that urinary proteomic analysis is also subject to the clinical status of the patient. Proteomic analysis of body fluids is complex and involves proper sample processing (i.e., extraction, isolation, and purification of proteins). Quantification of low-abundance proteins is also challenging requiring high-precision mass spectrometers, which are expensive.[5] Whether urinary proteomics analysis can add meaningful information to guide patient management in patients with podocytopathies beyond quantification of serum albumin, proteinuria, estimated glomerular filtration rate, kidney biopsy evaluation, and in the case of MN, autoantibodies (e.g. anti–phospholipase A2 receptor) remains to be demonstrated.

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Received 22 February 2026; accepted 3 March 2026; published online 10 March 2026

Kidney Int Rep (2026) **11,** 106474; https://doi.org/10.1016/j.ekir.2026.106474