COMMENTS AND RESPONSES

Comment on: Cherney and Sochett. Evolution of Renal Hyperfiltration and Arterial Stiffness From Adolescence Into Early Adulthood in Type 1 Diabetes. Diabetes Care 2011;34:1821–1826

We read the insightful article by Cherney and Sochett (1) with interest. The authors carefully compared changes in kidney hemodynamic function and arterial stiffness in young subjects with type 1 diabetes with and without renal hyperfiltration. During the transition from adolescence to early adulthood, hyperfiltration was not sustained, whereas glomerular filtration rate remained stable in normofiltering subjects. In contrast, arterial stiffness decreased in all patients regardless of filtration status, suggesting that age-related increases in arterial stiffness occur at older ages. It was also mentioned that a variety of factors influence hyperfiltration including the renin-angiotensin system (measured in the study by Cherney and Sochett), cyclooxygenase 2, reduced bioavailability of nitric oxide, etc. However, it was unclear why only a subgroup of type 1 diabetes attained hyperfiltration.

We would like to highlight another hormonal system, adrenomedullin (ADM), a powerful endothelial-derived vasodilator, as one of the possible key players in diabetes-associated vascular hyperperfusion. Our group recently reported elevated plasma ADM concentration in uncomplicated diabetic (0.42 ± 0.13 nmol/L) compared with prediabetic (0.29 ± 0.13) and healthy (0.27 ± 0.09) individuals (P = 0.04) (2) in a large population. We observed that high-sensitivity C-reactive protein, insulin resistance index, LDL cholesterol, and adiponectin were significant predictors of plasma ADM concentrations. This suggested a link between metabolic derangements/proinflammatory milieu and activation of the ADM system. Besides metabolic factors, genetic variation in the ADM system may also influence ADM concentration. ADM clearance may be receptor (ADM receptor) dependent. Preliminary observation from our group suggested an uncommon 5′ haplotype of ADM receptor (nucleotide T&G; formed by rs2279373 and rs12099695, D′ = 0.90, frequency 0.021) was associated with reduced plasma ADM concentration: carrier vs. noncarrier, 0.60 ± 0.34 vs. 0.74 ± 0.69 nmol/L (P = 0.017) (3).

Plasma ADM concentration may contribute to vascular hyperperfusion. We demonstrated that plasma ADM concentrations correlated significantly with laser Doppler–quantified resting forearm cutaneous microcirculatory perfusion (r = 0.43, P = 0.002) (2). Taken together, genetic susceptibility (e.g., in ADM receptor) and metabolic derangement (e.g., diabetes-associated activation of the ADM system) may jointly contribute to hyperfiltration. Therefore, measuring plasma ADM among the hyperfiltrators and normofiltrators in Cherney and Sochett would be interesting. (We speculate that ADM might be higher among hyperfiltrators at baseline.) Understanding the role of ADM in diabetic renal hyperfiltration is clinically relevant because pharmacological agents directed at neutral endopeptidase activity may modulate ADM action (4).

Cherney and Sochett initially hypothesized that arterial stiffness measured by radial artery wave augmentation index (AIx) would increase with time; however, their data were in contrary. The investigators elegantly explained this intriguing observation by documenting a decline in aldosterone and postulated possible influence from pubertal growth hormone elevation. Literature has suggested that AIx varies inversely with height (r = −0.45, P < 0.001) (5). Thus, the unexpected decrement in AIx in the study by Cherney and Sochett might be related to linear growth in study subjects (~4 cm in hyperfiltrator and 3 cm in normofiltrator) transitioning from adolescence to early adulthood. Consistent with this possibility, AIx at baseline was also lower in the taller (170.6 cm) hyperfiltrators (AIx = 1.2%) compared with the shorter (162 cm) normofiltrators (AIx = 14.3%).

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