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Urinary Angiotensinogen as a Novel Biomarker of Intrarenal Renin-Angiotensin System in Chronic Kidney Disease

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SUMMARY

An activated intrarenal reninangiotensin system (RAS) plays a crucial role in the pathogenesis of hypertension and chronic kidney diseases (CKD). Angiotensinogen (AGT) is the only known substrate for renin, which is the rate-limiting enzyme of the RAS. Because the levels of AGT are close to the Michaelis-Menten constant for renin, AGT levels can also control the RAS activity, and upregulation of AGT may lead to elevated angiotensin peptide levels and increases in blood pressure. Recent studies on experimental animal models have documented the involvement of AGT in the intrarenal RAS activation and development of hypertension. Enhanced intrarenal AGT mRNA and/or protein levels occur in experimental models of hypertension and kidney diseases supporting important roles in the development and progression of hypertension and kidney diseases. Urinary excretion rates of AGT provide a specific index of intrarenal RAS status in angiotensin II-infused rats. Also, a direct quantitative method was recently developed to measure urinary AGT using human AGT ELISA. These data prompted us to measure urinary AGT in patients with hypertension and CKD, and investigate correlations with clinical parameters. This brief review will address the potential of urinary AGT as a novel biomarker of the intrarenal RAS status in hypertension and CKD.

Introduction

The activation of the renin-angiotensin system (RAS) plays a crucial role in the pathogenesis of hypertension and chronic kidney diseases (CKD) [1]. In recent years, there has been increased 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] and kidneys [1,8]. Angiotensinogen (AGT) is the only known substrate for renin, which is the rate-limiting enzyme of the RAS. Although most of the circulating AGT is produced and secreted by the liver, the kidneys also produce AGT [9]. Intrarenal AGT mRNA and protein have been localized to proximal tubular cells [10–13]. The major fraction of angiotensin II present in renal tissues is generated locally from AGT delivered to the kidney as well as from AGT locally produced by proximal tubular cells [9,14]. The AGT produced in proximal tubular cells appears to be secreted directly into the tubular lumen in addition to producing its metabolites intracellularly and secreting them into the tubular lumen [15,16]. Because of its molecular size and protein binding, 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 tubular lumen (Figure 1A) [1]. Renin secreted by the juxtaglomerular apparatus cells into the renal interstitium and vascular compartment also provides a pathway for the local generation of angiotensin I [17]. Angiotensin converting enzyme is abundant in the kidneys and is present in proximal tubules, distal tubules, and the collecting ducts [18]. Angiotensin I delivered to the kidney can also be converted to angiotensin II [19]. Therefore, all components necessary to generate intrarenal angiotensin II are present along the nephron [1,8].

Because the levels of AGT are close to the Michaelis-Menten constant for renin, AGT levels can also control the activity of the RAS, and upregulation of AGT levels may lead to elevated angiotensin peptide levels and increases in blood pressure [20,21]. Recent studies on experimental animal models and transgenic mice have documented the involvement of AGT in the activation of the intrarenal RAS and development of hypertension [22–30]. Genetic manipulations that lead to overexpression of AGT have consistently been shown to cause hypertension [31,32]. In human genetic studies, a linkage has been established between the AGT gene and hypertension [33–36]. Enhanced intrarenal AGT mRNA and/or protein levels have also been observed in multiple experimental models of hypertension including angiotensin II-dependent hypertensive rats [13,37–41], Dahl salt-sensitive hypertensive rats [42,43], and spontaneously hypertensive rats [44] as well as in kidney diseases including diabetic nephropathy [45–50], IgA nephropathy [51,52], and radiation nephropathy [53]. Thus, AGT upregulation plays an important role in the development and progression of hypertension and kidney diseases [1,8].

Previous reports have demonstrated that urinary excretion rates of AGT provide a specific index of intrarenal RAS status in angiotensin II-infused rats (Figures 1B – 1D) [13,38–41]. Also, a direct quantitative method was recently developed to measure urinary AGT using human AGT enzyme-linked immunosorbent assay (ELISA) [54]. The ELISA facilitated measurements of urinary AGT in patients with hypertension and CKD, and investigated correlations with clinical parameters. This brief review will address the potential of urinary AGT as a novel biomarker of the intrarenal RAS status in hypertension and CKD.

Urinary AGT in Hypertension

The important role of the activated intrarenal RAS in the pathogenesis of hypertension has been discussed in a recent review article [55].

