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Circadian Variation of Intrarenal Renin-Angiotensin System Reflects Salt Sensitivity

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Summary

(Background) We have clarified that intrarenal renin-angiotensin system (RAS) activation is associated with renal damage in the patients of chronic kidney disease (CKD) and hypertension independent of circulating RAS, and that urinary angiotensinogen (AGT) is a useful biomarker that reflects intrarenal RAS activity.

Salt sensitive hypertension is often associated with renal damage in CKD patients, and blood pressure (BP) becomes salt sensitive as renal damage progresses. In addition, salt sensitivity is associated with urinary AGT excretion levels. Moreover, disruption of diurnal BP variation such as nocturnal hypertension is associated with intrarenal RAS activity independent of the absolute values of BP.

The reports about circadian variation for intrarenal RAS are limited. Therefore, we have clarified that the oscillation of intrarenal RAS activation leads to renal damage, hypertension, and diurnal BP variation. However, because the amount of salt intake was not equal, it was possible that the differences of salt intake affected the results. Moreover, it has not been clarified that the levels of salt sensitivity between daytime and nighttime influence BP, intrarenal RAS activity, and renal damage. Therefore, we performed this study to clarify these issues.

(Methods) We recruited 16 IgA nephropathy patients (5 men and 11 women and age: 44.9±16.0 years) without RAS blockers, diuretics or steroid. CKD patients consumed a standard diet (10 g/day of salt), and after data collection, low salt diet (6 g/day of salt) was fed. Daytime (6:00 am to 9:00 pm) and nighttime (9:00 pm to 6:00 am) urine collection were conducted, respectively. We divided the daytime and nighttime for 24-h ambulatory BP monitoring using sleep and waking times.

(Results) BP values, the levels of urinary albumin, protein and AGT excretion during the daytime were significantly higher than those during the nighttime in both a standard and low salt diets. Urinary AGT levels were significantly and positively correlated with the degree of hypertension and the levels of urinary albumin and protein excretion. In addition, urinary AGT fluctuations were significantly and positively correlated with diurnal BP changes and circadian fluctuation of albuminuria and proteinuria.

Urinary AGT levels were significantly and negatively correlated with urinary Na/h in daytime during a standard diet, and urinary protein levels during a standard diet were significantly increased compared with that during a low salt diet in daytime.

Salt sensitivity index in daytime was correlated with urinary AGT excretion in daytime during a standard diet, and tended to be correlated with urinary albumin and protein excretions in daytime during a standard diet.

(Conclusions) Salt loading causes sodium retention by intrarenal RAS activation in daytime, and sodium retention leads to increase of urinary protein excretion. Moreover, salt sensitivity index in daytime indicates a good surrogate marker to estimate the intrarenal RAS activity.

(Perspectives) It has not been confirmed that intrarenal RAS activation due to salt loading causes renal damage, and that amelioration of renal damage due to low salt diet is caused by decrease of BP. In addition, it has not been clarified that salt sensitivity index during salt loading reflects renal damage. We continue this research to clarify these issues.