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Urinary angiotensinogen as a potential biomarker of severity of chronic kidney diseases

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Abstract

We previously reported that urinary excretion rates of angiotensinogen (AGT) provide a specific index of the activity of the intrarenal renin-angiotensin system in angiotensin II-dependent hypertensive rats. Meanwhile, we have recently developed direct enzyme-linked immunosorbent assays (ELISAs) to measure plasma and urinary AGT in humans. This study was performed to test a hypothesis that urinary AGT levels are enhanced in chronic kidney disease (CKD) patients and correlated with some clinical parameters. Eighty patients with CKD (37 women and 43 men, from 18 to 94 years old) and seven healthy volunteers (two women and five men, from 27 to 43 years old) were included. Plasma AGT levels showed a normal distribution; however, urinary AGT-creatinine ratios (UAGT/UCre) deviated from the normal distribution. When a logarithmic transformation was executed, Log(UAGT/UCre) levels showed a normal distribution. Therefore, Log(UAGT/UCre) levels were used for further analyses. Log(UAGT/UCre) levels were not correlated with age, gender, height, body weight, body mass index, systolic blood pressure, diastolic blood pressure, serum sodium levels, serum potassium levels, urinary sodium-creatinine ratios, plasma renin activity, or plasma AGT levels. However, Log(UAGT/UCre) levels were significantly correlated positively with urinary albumin-creatinine ratios, fractional excretion of sodium, urinary protein-creatinine ratios, and serum creatinine, and correlated negatively with estimated glomerular filtration rate. Log(UAGT/UCre) levels were significantly increased in CKD patients compared with control subjects (1.8801 ± 0.0885 vs. 0.9417 ± 0.1048 ; $P = .0024$). These data confirmed our earlier report and showed that a new ELISA assay is a valid approach for measuring urinary AGT.

Keywords

Blood pressure; ELISA; renin-angiotensin system; plasma

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Conflict of interest: none.

Introduction

The renin-angiotensin system (RAS) is well known to play an important role in blood pressure (BP) regulation and fluid and electrolyte homeostasis.¹ In recent years, the focus of interest on the RAS has shifted to a main emphasis on the role of the local/tissue RAS in specific tissues.² Emerging evidence has demonstrated the importance of the tissue RAS in the brain,³ heart,⁴ adrenal glands,⁵ vasculature,^{6,7} as well as the kidneys.¹ There is substantial evidence that the major fraction of angiotensin (Ang II) present in renal tissues is generated locally from angiotensinogen (AGT) delivered to the kidney as well as from AGT locally produced by proximal tubule cells.⁸ Renin secreted by the juxtaglomerular apparatus cells into the renal interstitium and vascular compartment also provides a pathway for the local generation of Ang I.⁹ Angiotensin-converting enzyme (ACE) is abundant in the kidney and is present in proximal tubules, distal tubules, and the collecting ducts.¹⁰ Ang I delivered to the kidney can also be converted to Ang II.¹¹ Therefore, all of the components necessary to generate intrarenal Ang II are present along the nephron.¹

