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Serum Soluble (Pro) Renin Receptor Level is Increased in Association with Impaired Renal Function in Patients with Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background: The aim of this study was to examine the relationship between the serum soluble prorenin receptor [(P)RR] levels and various clinical parameters of autosomal dominant polycystic kidney disease (ADPKD) patients.

Methods: A total of 79 patients with ADPKD were enrolled and their serum soluble (P)RR levels were measured with ELISA kits. Serum creatinine (Cr), urea nitrogen (UN), uric acid (UA), and albumin levels, blood haemoglobin (Hb) concentration, plasma renin activity (PRA), plasma aldosterone concentration (PAC), and urinary protein/Cr ratio were also measured.

Results: Univariate analyses showed positive correlations between soluble (P)RR levels and age ($P=0.02$, $r=0.27$), serum Cr ($P<0.0001$, $r=0.50$), UN ($P<0.0001$, $r=0.45$), UA ($P=0.04$, $r=0.23$) levels and urinary protein/Cr ratio ($P<0.001$, $r=0.42$), negative correlations with estimated glomerular filtration rate (eGFR) ($P<0.0001$, $r=-0.49$) and Hb concentrations ($P=0.02$, $r=-0.26$), and no correlation with PRA or PAC levels. Soluble (P)RR levels were positively correlated with total kidney volume (TKV, $P<0.01$, $r=0.35$). There was no correlation between soluble (P)RR levels and prescription of renin-angiotensin system inhibitors. Finally, multiple regression analyses showed that serum soluble (P)RR concentration was significantly associated with eGFR after correction TKV.

Conclusions: The serum soluble (P)RR levels correlated with their kidney function of the ADPKD patients, suggesting that soluble (P)RR may be involved in kidney injury and promote the progression of renal dysfunction of ADPKD patients.

Keywords: Polycystin kidney disease; Soluble (pro) renin receptor; Renal function; Total kidney volumes

Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is caused by mutations in *PKD1* or *PKD2*, the genes encoding polycystin-1 and -2. ADPKD affects between 1 in 500 to 1000 people and is characterized by the slow development of large fluid-filled cysts in the kidneys [1]. The cysts cause dramatic enlargement of the kidneys and compromise the functional integrity of the remaining parenchyma. Renal function begins to decline in the fourth decade of life, when the glomerular filtration rate (GFR) starts decrease by 4.4 to 5.9 ml/min per year, and significant impairments of renal function develop by late middle age [2]. The declining GFR rate has been found to be relatively constant in Japanese ADPKD patients and not to be correlated with age or with GFR after adolescence [3].

Patients with ADPKD develop hypertension earlier than those with essential hypertension and early-onset hypertension is the major predictor of renal outcome in ADPKD [4]. Renin, angiotensinogen, and angiotensin (AT)-II are produced in cysts and dilated tubules, and are detected in cystic fluid [5]. Treatment of hypertension by renin-angiotensin system (RAS) inhibitors is effective in delaying decrease of renal function [6,7].

The serum level of prorenin, a precursor of renin, is elevated up to several hundred fold in diabetes patients [8] and is a predictive marker of the onset of microvascular damage. In particular, young diabetic patients with high serum prorenin levels are at increased risk of developing retinopathy and microalbuminuria [9,10]. The (pro)renin receptor [(P)RR] is a specific receptor for renin and prorenin and was identified as a member of the renin-angiotensin system (RAS) by Nguyen et al. [11,12]. (P)RR is a 350-aminoacid protein with a single trans membrane domain and is widely expressed in various organs, including the brain, heart, and kidney [12]. It is possible that increased (P)RR expression may have a role in the pathogenesis of ADPKD via increased intrarenal RAS.

However, despite recent elucidation of the disconnected ligand binding sites of (P)RR and their presence in serum and urine in the form of soluble (P)RR and a possible role of serum soluble (P)RR concentration as a biomarker to reflect the tissue RAS status, the pathophysiology and clinical significance of serum prorenin and soluble (P)RR in ADPKD patients are unclear despite recent progress in kidney disease research [13]. Although it is anticipated that serum soluble (P)RR concentration might be associated with renal function, deterioration of renal function, and total kidney volume (TKV) in these patients, these issues remain to be determined. Therefore, the aim of this study to examine the pathophysiological roles of serum soluble (P)RR in ADPKD patients by investigating the influence of their age, clinical parameters, including renal function, progression of renal dysfunction, and TKV on their serum soluble (P)RR levels.

