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Urinary Plasmin(ogen): New Predictor of Hypertension?

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Activation of the epithelial sodium channel (ENaC) by serine proteases may have physiological and pathophysiological relevance. As ENaC transverses the trans-Golgi apparatus, the α-subunit is cleaved twice by furin, releasing a small inhibitory peptide, whereas the γ-subunit is cleaved once; together this converts ENaC from a low- to a moderate-activity state.[1] A second cleavage of ENaC-γ occurs at the plasma membrane and releases an inhibitory peptide from the extracellular region, converting ENaC to a high activity state.[1] This second cleavage of ENaC-γ can be mediated by several serine proteases, including plasmin and prostasin. Prostasin is released by collecting duct cells; however, plasmin is not normally found in tubule fluid.[1] When the glomerular filtration barrier is compromised, plasminogen can reach the tubule lumen where, after proteolysis by urokinase, which is normally present in urine, plasmin is generated with resultant potential activation of ENaC.[1] Plasmin-mediated ENaC activation may be of pathological importance in that an increasing number of reports describe elevated urinary plasmin(ogen) (assays typically do not distinguish between plasminogen and plasmin) in patients with proteinuria and increased blood pressure, including type 2 diabetes mellitus with resistant hypertension,[2] type 1 diabetes,[3] hydronephrosis,[4] kidney transplants,[5] chronic kidney disease with overhydration,[6] preeclampsia,[7] and other conditions. Furthermore, urine from patients with diabetic (types 1 and 2) nephropathy or proteinuric renal transplant recipients showed increased ENaC activity in cultured collecting duct cells and contained elevated cleaved ENaC-γ.[2,3,5] Finally, administration of the serine protease inhibitor aprotinin normalized urinary serine protease activity and cleaved ENaC-γ expression and sodium excretion in experimental nephrotic syndrome.[8] Taken together, these findings suggest that elevated tubule fluid plasminogen/urokinase/plasmin contributes to sodium retention and hypertension in proteinuric kidney diseases.

If glomerular plasminogen leak promotes hypertension, then urinary plasmin(ogen) excretion might not only correlate with coincident hypertension but may also predict hypertension development. One study found that the urine plasmin(ogen)/creatinine ratio (uPl/Cr) at 36 weeks of gestation predicted the development of preeclampsia[7]; however no studies have otherwise examined the relationship between urine plasmin(ogen) and future hypertension development. Now, in this issue of *Kidney International Reports*, Ray and colleagues[9] examine the association between baseline uPl/Cr and subsequent blood pressure (BP) changes. They identified 70 subjects with type 1 diabetes with varying degrees of albuminuria (<30, 30−300, or >300 mg/g albumin/creatinine) who were followed for up to 25 years in the Pittsburgh Epidemiology of Diabetes Complications study. The primary outcomes were increased BP between baseline and the following 2 years (defined as ≥1 SD increase over baseline BP or starting on a new antihypertensive agent), and 25-year incident hypertension (≥140/90 mm Hg); secondary outcomes included 25-year all-cause and cardiovascular mortality. The authors report that baseline uPl/Cr directly correlated with BP and was higher in subjects with an increase in BP over the initial 2-year follow-up period (Figure 1). In addition, subjects in the highest tertile of baseline uPl/Cr (as compared to the lower tertiles) had a greater incidence of hypertension during the 25-year follow-up period. Finally, subjects in the top tertile of baseline uPl/Cr had higher cardiovascular mortality compared to those in the lower tertiles. In general, adjustment for diabetes duration, age, sex, body mass index, estimated glomerular

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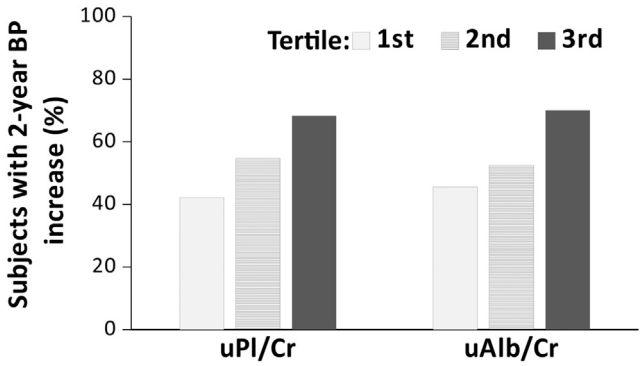

Figure 1. Percent of subjects developing an increase in blood pressure (BP) 2 years after baseline BP determination (defined as ≥1 SD over baseline BP or addition of new BP medications) as a function of lowest (1st tertile), middle (2nd tertile) or highest (3rd tertile) baseline urine plasmin(ogen)/creatinine ratio (uPl/Cr) or baseline urine albumin/creatinine ratio (uAlb/Cr). Adapted from Ray EC, Miller RG, Demko JE, et al. Urinary plasmin(ogen) as a prognostic factor for hypertension [e-pub ahead of print]. *Kidney Int Rep*. https://doi.org/10.1016/j.ekir.2018.06.007. Accessed July 31, 2018.[9]

filtration rate (eGFR), and/or baseline BP did not affect the model fits for hypertension or mortality. In contrast, urine albumin/creatinine ratio (uAlb/Cr) strongly correlated with uPl/Cr, increased 2-year BP (Figure 1), and mortality; adjustment for uAlb/Cr eliminated or substantially reduced the association of uPl/Cr with hypertension and cardiovascular mortality.

What message can be taken away from these findings? A strength of this study is that it analyzed patients longitudinally over up to 25 years who were relatively young (27.8 years), without reduced GFR (baseline eGFR 104 ml/ml per 1.73 m^2) and had low (20% of subjects) prevalent baseline hypertension. This facilitated detection, despite the small sample size, of a direct association between uPl/Cr and incident hypertension and BP increase. However, a major confounder to interpretation is the strong association among albuminuria, uPl/Cr, and the measured outcomes. Any conditions with glomerular leakage of plasminogen (~91 kDa) would likely have impaired glomerular albumin (~67 kDa) permselectivity. Indeed, in this and several other studies, urine plasmin(ogen) directly correlated with urine albumin.[2–7] Furthermore, albuminuria is widely accepted to prognosticate adverse renal and cardiovascular outcomes; tubular luminal albumin may exert direct pathogenic actions and/or is associated with other pathogenic factors when the glomerular filtration barrier is compromised. Notably, uPl/Cr did not improve the prediction of primary or secondary outcomes in the current study beyond that of uAlb/Cr; in the one other uPl/Cr prognostication study, albuminuria was a stronger predictor of preeclampsia than uPl/Cr.[7] Thus, although urinary plasmin(ogen) may be of pathogenic importance in proteinuric states, it is not currently possible to differentiate its contribution to increased BP from that of albuminuria or other factors. Nonetheless, Ray and colleagues are to be congratulated for conducting the first long-term longitudinal study evaluating the association between urinary plasmin(ogen) and increased BP; although substantial challenges exist in discriminating the effects of urinary plasmin(ogen) from those of albumin (and associated factors), these studies represent important steps in identifying pathological mechanisms and novel prognostic markers in hypertension development associated with proteinuric states.

DISCLOSURE

The author declared no competing interests.

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