RESEARCH PAPER

Renalase Levels in Children with Solitary Functioning Kidney

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Objective: To measure serum and urine renalase levels in children with a single kidney, and to compare with a reference group.

Methods: Participants were: solitary kidney (*n*=36) and healthy children (*n*=57). Renalase levels were measured using the immunoenzymatic method.

Results: Serum and urine renalase levels were significantly lower in patients with a solitary kidney compared to healthy children. Urine renalase/creatinine values were negatively related to serum creatinine and positively related to glomerular filtration rate. Significant correlations between renalase levels and blood pressure were not found.

Conclusions: Prognostic importance of reduced renalase levels in children with a single kidney can only be quantified by further longitudinal study.

Keywords: *Chronic kidney disease, Nephrectomy, Solitary functioning kidney*

The long-term outlook for patients born with a single kidney or following unilateral nephrectomy in childhood is controversial. Animal studies suggest that the resultant compensatory increase in single nephron glomerular filtration rate may lead to progressive damage of the remaining renal tissue leading to hypertension [1]. Low nephron number is reported to be associated with hypertension and chronic kidney disease in humans [2,3].

Xu, *et al*. [4] described a novel substance called renalase, and its possible role in the pathogenesis of cardiovascular complications. Renalase is a monoamine oxidase of renal origin responsible for the degradation of catecholamines. Renalase lowers blood pressure by decreasing cardiac contractility and heart rate and by preventing the expected compensatory increase in peripheral vascular tone. Abnormalities in the renalase pathway are described in animal models of hypertension and chronic kidney disease [5].

This study was performed to measure serum and urine renalase levels in children with a solitary functioning kidney, and compare these with healthy children.

METHODS

Inclusion criteria for cases were: age <18 years, and a solitary functioning kidney (congenital or acquired) demonstrated by ultrasonography and renal scintigraphy. Exclusion criteria were: clinical and laboratory signs of infection, history of urinary tract infection, use of medications that might influence renal function or any kidney abnormalities detectable by ultrasonography. The reference group was recruited from participants of the OLAF study [6], whose physical examination, urine and blood tests, and renal ultrasonography were normal. The study was approved by the Medical University Ethics Committee.

Research methodology involved recording clinical history, demographic data, and physical examination. Hypertension was defined as blood pressure >95th percentile for age, sex, and height. Venous peripheral blood after overnight fasting, and morning urine samples were collected. Serum and urine samples were frozen and stored at –80°C. Laboratory tests included: serum creatinine, urea, uric acid and urinalysis. Glomerular filtration rate was assessed by an updated Schwartz formula. Microalbuminuria was defined as urinary albumin/creatinine ratio of 30-300 µg/mg.

Using a commercial enzyme-linked immunosorbent assay kit (USCN Life Science Inc., China), serum and urine renalase levels were measured and expressed as micrograms per milliliter (µg/mL) in the serum, and nanograms per milliliter (ng/mL) in the urine. The intra- and inter-assay coefficients of variance were 10% and 12%, respectively. Detection range was 3.12-200 ng/mL.

The data were analyzed using Statistica 10.0 software (StatSoft, Tulsa, OK, USA).

RESULTS

The study cohort consisted of 93 participants divided into: children with a single kidney (*n*=36). and reference groups (*n*=57). Clinical and biochemical data of recruited patients are summarized in ***Table* I**. Of 36 patients eligible for analysis, 27 (75%) had a congenital and 9 (25%) had an acquired solitary functioning kidney. The etiologies of the acquired single kidney were: ureteropelvic junction obstruction (*n*=12), ureterovesical junction obstruction (*n*=57), and reflux nephropathy (*n*=57). Clinical and laboratory data of congenital single kidney patients did not differ from those with acquired single kidneys. None of our single kidney patients had proteinuria in morning samples; however, 4/36 patients (11%) were diagnosed with albuminuria. In the single kidney group, 10 children (27.7%) were hypertensive. Glomerular filtration rate <90 mL/min/1.73m^2 was found in six patients.

Median serum and urine renalase levels were significantly lower in single kidney patients when compared to the reference group (*P*<0.05). Urinary renalase/creatinine levels were comparable in both groups (***Fig.* 1**).

Between the congenital and acquired single kidney participants, or children with various etiologies of acquired solitary functioning kidney, we found no differences in the serum and urine renalase concentrations. Identical results were also obtained from hypertensive and normotensive children.

We did not find significant correlation between renalase levels and blood pressure. In the single kidney group, no statistically significant difference was stand between the number of children with decreased urine renalase/creatinine levels (<50th centile) who were normotensive and hypertensive (*P*=0.71). Reduction in urine renalase excretion was estimated according to reference urine renalase values from the study of Rybi-Szumińska, *et al*. [7].

Serum renalase positively correlated with urine renalase (r=0.35, *P*<0.05). The urine renalase/creatinine values were negatively related to serum creatinine (r=-0.35; *P*<0.05), and positively to glomerular filtration rate (r=0.37; *P*<0.05). Kidney overgrowth did not correlate with serum and urinary renalase, glomerular filtration rate, and urinary albumin/creatinine ratio.

ROC analyses were performed in order to define the diagnostic efficiency of serum and urine renalase in identifying children with renal dysfunction (glomerular filtration rate <90 mL/min/1.73m^2) among patients with a solitary functioning kidney. In this analysis AUC for serum (µg/mL) and urine renalase (ng/mL) did not reveal good diagnostic accuracy in comparison to the urinary albumin/creatinine ratio, and was 0.425, 0.587, and 0.985, respectively.