In a cross-sectional study, Kobori et al reported that urinary AGT levels are significantly greater in hypertensive patients not treated with RAS blockers compared with normotensive subjects (Figure 2A) [56]. Moreover, patients treated with RAS blockers exhibit a marked attenuation of this augmentation. These data suggest that the efficacy of RAS blockade to reduce the intrarenal RAS activity can be assessed by measurements of urinary AGT [56].

In a population study, Kobori et al demonstrated that an activated intrarenal RAS is correlated with high blood pressure in humans [57]. They recruited 251 subjects and collected a single random spot urine sample from each subject. Because urinary AGT levels are significantly increased in patients with diabetes [58] and the use of antihypertensive drugs affects urinary AGT levels [56], they excluded patients who had diabetes and/or were receiving antihypertensive treatment. Consequently, 190 samples were included for this analysis. Urinary AGT levels did not differ with race or gender, but were significantly correlated with systolic and diastolic blood pressure. Moreover, high correlations were shown in men, especially in Black men [57].

These data suggest that urinary AGT provides a novel reflection of the intrarenal RAS status in hypertension.

Urinary AGT in CKD

The important role of an activated intrarenal RAS in the pathogenesis of CKD is extensively discussed in a recent review article [59].

In order to test the hypothesis that urinary AGT levels are enhanced in 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 recruited [58]. Plasma AGT levels showed a normal distribution; however, urinary AGT-to-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 (Figure 2B, 1.8801 +/− 0.0885 vs. 0.9417 +/− 0.1048; P = .0024). These data suggest that urinary angiotensinogen levels can be a potential biomarker of severity of CKD [58].

In order to test the hypothesis that urinary AGT levels are increased in chronic glomerulonephritis patients, 100 urine samples from 70 chronic glomerulonephritis patients (26 from IgA nephropathy, 24 from purpura nephritis, 8 from lupus nephritis, 7 from focal segmental glomerulosclerosis, and 5 from non-IgA mesangial proliferative glomerulonephritis) and 30 normal control subjects were analyzed [60]. UAGT/UCre was correlated positively with diastolic blood pressure ($p = 0.0326$), urinary albumin-creatinine ratio ($p < 0.0001$), urinary protein-creatinine ratio ($p < 0.0001$) and urinary occult blood ($p = 0.0094$). UAGT/UCre was significantly increased in chronic glomerulonephritis patients not treated with RAS blockers compared with control subjects (Figure 3A, $p < 0.0001$). Importantly, patients with glomerulonephritis treated with RAS blockers had a marked attenuation of this augmentation ($p = 0.0021$). These data indicate that urinary AGT are increased in patients with chronic glomerulonephritis and treatment with RAS blockers suppressed UAGT. Thus, the efficacy of RAS blockade to reduce the intrarenal RAS activity can be confirmed by measurement of UAGT in chronic glomerulonephritis patients [60].

In order to test the hypothesis that urinary AGT provides a specific index of intrarenal RAS status in patients with IgA nephropathy, an observational study was performed [61]. This paper is a survey of urine specimens from three groups: healthy volunteers, patients with IgA nephropathy and patients with minor glomerular abnormality. Patients with hypertension, diabetes, reduced glomerular filtration rate and/or who were under any medication were excluded from this study. Urinary AGT levels were not different between healthy volunteers and patients with minor glomerular abnormality. However, urinary AGT levels, renal tissue AGT expression and angiotensin II immunoreactivity were significantly higher in patients with IgA nephropathy than in patients with minor glomerular abnormality. Baseline urinary AGT levels were positively correlated with renal AGT gene expression and angiotensin II immunoreactivity but not with plasma renin activity or the urinary protein excretion rate (Figures 3B – 3E). In patients with IgA nephropathy, treatment with an ARB significantly increased renal plasma flow and decreased filtration fraction, which were associated with reductions in urinary AGT levels. These data indicate that urinary AGT is a powerful tool for determining intrarenal RAS status and associated renal derangement in patients with IgA nephropathy [61].

These data suggest that urinary AGT levels can be used as a novel biomarker of the intrarenal RAS status in patients with CKD.

Summary and Conclusion

This brief review discussed the important role of the activated intrarenal RAS in the pathogenesis of hypertension and CKD. In addition, the potential of urinary AGT as a novel biomarker of the intrarenal RAS status in hypertension and CKD was also addressed. The complicated and pleiotropic roles of an activated RAS in pathogenesis of hypertension and CKD continue to receive recognition from emerging and ongoing studies. Clearly, the use of ARBs and angiotensin converting enzyme inhibitors has become common practice in treating patients with CKD. Since RAS activation plays such a central role in the development and progression of CKD, there has been extensive interest in the potential hope for reduction in morbidity and mortality by using agents that block one or more steps in the RAS. Accordingly, the assessment of urinary AGT as an early biomarker of the status of the intrarenal RAS may be of substantial importance. It may be particularly helpful in serving as a means to determine efficacy of the treatment to reduce intrarenal angiotensin II levels.