Materials and Methods

Study population

Patients with previously diagnosed ADPKD or a positive family history for ADPKD had been screened for enrolment, and the diagnosis of ADPKD was based on ultrasonography diagnostic criteria [14]. The ADPKD patients were classified according to estimated GFR (eGFR) calculated by using the formula devised for the Japanese population-eGFR in mL/min/1.73 m²=194 × serum creatinine-1.094 × age-0.287 × 0.739 (for women), as previously described [15]. The rate of change in eGFR (Δ eGFR) was calculated as [(followed eGFR after 5 years-baseline eGFR)/baseline eGFR].

The exclusion criteria were: previous dialysis or kidney transplantation, any type of heart failure, liver cirrhosis, past or current malignancy, pregnancy, acute coronary syndrome or ischemic stroke within 3 months prior to enrolment in the study, initiation of dialysis therapy within 6 months after the diagnosis of ADPKD, immunosuppressant use, and life expectancy less than 1 year. Ultimately, 79 patients were enrolled in the study. The study was approved (No. 2409) by the institutional ethics committee and all participants gave written informed consent to participation in the study. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki.

Measurements of biochemical parameters and TKV

The following baseline demographic and clinical data were recorded: age, gender, body mass index (BMI), and blood pressure (BP). Blood samples for laboratory measurements were drawn in the morning after an at least 8 h overnight fast, and after centrifuging immediately at 1,500 g and 4 for 10 min, the supernatants were stored in aliquots at -80. Blood hemoglobin (Hb) concentrations were analyzed separately.

Laboratory measurements included serum creatinine (Cr), albumin, urea nitrogen (UN), uric acid (UA), total cholesterol, and triglyceride, and the measurements were made by using standard methods. Plasma renin activity (PRA) and plasma aldosterone concentration were measured by

radioimmunoassay. We also calculated the urinary protein/Cr ratio. Total kidney volume (TKV) was measured by high-resolution magnetic resonance imaging based on volumetric measurements of cross-sectional images, as described in the report by the CRISP study [16].

Serum soluble (P)RR levels were measured by using an enzyme-linked immunosorbent assay (ELISA) kit (Takara Bio Inc., Otsu City, Japan) that consisted of a solid-phase sandwich ELISA with antibodies highly specific for each protein [17,18]. The relationships between initial serum soluble (P)RR data, and follow-up clinical parameters on kidney function were then evaluated.

Statistical analysis

All data whose values showed a normal distribution are expressed as the mean \pm standard deviation (SD). Single linear univariate correlations were evaluated using Pearson's correlation coefficient. Groups were compared using one-way analysis of variance, Dunnett's test, and the chi-squared test, as appropriate.

Multiple regression analyses with serum soluble (P)RR levels and eGFR as dependent variables were conducted by a least squares method and a stepwise forward selection method, respectively. Statistical significance was concluded to be present when the P value was <0.05. All statistical analyses were performed using the JMP (Ver. 9) statistical program.

Results

Subjects were subdivided into 5 grades according to their eGFR, and the numbers of patients according to the grade are shown in (Figure 1).

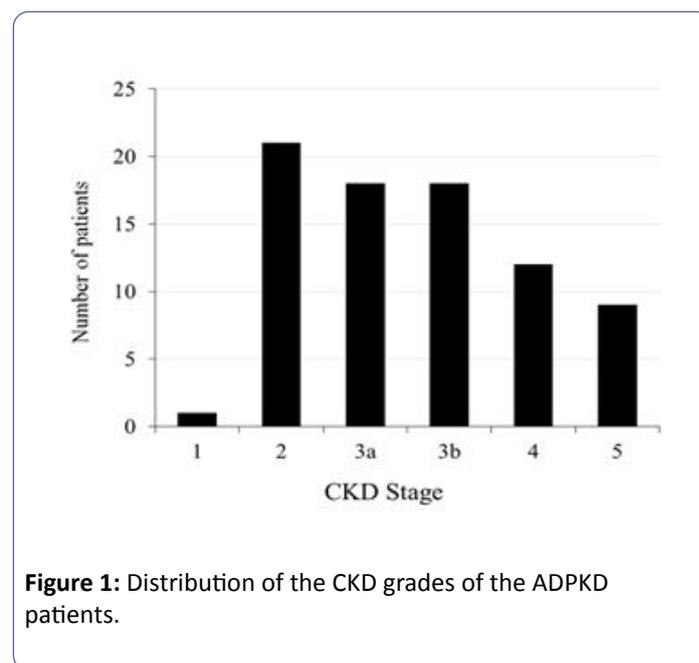


Figure 1: Distribution of the CKD grades of the ADPKD patients.

