

## Kidney hemodynamic profile and systemic vascular function in adults with type 2 diabetes: analysis of four clinical trials

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**Background:** Glomerular hyperfiltration is indicated to play a key role in the pathophysiology of diabetic kidney disease (DKD). Mechanisms underlying this adverse hemodynamic profile are incompletely understood. We hypothesized that systemic vascular pathology, a common observation in type 2 diabetes (T2D), relates to glomerular hyperfiltration.

**Methods:** We used baseline data of three randomized trials in adults with T2D (Cohort A,  $n = 111$ ) which assessed kidney hemodynamics including glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and their quotient filtration fraction (FF), with gold-standard measurements of inulin and para-aminohippurate clearance. Systemic vascular resistance (SVR) and pulse pressure (PP) were derived from continuous beat-to-beat monitoring. Additionally, we examined the effects of the nitric oxide synthase inhibitor L-N<sup>G</sup>-monomethyl Arginine (L-NMMA) on these parameters in healthy overweight males (Cohort B;  $n=10$ ).

**Results:** In cohort A, SVR negatively related to GFR ( $\beta:-0.382$ ,  $p<0.001$ ) and ERPF ( $\beta:-0.475$ ,  $p<0.001$ ), and positively related to FF ( $\beta:0.369$   $p<0.001$ ). Associations between SVR, ERPF and FF persisted after multivariable adjustments. PP negatively associated to ERPF ( $\beta:-0.190$ ,  $p=0.048$ ), and positively related to FF ( $\beta:0.232$ ,  $p=0.030$ ), of which the latter remained significant in multivariable regression. In cohort B, L-NMMA increased SVR (median difference ( $\Delta$ )  $138.9 \text{ dyn}\cdot\text{s}/\text{cm}^{-5}$ ,  $p=0.022$ ), in parallel with decreased ERPF (median  $\Delta-108.0 \text{ ml}/\text{min}$   $p=0.011$ ) and increased FF (median  $\Delta 5\%$ ,  $p=0.007$ ), while GFR remained unchanged. SVR and FF were significantly related during L-NMMA infusion ( $r0.638$ ,  $p=0.047$ ).

**Conclusion:** Parameters of systemic vascular function including SVR (suggestive of endothelial dysfunction), and PP (common marker for extent of arterial stiffness), are positively related to FF (indicative for glomerular hyperfiltration). Based on these findings, systemic vascular dysfunction could contribute to the adverse kidney hemodynamic profile, promoting hyperfiltration and predisposing to the development of DKD.