Chronic kidney disease (CKD) is widely recognized as a major health problem all over the world. The renoprotective effects of ACE inhibitors and Ang II type 1 receptor blockers on CKD patients are established in diabetic nephropathy^{12–15} as well as in nondiabetic nephropathy.^{16,17} In order to account for these renoprotective effects, the activated intrarenal RAS was recently proposed to be involved in the progression of renal injury in CKD.¹⁸ The differential regulation of Ang II levels in plasma and kidney is now acknowledged.^{1,18} Recently we reported that urinary excretion rates of AGT provide a specific index of intrarenal RAS status in Ang II-dependent hypertensive rats.^{19–23} We also recently reported that intrarenal AGT immunoreactivity is enhanced in IgA nephropathy patients.²⁴ Moreover, intrarenal AGT immunoreactivity is significantly correlated positively with urinary occult blood, urinary protein-creatinine ratio (UPro/UCre), and serum creatinine, and correlated negatively with creatinine clearance.²⁴ Recently, we provided evidence demonstrating that urinary AGT levels reflect intrarenal Ang II activity associated with increased risk for deterioration of renal function in CKD patients.²⁵ However, in that study, AGT levels were measured by conversion assay.²⁵ This conversion assay requires three steps. First, samples are incubated with and without exogenous renin. Then, Ang I concentrations in paired test tubes are measured by radioimmunoassay. Finally, converted Ang I is calculated as the difference between paired Ang I concentrations. Therefore, this conversion assay needs time-consuming procedures (~2 days), indirect measurements, radioisotopes, and purified renin that is expensive and unobtainable. Meanwhile, we recently developed a direct quantitative method to measure plasma and urinary AGT using human AGT enzyme-linked immunosorbent assays (ELISAs).²⁶ In contrast to the aforementioned conversion assay, the newly developed ELISA does not need time-consuming procedures (~3 hours), indirect measurements, radioisotopes, or purified renin. These data prompted us to measure urinary AGT in CKD patients and investigate correlations with clinical parameters. Therefore, this study was performed to test a hypothesis that urinary AGT levels are enhanced in CKD patients and correlated with some clinical parameters.

Methods

Protocol

The experimental protocol of this study was approved by the Institutional Review Board of Hamamatsu University and Tulane University. Eighty patients with CKD and seven healthy volunteers were included in this study, and all samples were obtained with written informed consent. No subjects received ACE inhibitor or Ang II type 1 receptor blocker. The patients included 37 women and 43 men (from 18 to 94 years) and the volunteers included two women and five men (from 27 to 43 years). The background renal diseases were IgA nephropathy (n

= 17), diabetic nephropathy (n = 14), lupus nephritis (n = 8), membranous nephropathy (n = 4), minimal change nephrotic syndrome (n = 3), nephrosclerosis (n = 3), purpura nephritis (n = 3), non-IgA nephropathy (n = 3), chronic interstitial nephritis (n = 3), membranoproliferative glomerulonephritis (n = 2), focal segmental glomerulosclerosis (n = 1), and chronic renal failure without renal biopsy data (n = 19).

Measurements

Serum concentrations of creatinine, sodium, and potassium, plasma renin activity, and urinary concentrations of sodium and protein were measured in the clinical laboratory in the Hospital of Hamamatsu University School of Medicine. Urinary concentrations of albumin and creatinine were measured by an automated machine (DCA 2000+; Bayer, Tarrytown, NY) with reagent kits (Bayer). Plasma and urinary concentrations of AGT were measured with ELISA kits as previously described.²⁶ The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Formula ($\text{eGFR} = 175 \times \text{standardized serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.741 [\text{if Asian}] \times 0.742 [\text{if female}]$),²⁷ which was found to correlate well with GFR corrected for body surface area in adults.²⁸

Statistical Analysis

Shapiro–Wilk *W* test was used to test the null hypothesis that the data is from the normal distribution. Pearson single regression analyses and Spearman single regression analyses were used for parametric data and nonparametric data, respectively. Standard least squares method was used for multiple regression analysis. Dunnett's test was used to compare group means. All data are presented as mean $\pm$ standard error. A value of $P < .05$ was considered significant. All computations were performed with JMP software (SAS Institute Inc., Cary, NC).

Results

Distributions of Plasma and Urinary AGT Levels

Figure 1 illustrated distributions of plasma AGT levels (Figure 1A), urinary AGT-creatinine ratios (UAGT/UCre) (Figure 1B), and logarithmically transformed UAGT/UCre levels (Log [UAGT/UCre]) (Figure 1C), respectively. Plasma AGT levels showed a normal distribution ($P = .4163$); however, UAGT/UCre levels deviated from the normal distribution ($P < .0001$). When a logarithmic transformation was executed on UAGT/UCre levels, Log(UAGT/UCre) levels showed a normal distribution ($P = .0540$). Therefore, Log(UAGT/UCre) levels were used for further analyses in this study. The differential distribution pattern between plasma and urinary AGT levels implies an independent regulation of plasma AGT and urinary AGT.

