

Obesity-Related Glomerulopathy: Hyperfiltration May Contribute to Early Proteinuria



To the Editor: We read with great interest the paper on Obesity-Related Glomerulopathy (ORG) and Single-Nephron GFR (SNGFR) by Okabayashi *et al.* and Denic and Glassock's editorial.^{1,2} Clinicopathological features of ORG include initial glomerulomegaly, podocyte failure and glomerulosclerosis. Marked proteinuria occurs even in early ORG, 874±770 mg/day compared with 29±41 in obese renal donors, an approximately 30-fold increase (CKD Stages 1 and 2, Table 2). Corresponding SNGFR values are 97±43 nl/min and 64±21 nl/min. We recently described a human model of the handling of multiple proteins by the proximal renal tubule, assuming a normal SNGFR value of 80±40 nl/min as determined by Denic *et al.*^{2,3} This model suggests that hyperfiltration itself may cause proteinuria, since renal protein excretion appears very sensitive to SNGFR. This agrees with a previous albumin-handling model in rats.⁴ Increased SNGFR decreases the time glomerular filtrate proteins are available for proximal tubular endocytosis so protein reabsorption decreases and proteinuria develops. Our model predictions of the urinary excretion of the four major proteins in the glomerular filtrate (albumin; α_1 -microglobulin; retinol-binding protein 4 and β_2 -microglobulin) indicate that hyperfiltration may be a key determinant of the proteinuria in early ORG found by Okabayashi *et al.* We estimate that the change in SNGFR observed by Okabayashi *et al.* will *per se* increase albumin excretion approximately five-fold. So hyperfiltration may make a substantial contribution to the proteinuria of early ORG before major podocyte damage increases proteinuria further. Measurements of individual urinary proteins from early ORG patients might confirm this suggestion.

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2. Denic A, Glassock RJ. Obesity-Related Glomerulopathy and Single-Nephron GFR. *Kidney Int Rep.* 2020;5:1126–1128.

3. Edwards A, Christensen EI, Unwin RJ, Norden AGW. Predicting the protein composition of human urine in normal and pathological states: Quantitative description based on Dent1 disease (CLCN5 mutation). *J Physiol.* 2021;599:323–341.
4. Lazzara MJ, Deen WM. Model of albumin reabsorption in the proximal tubule. *Am J Physiol Renal Physiol.* 2007;292:F430–F439.

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Response to Obesity-Related Glomerulopathy: Hyperfiltration may Contribute to early Proteinuria



The Authors Reply: We thank Edwards *et al.*¹ for their letter regarding our article reporting the single-nephron GFR in patients with obesity-related glomerulopathy (ORG).² Glomerulomegaly with focal segmental glomerulosclerosis of perihilar location is a typical renal histopathological finding in ORG, which has long-been considered to represent a state of single-nephron glomerular hyperfiltration. Our results demonstrated single-nephron hyperfiltration in ORG patients and were consistent with the hypothesis of podocyte failure due to intraglomerular hypertension. Another important aspect of glomerular hyperfiltration is the