The clinical characteristics of the 79 ADPKD patients are shown in (Table 1). Their mean age was 51 ± 12 years, and the following were their mean serum Cr level 1.7 ± 1.4 mg/dL, UN

24.9 ± 16.8 mg/dL, UA 6.0 ± 1.2 mg/dL, and eGFR 45.7 ± 23.6 mL/min/1.73 m², and their urinary protein/Cr ratio was 0.1 ± 0.2 mg/g Cr.

Table 1: Clinical characteristics of study population.

Patient characteristics	
Male, n (%)	33 (42.0)
Age (years)	51 ± 12
Body mass index (kg/m ²)	21.4 ± 2.3
Systolic blood pressure (mmHg)	123 ± 12
Diastolic blood pressure (mmHg)	76 ± 8
Mean blood pressure (mmHg)	91 ± 8
Laboratory data	
Hemoglobin (g/dl)	12.6 ± 1.7
Albumin (g/dl)	4.3 ± 0.4
Urea nitrogen (mg/dl)	24.9 ± 16.8
Triglyceride (mg/dl)	129 ± 78
Total cholesterol (mg/dl)	160 ± 54
LDL cholesterol (mg/dl)	107 ± 23
HDL cholesterol (mg/dl)	66 ± 18
Creatinine (Cr, mg/dl)	1.7 ± 1.4
eGFR (ml/min/1.73 m ²)	45.7 ± 23.6
ΔeGFR 5 years rate of change* ¹ (%)	-25.2 ± 22.5
Uric acid (mg/dl)	6.0 ± 1.2
HbA1c (%)	5.6 ± 0.3
Serum soluble (P)RR (ng/ml)	20.3 ± 4.4
Plasma renin activation (ng/ml/h)	4.38 ± 5.91
Plasma aldosterone concentration (pg/ml)	213.8 ± 161.1
Urinary protein to creatinine ratio (g/gCr)	0.1 ± 0.2
Urinary occult blood index* ²	1.1 ± 0.3
Total kidney volume (ml)	1292 ± 679
Anti-hypertensive agents	
ACE inhibitor, n (%)	5 (6.3)
ARB, n (%)	50 (63.3)
Renin inhibitor, n (%)	10 (12.7)
CCB, n (%)	18 (22.8)
* ¹ : (At registration–5 years ago)/5 years ago	
* ² : Count of red blood cells in the urine (0-4/HF=0, 5-9/HF=1, 10-29/HF=2, 30-49/HF=3, 50- 99/HF=4, >100/HF=5)	

The serum soluble (P)RR levels were analyzed for Cr, eGFR, ΔeGFR, UN, UA, age, and the urinary protein/Cr ratio (**Table 2**).

Their soluble (P)RR levels were positively correlated with their serum levels of Cr (P<0.0001, r=0.50), UN (P<0.0001, r=0.45),

and UA (P=0.04, r=0.23), and with their age (P=0.02, r=0.27), and negatively correlated with their Hb concentrations (P=0.02, r=-0.26), eGFR (P<0.0001, r=-0.49) (**Figure 2A**), and ΔeGFR (P<0.01, r=-0.44) (**Figure 2B**).

Table 2: Correlation between serum soluble (P)RR and clinical parameters.

Variables	R	P-value
Male		0.41
Age	0.27	0.02
Body mass index	0.01	0.91
Systolic blood pressure	0.09	0.45
Diastolic blood pressure	0.03	0.82
Mean blood pressure	0.06	0.60
Hemoglobin	-0.26	0.02
Albumin	-0.12	0.29
Triglyceride	0.17	0.18
Total cholesterol	0.29	0.41
Ldl cholesterol	0.19	0.13
Hdl cholesterol	-0.28	0.04
Urea nitrogen	0.45	<0.0001
Creatinine (Cr)	0.5	<0.0001
eGFR	-0.49	<0.0001
5 years rate of change	-0.44	<0.01
Uric acid	0.23	0.04
Hb A1c	-0.06	0.72
Plasma renin activity	-0.10	0.48
Plasma aldosterone concentration	-0.06	0.69
Urinary protein to creatinine ratio	0.42	<0.001
Urinary occult blood index	0.02	0.86
Total kidney volume	0.35	<0.01