Single Regression Analyses

Log(UAGT/UCre) levels were not correlated with age, gender, height, body weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum sodium levels, serum potassium levels, urinary sodium-creatinine ratios, plasma renin activity, or plasma AGT levels (Figure 2A) ($r = 0.0410$; $R^2 = 0.0017$; $P = .7127$). However, Log(UAGT/UCre) levels were significantly correlated positively with urinary albumin-creatinine ratios (UAlb/UCre), fractional excretion of sodium, UPro/UCre, and serum creatinine, and correlated negatively with estimated eGFR (Figure 2B) ($r = -0.6025$; $R^2 = 0.3630$; $P < .0001$). As described previously, we reported that intrarenal AGT immunoreactivity is significantly correlated positively with urinary occult blood, UPro/UCre, and serum creatinine, and correlated negatively with creatinine clearance in IgA nephropathy patients.²⁴ We do not have any data regarding urinary occult blood or intrarenal AGT immunoreactivity in this study; however, these similar correlation patterns may suggest that urinary AGT levels reflect intrarenal AGT protein levels. In general, the increases in UAlb/UCre, UPro/UCre, and serum

creatinine, and the decrease in eGFR represent severity or aggravated renal function in CKD. Therefore, urinary AGT levels were associated with severity or exaggerated renal function in CKD patients.

Multiple Regression Analyses

Factors with significant single correlation with Log(UAGT/UCre) levels were adopted as explanatory variables in multiple regression analysis. To reduce the impact of multicollinearity, we selected explanatory variables so that the mean sum of squares for the residual would be minimal in multiple regression analysis. As a result, fractional excretion of sodium and serum creatinine was excluded as described in the Table. Using remaining three parameters, multiple regression analysis was re-evaluated. As described in Figure 2C, only three parameters can account for almost 60% of variation of Log(UAGT/UCre) levels ($r = 0.7724$; $R^2 = 0.5966$; $P < .0001$).

Urinary AGT Levels in CKD Patients

Figure 3 illustrated Log(UAGT/UCre) levels in CKD patients and in healthy volunteers. Log (UAGT/UCre) levels were significantly increased in CKD patients compared with control subjects (1.8801 ± 0.0885 vs. 0.9417 ± 0.1048 ; $P = .0024$).

Discussion

Origin of Urinary AGT

Although most of the circulating AGT is produced and secreted by the liver, the kidneys also produce AGT.¹⁸ Intrarenal AGT mRNA and protein have been localized to proximal tubule cells indicating that the intratubular Ang II could be derived from locally formed and secreted AGT.^{29,30} The AGT produced in proximal tubule cells appears to be secreted directly into the tubular lumen in addition to producing its metabolites intracellularly and secreting them into the tubular lumen.³¹ Proximal tubular AGT concentrations in anesthetized rats have been reported in the range of 300 to 600 nmol/L, which greatly exceed the free Ang I and Ang II tubular fluid concentrations.¹ Because of its molecular size (50 to ~60-kDa), it seems unlikely that much of the plasma AGT filters across the glomerular membrane further supporting the concept that proximal tubular cells secrete AGT directly into the tubules.³² To determine if circulating AGT is a source of urinary AGT, we infused human AGT into hypertensive and normotensive rats.²² However, circulating human AGT was not detectable in the urine.²² The failure to detect human AGT in the urine indicates limited glomerular permeability and/or tubular degradation. These findings support the hypothesis that urinary AGT originates from the AGT that is formed and secreted by the proximal tubules and not from plasma.

Is Enhanced Urinary AGT in CKD Patients Just a Nonspecific Consequence of Proteinuria?

