Commentary on Intraglomerular dysfunction predicts kidney failure in the type 2 diabetes

The substantial renoprotective effects of sodium–glucose cotransporter 2 inhibitors in diabetic kidney disease (DKD) has been reported, and many researchers focus on the glomerular hemodynamic dysfunction for the progression mechanism of DKD. In type 1 diabetes, Cherney et al. measured the inulin (glomerular filtration rate [GFR]) and para-aminohippurate (effective renal plasma flow) clearances, and reported that empagliflozin ameliorated renal glomerular hyperfiltration by affecting tubular–glomerular feedback mechanisms. In diabetes animal models of Akita mice, Kidokoro et al. carried out in vivo multiphoton microscope imaging, and they clearly showed that elevated single-nephron GFR was reversed by empagliflozin associated with amelioration of afferent arteriolar dilatation. The key physiological parameters that determine GFR levels are renal plasma flow, filtration fraction, intraglomerular pressure (PGLO), and balance between afferent and efferent glomerular arteriolar resistance (RA/RE ratio; Figure 1). These parameters are not directly measured in humans; however, they can be estimated from the equations by Gomez. Van Bommel et al. accessed these parameters by inulin and para-aminohippurate clearances in the fasted state, during clamped euglycemia (5 mmol/L) and during clamped hyperglycemia (15 mmol/L) in patients with type 2 diabetes treated with dapagliflozin for 12 weeks. They showed that the reduction of GFR by sodium–glucose cotransporter 2 inhibitor was caused by reduced RG; that is, post-glomerular vasoconstriction.

![](image)

Figure 1 | Gomez equation parameters. By the Gomez equation, afferent renal arteriolar resistance (RA) and efferent renal arteriolar resistance (RE) are calculated by using measured values of the glomerular filtration rate (GFR), renal blood flow (RBF), effective renal plasma flow (RPF), hematocrit (Hct), and serum protein. CM, plasma protein mean concentration; FF, filtration fraction; Cm, gross filtration coefficient; MAP, mean arterial pressure; PBOW, hydrostatic pressure in Bowman’s space; PGLO, glomerular hydrostatic pressure; TP, total protein; PG, glomerular oncotic pressure.

The glomerular hemodynamic studies under treatment with sodium–glucose cotransporter 2 inhibitors were restricted to short-term observation, and it is totally unexplored whether these parameters are critical for the prediction for progression of DKD and renal outcomes by long-term observation studies. A study by Saulnier et al. published in Diabetes in July 2021 reported that significant intraglomerular hemodynamic dysfunction is critical for the progression to end-stage kidney disease in an American Pima people cohort with type 2 diabetes. Of 237 participants with the mean age of 42 years, GFR 153 ml/min and median albumin excretion 36 mg/g creatinine, 69 patients progressed to end-stage kidney disease during the median follow-up period of 17.5 years. After the multivariate adjustment for age, sex, diabetes duration, body mass index, glycated hemoglobin, renin–angiotensin–aldosterone system inhibitor treatment and GFR, increases in renal plasma flow (hazard ratio [HR] 1.91, 95% confidence interval [CI] 1.0–3.03, P = 0.006), RBF (HR 1.76, 95% CI 1.12–2.79, P = 0.007) and RA/RE ratio (HR 2.19, 95% CI 1.21–3.95, P = 0.009), and decreases in filtration fraction (HR 0.53, 95% CI 0.34–0.84, P = 0.015) and PGLO (HR 0.28, 95% CI 0.12–0.64, P = 0.002) predicted end-stage kidney disease risk.

The results are contradictory to previous short-term mechanistic trials to explain hard kidney outcome. As the authors showed that reduced PGLO and increased RA/RE ratio correlated with mesangial expansion by electron microscopy, the reduction of PGLO and elevation of RA/RE ratio might reflect the amelioration of glomerular filtration, as well as histological progression of DKD. Interestingly, the authors elegantly showed distinct trajectory groups by latent class analysis to explain this issue. The unstable trajectory of PGLO (class 1) showed higher PGLO at baseline and progressive decline compared with stable trajectory (class 2). The unstable trajectory of the RA/RE ratio (class 1) showed a

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progressive increase of the $R_A/R_E$ ratio, whereas the $R_A/R_E$ ratio remained at lower levels in the stable trajectory (class 1). The serial time-course evaluation of hemodynamic dysfunction is useful for the classification of patients with DKD and the evaluation of responsiveness to the therapies. As Gomez equation parameters do not reflect the single-nephron function, the development of in vivo methods to evaluate the nephron numbers and single-nephron hemodynamics is required.

**DISCLOSURE**
The author declares no conflict of interest.

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