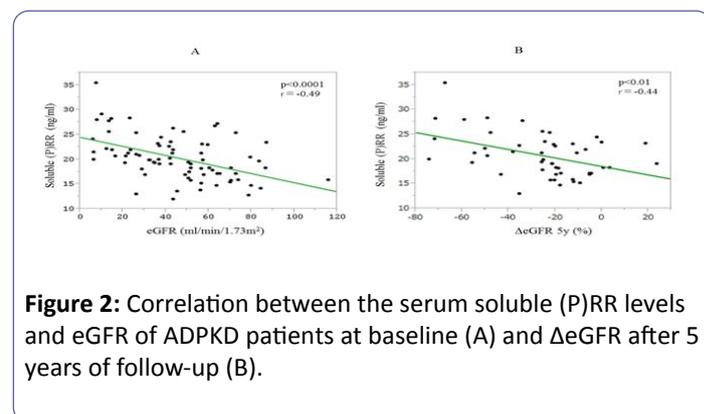


Figure 2: Correlation between the serum soluble (P)RR levels and eGFR of ADPKD patients at baseline (A) and ΔeGFR after 5 years of follow-up (B).

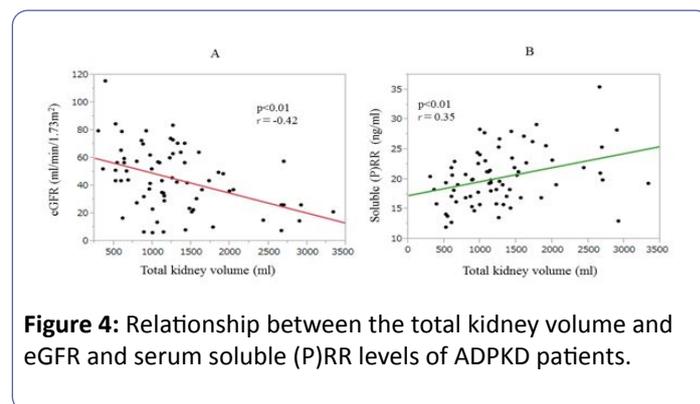
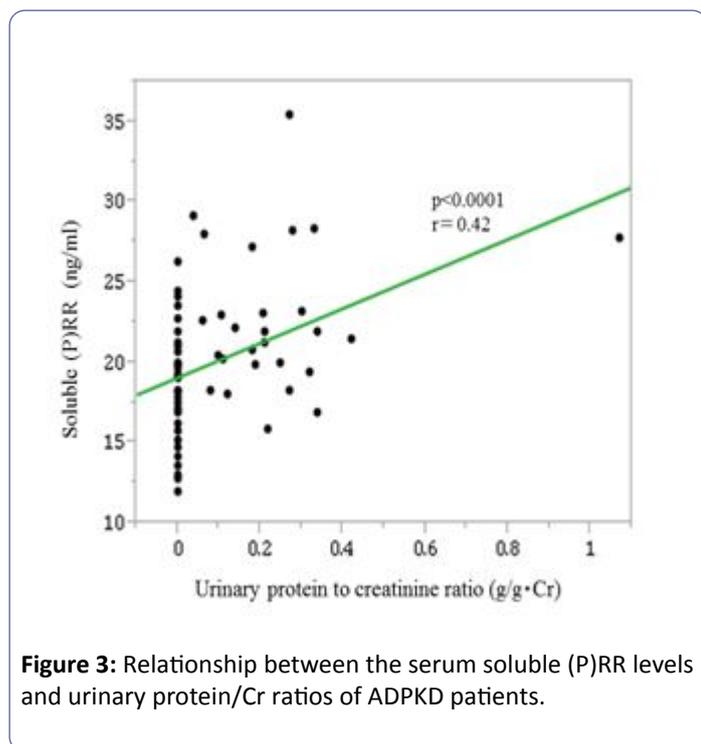


Figure 4: Relationship between the total kidney volume and eGFR and serum soluble (P)RR levels of ADPKD patients.