As described previously, we reported that urinary excretion rates of AGT provide a specific index of intrarenal RAS status in Ang II-dependent hypertensive rats.^{19–23} To determine if the increase in urinary AGT excretion was simply a nonspecific consequence of the proteinuria and hypertension, further studies were done in rats made hypertensive with deoxycorticosterone acetate salt plus a high-salt diet.²² Although urinary protein excretion in deoxycorticosterone acetate salt-induced volume-dependent hypertensive rats was increased to the same or greater extent, urinary AGT was significantly lower in volume-dependent hypertensive rats than in Ang II-dependent hypertensive rats and was not greater than in control rats.²²

Similar observations were obtained in this study. Log(UAGT/UCre) levels in diabetic nephropathy patients (2.6013 ± 0.1326) and that in membranous nephropathy ($2.3890 \pm$

0.3294) were much higher than the average in CKD patients (1.8801 ± 0.0885). It is important to emphasize here that the activated intrarenal RAS was reported in the progression of renal injury in diabetic nephropathy^{33,34} as well as in membranous nephropathy³⁵ in human subjects. In contrast, Log(UAGT/UCre) levels in minimal change (0.8256 ± 0.2034) were similar with control subjects (0.9417 ± 0.1048) even though patients with minimal change showed severe proteinuria. These findings support the hypothesis that the enhanced urinary AGT in CKD patients is not a nonspecific consequence of proteinuria.

Conclusions

Urinary AGT levels were investigated in CKD patients and control subjects. Urinary AGT levels were significantly correlated positively with UAlb/UCre, fractional excretion of sodium, UPro/UCre, and serum creatinine, and correlated negatively with eGFR. Urinary AGT levels were not correlated with age, gender, height, body weight, BMI, SBP, DBP, serum sodium levels, serum potassium levels, urinary sodium-creatinine ratios, plasma renin activity, or plasma AGT levels. Urinary AGT levels were enhanced in CKD patients compared with control subjects. It seems likely that urinary AGT originates from the AGT that is formed and secreted by the proximal tubules and not from plasma, and that the enhanced urinary AGT in CKD patients is not a nonspecific consequence of proteinuria. These data confirmed our earlier report that suggested urinary AGT can be a potential biomarker of severity of CKD, and showed that a new ELISA assay is a valid approach for measuring urinary AGT.

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Figure 1. Distributions of PAGT levels (A), UAGT/UCre (B), and logarithmically transformed UAGT/UCre levels Log(UAGT/UCre), (C), respectively. PAGT, plasma angiotensinogen; UAGT/UCre, urinary AGT-creatinine ratios.

Figure 2.

Single regression analyses for Log(UAGT/UCre) levels with plasma AGT levels (PAGT) (A) and with eGFR (B). (C) Multiple regression analysis for Log(UAGT/UCre) levels. AGT, angiotensinogen; eGFR, estimated glomerular filtration rate; PAGT, plasma angiotensinogen; UAGT/UCre, urinary AGT-creatinine ratios.

Figure 3.

Log(UAGT/UCre) levels in CKD patients and in healthy volunteers. Log(UAGT/UCre) levels were significantly increased in CKD patients compared with that in control subjects. CKD, chronic kidney disease; UAGT/UCre, urinary AGT-creatinine ratios.

Table

Multiple regression analysis by stepwise method for Log(UAGT/UCre)

Term	Estimate	SE	T Ratio	P
Intercept	1.6433	0.2775	5.9227	<.0001*
UPro/UCre	0.0877	0.0263	3.3372	.0013*
UAlb/UCre	0.0006	0.0002	3.2080	.0020*
eGFR	-0.0081	0.0037	-2.2060	.0305*
FENa	5.8406	4.2746	1.3664	.1760
Serum creatinine	0.0044	0.0532	0.0821	.9348

eGFR, estimated glomerular filtration rate; FENa, fractional excretion of sodium; SE, standard error; UAGT/UCre, urinary angiotensinogen-creatinine ratio; UAlb/UCre, urinary albumin-creatinine ratio; UPro/UCre, urinary protein-creatinine ratio.

* $P < .05$.