DISCUSSION

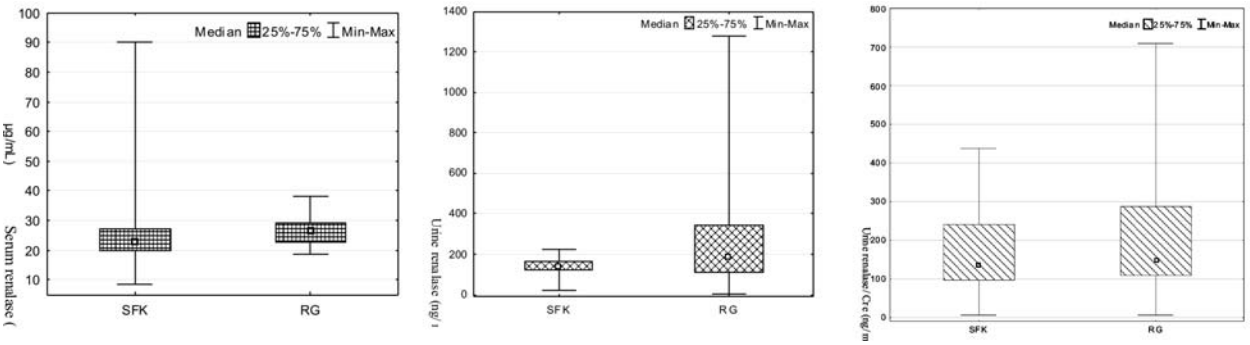
Our study, designed to explore serum and urine renalase levels and their relation to kidney function in children

TABLE I CLINICAL AND LABORATORY DATA OF THE CHILDREN WITH SOLITARY FUNCTIONING KIDNEY AND REFERENCE GROUP

	Solitary functioning kidney median (IQR) (N=36)	*Reference median (IQR) (N=57)*	*P value*
Gender (M/F)	23/13	35/22	
Age (y)	11.25 (6, 14)	12 (7.5, 16)	0.26
Weight (kg)	37 (27.7, 60.5)	37 (25.0, 58.6)	0.94
Height (cm)	145.7 (124.7, 163.5)	143 (126.3, 169)	0.49
Body mass index Z-score	1.01 (–0.19, 1.79)	0.28 (–0.26, 1.23)	0.09
Serum creatinine (mg/dL)	0.55 (0.46, 0.66)	0.62 (0.49, 0.73)	0.19
Glomerular filtration rate (mL/min/1.73 m^2)	107.38 (94.87 , 124.77)	106.31 (97.11, 134.22)	0.72
Serum renalase (µg/mL)	23.07 (19.96, 27.22)	26.75 (22.64, 29.20)	0.04
Urine renalase (ng/mL)	145.28 (121.15, 163.33)	187.93 (112.83, 342.25)	0.01
Urinary renalase-to-creatinine ratio (ng/mg)	137.68 (96.05, 239.43)	187.93 (110.45, 286.66)	0.64
Kidney overgrowth (%)	41.20 (20.25, 55.10)	–	–
Urinary albumin-to-creatinine ratio (µg/mg)	69.15 (37.68, 91.71)	–	–
Systolic blood pressure (centile)	71 (44, 89)	58 (10, 63)	0.44
Diastolic blood pressure (centile)	60 (40, 73)	49 (12, 72)	0.47

WHAT THIS STUDY ADDS?

- Serum and urine renalase levels are significantly lower in patients with a solitary functioning kidney in comparison to healthy children.
- Prognostic importance of reduced levels of renalase does not seem to be suitable for the detection of early renal damage in children with solitary functioning kidney.



(a) *(b)* *(c)*

FIG. 1 *Comparison of serum (a), and urine renalase levels (b and c) in patients with solitary functioning kidney (SFK) and healthy participants (RG).*

with a single kidney, reported that serum and urine renalase levels were significantly lower in single kidney patients. We did not find significant differences in urine renalase/creatinine levels between children with a solitary functioning kidney and the reference groups. Moreover, urine renalase/creatinine values in single kidney patients was related to parameters of kidney function: negatively with serum creatinine and positively with glomerular filtration rate. Neither serum nor urine renalase correlated with age, gender, or blood pressure.

The limitations of the study are: small sample size, single center, and cross-sectional. Additionally, an appropriate measurement of blood pressure in small children is difficult because of "white coat" anxiety and poor cooperation. Furthermore, in prepubertal and younger children no formula of glomerular filtration rate estimation gives acceptable results.

Recent experimental data in animal models support the hypothesis that renalase is an important marker of chronic kidney disease [5]. In humans, several studies have examined the likelihood that the presence of a solitary functioning kidney increases the risk of hypertension, proteinuria, and renal failure during childhood [8]. It has been shown that an apparently normal kidney is usually associated with hypertrophy of the surviving nephrons and accompanied by renal hyperfiltration which may contribute to albuminuria and a decline in glomerular filtration rate.

Patients with chronic kidney disease demonstrate markedly reduced levels of plasma renalase [9]. Based on our findings, significant reductions in serum and urine renalase levels dependent on kidney function were reported in single kidney patients compared with healthy volunteers. Our finding of no significant relationships between serum or urine renalase levels with age, gender, or blood pressure is in agreement with studies in dialyzed adult patients [10].

Based upon these results, a decrease in renalase levels may be related to early renal damage. However, these findings should be interpreted with caution because data from our ROC analyses did not show good diagnostic profiles for renalase in detection of renal dysfunction.

We conclude that renalase levels are altered but are unlikely to be suitable for the detection of early renal damage. Prognostic importance of reduced levels of renalase in children with a solitary functioning kidney to detect early deterioration of kidney functions before hypertension develops should be quantified by further longitudinal studies.

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