Their soluble (P)RR levels were positively correlated with their urinary protein/Cr ratios ($P < 0.0001$, $r = 0.42$) (Figure 3), but they were not significantly correlated with PRA ($P = 0.48$, $r = -0.10$) or PAC ($P = 0.69$, $r = -0.06$).

Table 3: Relationship between soluble (P)RR and use of antihypertensive agents.

Variables	P-value
RAS inhibitor	0.65
ACE inhibitor	0.65
ARB	0.77
Renin inhibitor	0.43
CCB	0.10

RAS: Renin-angiotensin System; ACE: Angiotensin-converting Enzyme; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker

Table 4: Multiple regression analysis for correlation with total kidney volume.

Variables	β	P-value
Soluble (P)RR	0.18	0.15
eGFR	-0.34	<math>< 0.01</math>

Investigation of the relationships between soluble (P)RR levels and use of antihypertensive drugs showed no significant differences between soluble (P)RR levels according to whether patients were treated with antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEIs, $P = 0.65$), angiotensin receptor blockers (ARBs, $P = 0.77$), and calcium channel blockers ($P = 0.10$) (Table 3).

The TKVs were negatively correlated with eGFR ($P < 0.01$, $r = -0.42$) (Figure 4A). Interestingly, the soluble (P)RR levels of the ADPKD patients were positively correlated with their TKVs ($P < 0.01$, $r = 0.35$) (Figure 4B), and the multiple regression analysis showed that their TKVs were negatively correlated with eGFR ($P < 0.01$, $r = -0.34$) but not with their serum soluble (P)RR levels ($P = 0.15$, $r = 0.18$) (Table 4).

Discussion

The results of this study showed that the soluble (P)RR levels of the ADPKD patients were positively correlated with their serum Cr, UN, and UA levels, and with their urinary protein/Cr ratios, and negatively correlated with their eGFR and Hb values. Notably, the simple regression analyses showed that their soluble (P)RR levels were significantly correlated with their TKVs. Interestingly, the basal soluble (P)RR levels were negatively correlated with their Δ eGFR at 5 years. In addition, serum soluble (P)RR concentration was significantly negatively associated with eGFR independent of other factors including TKV. To the best of our knowledge, this is the first study to demonstrate relationships between the serum soluble (P)RR levels of ADPKD patients and their disease severity and progression, TKVs, and antihypertensive therapy.

The expression of (P)RR in the kidneys suggested that prorenin may be able to generate angiotensin (AT)-I from angiotensinogen by binding to (P)RR. If it does, the subsequent overproduction of AT-II may then stimulate inflammation and fibrosis in the renal interstitial space. Alternatively, (P)RR may play a role in the tubular transport of water and electrolytes, including H₂O. A previous study reported observing increased (P)RR expression in the remnant kidneys of 5/6 nephrectomised rats [20]. A study conducted by Ichihara et al. showed that a (P)RR blocker administered to rats with streptozotocin-induced diabetes or spontaneous hypertension was able to inhibit the development and progression of end-organ damage and that it had a greater benefit than conventional inhibitors in relation to the RAS in diabetic AT-II type 1a receptor-deficient mice [21].

(P)RR has recently been shown to function as an adaptor between Wnt receptors in a renin-independent manner and the vacuolar H-adenosine triphosphatase (V-ATPase) complex, and (P)RR and V-ATPase are required to mediate Wnt signalling [22]. If soluble (P)RR levels reflect (P)RR levels in the kidneys, the increased levels of soluble (P)RR might reflect activation of renal

(P)RR to promote the progression of kidney injury and fibrosis in ADPKD. However, the increased soluble (P)RR levels may have simply been the results of decreased GFR. A recent report suggested that soluble (P)RR in the renal medulla is stimulated during AT-II-dependent hypertension and that this form of the (P)RR is secreted into the tubular fluid [23]. This finding indicates that soluble (P)RR levels might be increased as a result of decreased GFR. Although (P)RR-mediated signalling is thought to be involved in the development of glomerular diseases, (P)RR expression in podocytes and its function in autophagy suggests a physiological rather than a pathological role in the kidneys [24]. The function of (P)RR in ADPKD remains unknown, but based on our findings in this study, we hypothesized that elevated serum (P)RR levels may imply increase expression of (P)RR in the kidneys to promote the deterioration of renal function in ADPKD.