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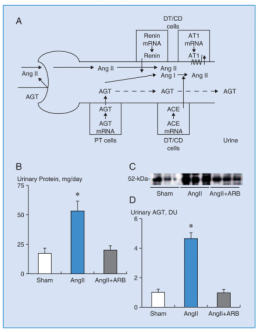

Figure 1.

Figure 1A. Intrarenal renin-angiotensin (Ang) system (RAS) in proximal and distal nephron segments [1]. Because of its molecular size, it seems unlikely that much of the plasma angiotensinogen (AGT) filters across the glomerular membrane. In Ang II-dependent hypertension, increased proximal tubular (PT) secretion of AGT spills over into the distal nephron and increases Ang II effects on distal tubular (DT) reabsorption.

CD, collecting ducts. ACE, Ang converting enzyme. AT1, Ang II type 1 receptors.

Figures 1B – 1D. Urinary protein and AGT excretion rates of each group [38].

B. Urinary excretion rates of total protein were greater in Ang II-infused animals. ARB treatment prevented this augmentation.

C. Representative western blot analysis of urinary AGT levels among groups showing the stimulation in Ang II-infused group.

D. Urinary excretion rates of AGT were increased by 4.7-times in Ang II-infused animals. ARB treatment prevented this augmentation.

ARB, AT1 blocker. DU, densitometric units. *, $p < 0.05$ compared to the sham group.

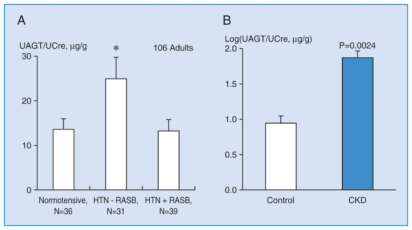

Figure 2.

Figure 2A. UAGT/UCre levels were significantly increased in hypertensive patients not treated with RAS blockers (RASB) compared with normotensive subjects [56]. Patients treated with RAS blockers exhibited a marked attenuation of this augmentation.

*, $p < 0.05$ vs. Normotensive. †, $p < 0.05$ vs. HTN - RASB.

Figure 2B. Log(UAGT/UCre) levels in chronic kidney disease (CKD) patients and in healthy volunteers [58]. Log(UAGT/UCre) levels were significantly increased in CKD patients compared with that in control subjects.

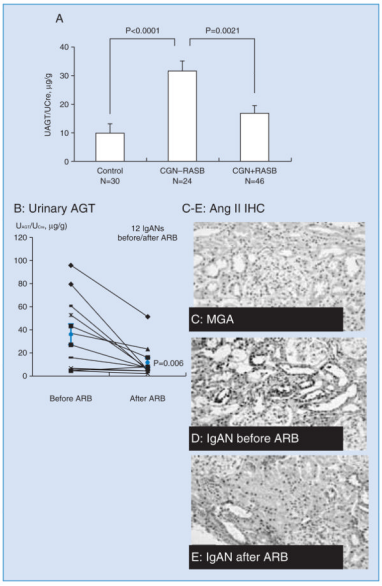

Figure 3.

Figure 3A. UAGT/UCre levels in chronic glomerulonephritis patients (CGN) with/without renin-angiotensin system blockade (RASB) and in control subjects [60].

*, P < 0.05 vs. Control subjects. †, P < 0.05 vs. CGN - RASB.

Figures 3B – 3E. Intrarenal Ang II and urinary AGT in patients with IgA nephropathy [61].

B. Urinary AGT levels were significantly suppressed by ARB treatments.

C–E. Representative images of immunostaining of Ang II in renal tissues from biopsy samples in patients with minor glomerular abnormality (MGA, C) and IgA nephropathy (D–E) are shown.

In the patient with IgA nephropathy, renal biopsy samples were also collected after treatment with an ARB, and Ang II immunostaining was determined. Each pair of the panels D and E comes from one IgA nephropathy patient (pretreatment; D vs. post treatment; E). Immunoreactivity of Ang II in tubules appeared to be higher in patients with IgA nephropathy than in patients with MGA. Furthermore, treatment with ARB decreased immunoreactivity of Ang II in tubules from patients with IgA nephropathy.