Letter Regarding Normal Albuminuria in Patients With Autopsy-Proven Advanced Diabetic Nephropathy

To the Editor: In the 2021 December issue of the *KI Report*, Sasaki *et al.*[1] point out that nearly half of 106 Japanese patients with a stage IIa or higher diabetic glomerulopathy, evident on autopsy, were "normoalbuminuric" (urine albumin-to-creatinine ratio <30 mg/g) up to 3 years before death. While addressing this enigma, they ignored the mitigating impact of tubular handling of filtered albumin on albuminuria. Approximately 3.2 g of albumin and additional 10 g of low-molecular proteins are normally filtered daily and are almost entirely uptaken or degraded along the nephron.[2] More than 70% of filtered albumin is reabsorbed in the proximal tubules in rats, and the rest is uptaken by distal nephron segments. Proximal tubular reclaim of filtered albumin declines in early experimental diabetes in rats,[3] whereas distal tubular reuptake is reciprocally enhanced.[3] Tubular uptake of albumin leads to the formation of endocytic vesicles with lysosomal breakdown to amino acids that recirculate in the bloodstream. Paracellular reclaim of albumin likely takes place as well,[2] as is albumin degradation by brush-border enzymes with urinary clearance of albumin fragments and amino acids.

Thus, diabetic nephropathy may be concealed if filtered albumin is fully reclaimed and degraded, although overt albuminuria reflects glomerular leak of albumin beyond the tubular reabsorptive capacity. Importantly, proteinuria *per se* induces tubuointerstital damage and may reduce tubular capability of albumin reuptake.[4] Therefore, we urge Sasaki *et al.*[1] to further evaluate the presence and extent of nonglomerular parenchymal damage in their autopsy samples, anticipating a plausible association of tubulointerstitial disease and albuminuria. We also propose to explore the possible impact of medications that reduce transglomerular pressure on the unexpected absence of albuminuria in the presence of structural glomerulopathy.

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Response to "Letter Regarding Normal Albuminuria in Patients With Autopsy-Proven Advanced Diabetic Nephropathy"

The Authors Reply: We thank Heyman *et al.*[1] for their letter regarding our article reporting the association between albuminuria levels and pathologic diabetic nephropathy from a Japanese community-based study.[2] They suggest further evaluating the association between albuminuria and the extent of

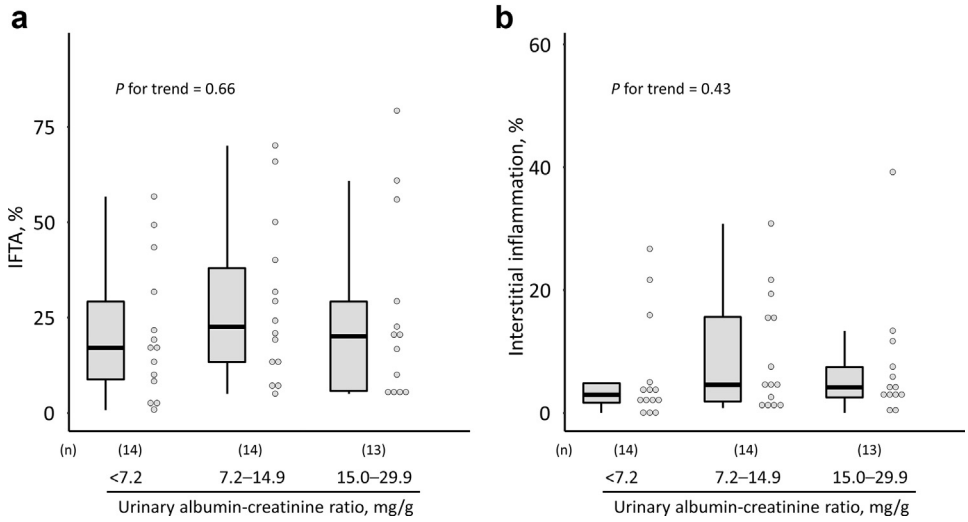

Figure 1. Box- and dot-plots of the extent of the pathologic index for tubulointerstitial lesions according to urinary albumin-to-creatinine ratio levels among the autopsied diabetic cases with normoalbuminuria. (a) IFTA; (b) interstitial inflammation. The bold horizontal line represents the median, the box represents the 25th to 75th percentiles, the vertical bar represents the minimum to the maximum except for outliers, and the dots represent individual cases. Trends in the difference across albuminuria levels were tested by using a Jonckheere-Terpstra test. IFTA, interstitial fibrosis and tubular atrophy.

tubulointerstitial lesions because much of the albumin filtered by the glomeruli is reabsorbed and degraded in the tubules even in physiological status.[3] We agree that tubulointerstitial lesions are important. Therefore, we semiquantitatively evaluated the extent of tubulointerstitial lesions, including interstitial fibrosis/tubular atrophy and interstitial inflammation, and found that as the urinary albumin-to-creatinine ratio levels increased from $<$30.0, 30 to 299.9, and $\geq$300.0 mg/g, the extent of tubulointerstitial lesions significantly increased, as illustrated in Figure 2 reported in Sasaki *et al.*[2] Furthermore, in line with the suggestion of Heyman *et al.*,[1] we further evaluated the association between the urinary albumin-to-creatinine ratio levels and the extent of tubulointerstitial lesions among the autopsied cases with normoalbuminuria (urinary albumin-to-creatinine ratio $<$30 mg/g, [$n = 41$]). Nevertheless, this additional analysis did not provide evidence of a significant association between the urinary albumin-to-creatinine ratio levels and the extent of tubulointerstitial lesions (Figure 1). Therefore, these results do not rule out the possibility that the protein leakage associated with glomerular lesions may be masked in cases with normoalbuminuria because the function of reabsorption and degradation in the tubules is preserved owing to relatively mild tubulointerstitial lesions. Nevertheless, given the limited sample size and the influence of postmortem changes in autopsy samples, it would be difficult to prove this issue in our study.

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