While relatively few studies have described the regulatory mechanisms of (P)RR expression, the results of a recent study suggest that (P)RR expression may be regulated by renin through a negative feedback loop [25]. In fact, up-regulation of renal renin and down regulation of renal (P)RR have been observed after ACE inhibition and a change to a low-salt diet [26]. Renin down-regulates (P)RR expression by a process involving the transcription factor promyelocytic zinc finger protein [24]. Whether the increased serum (P)RR levels in ADPKD are the result of a negative feedback signal in the form of decreased intrarenal renin remains to be clarified [26].

Hamada et al. have recently measured the serum soluble (P)RR levels of 374 patients with chronic kidney disease (CKD) [27], and shown that they were positively correlated with their serum Cr, UN, and UA levels, urinary protein/Cr ratio, and negatively correlated with their eGFRs and Hb concentrations. These results are consistent with findings in the present study. The results obtained by Hamada et al. with respect to antihypertensive drugs showed that the soluble (P)RR levels of the group with an ARB were significantly lower than in the group not treated with an ARB [27]. Their results for the relationship between basal soluble (P)RR levels and renal dysfunction showed that soluble (P)RR levels were inversely associated with Δ eGFR, suggesting that soluble (P)RR may be involved in kidney injury and promote the progression of CKD.

The plasma soluble (P)RR levels of healthy subjects have been found not to correlate with their renin, prorenin, or aldosterone levels [28], but the serum soluble (P)RR levels have been shown to be negatively correlated with eGFR independent of age, blood pressure, and glucose metabolism in essential hypertension and normotensive subjects [29]. In addition, the serum soluble (P)RR levels have been shown to be positively correlated with their urinary levels of angiotensinogen, a biomarker of intrarenal RAS [29,30]. In human kidneys with end-stage renal disease (ESRD), intrarenal (P)RR was immunostained mainly in the tubules, suggesting a possible contribution of increased renal (P)RR expression to the elevated serum soluble (P)RR levels in ESRD [31]. The above findings suggest that soluble (P)RR might reflect intrarenal RAS status. It is proposed that over activity of the intrarenal RAS might be associated with the sustained increases

in intratubular AT-II concentrations, whereby the intrarenal RAS activation induces cyst enlargement in ADPKD [5].

In the present study, multiple regression analysis revealed that serum soluble (P)RR concentration was significantly associated with eGFR after correction for other factors including TKV. This finding is noteworthy because it may suggest that renal dysfunction is due not only to cyst formation but also to increase AT-II synthesized by (P)RR in non-cystic renal parenchyma of the kidney. It is expected that intervention to inhibit intrarenal (P)RR expression may be beneficial in protecting renal function in ADPKD, although this presumption needs to be tested by further examinations.

The present study had several limitations. First, we did not include healthy volunteers and were therefore unable to measure the soluble (P)RR levels of healthy subjects for comparison. Age may also be associated with changes in soluble (P)RR levels, and we hope to investigate the possible association in future studies. Second, our study was retrospective and cross-sectional in nature, and we did not investigate for possible changes in soluble (P)RR levels over time. Monitoring the soluble (P)RR levels of ADPKD patients over time would be useful as a means of assessing its potential role as a biomarker of kidney disease progression. Based on the results of this study, we would like to determine the relationship between soluble (P)RR and the (P)RR levels in kidney tissue in a future prospective study. Third, we were unable to determine prorenin activation levels, because the samples had been preserved before testing. Such information would have provided further insight into the role of soluble (P)RR in the RAS.

In summary, the results of this study showed that the serum soluble (P)RR levels are correlated with their renal function of ADPKD patients. We speculate that elevated serum soluble (P)RR level might reflect increased expression of renal (P)RR which might promote the progression of kidney injury in ADPKD patients. The results of previous studies in animal disease models in which (P)RR function was blocked have suggested that (P)RR is involved in the pathogenesis of CKD, and that prorenin/(P)RR is involved in the onset and progression of organ injury. Thus, further study of prorenin/(P)RR in ADPKD may clarify disease progression and the potential role of soluble (P)RR as a marker of renal disease progression.

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Statements of Ethics

All participants provided written informed consent. The study was supported by grants from Otsuka Pharmaceutical Co., Chugai Pharmaceutical Co., Kyowa Hakko Kirin Co., MSD Co. and JMS Co.

Disclosure Statement

The authors have no conflicts of interest to declare.

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