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RESEARCH REPORT

Urine Beta2-Microglobulin Is an Early Marker of Renal Involvement in LPI

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Abstract *Objective*: Lysinuric protein intolerance (LPI) is a rare autosomal recessive disorder affecting the transport of cationic amino acids. It has previously been shown that approximately one third of the Finnish LPI patients have impaired renal function. The aim of this study was to analyse in detail urine beta2-microglobulin values, renal dysfunction, oral L-citrulline doses and plasma citrulline concentrations in Finnish LPI patients.

Methods and results: Of the 41 Finnish LPI patients, 56% had proteinuria and 53% hematuria. Mean plasma creatinine concentration was elevated in 48%, serum cystatin C in 62%, and urine beta2-microglobulin in 90% of the patients. Seventeen per cent of the patients developed ESRD, and five of them received a kidney transplant.

L-citrulline doses and fasting plasma citrulline concentrations were similar in adult LPI patients with decreased and normal GFR (mean ± SD 79.5 ± 29.2 vs. 82.4 ± 21.9 mg/kg/day, $P = 0.619$, and 80.3 ± 20.1 vs. 64.8 ± 23.0 μmol/l, $P = 0.362$, respectively).

Conclusions: Urine beta2-microglobulin is a sensitive early marker of renal involvement, and it should be monitored regularly in LPI patients. Weight-based oral L-citrulline doses and plasma citrulline concentrations were not associated with renal function. LPI patients with ESRD were successfully treated with dialysis and kidney transplantation.

Abbreviations

CKD-EPI	The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
LPI	Lysinuric protein intolerance
MDRD	Modification of diet in renal disease
SLC7A7	Solute carrier family 7, member 7
y+LAT-1	y+L amino acid transporter-1

Introduction

Lysinuric protein intolerance (LPI) is a rare autosomal recessive disorder affecting transport of dibasic cationic amino acids lysine, arginine and ornithine in the basolateral membrane in intestine and renal tubules (Perheentupa and Visakorpi 1965; Norio et al. 1971; Rajantie et al. 1980a). It is caused by mutations in the gene SLC7A7 (solute carrier family 7, member 7) which encodes the y+LAT-1 protein, the catalytic light chain subunit of the heteromeric amino acid transporter. All Finnish patients share the same homozygous mutation, a substitution of T for A at cDNA position 1181–2 (Borsani et al. 1999; Torrents et al. 1998, 1999). LPI is more prevalent in Finland than elsewhere in the world, but several patients have been reported from, e.g. Italy and Japan (Incerti et al. 1993; Koizumi et al. 2000).

Because of reduced intestinal absorption and renal reabsorption of dibasic cationic amino acids, plasma

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concentrations of lysine, arginine and ornithine are low in patients with LPI. It is believed that the lack of arginine and ornithine causes secondary dysfunction of the urea cycle, resulting in protein aversion and hyperammonemia after dietary protein loads. Lysine deficiency is supposed to have an influence on immune system and growth.

LPI was first described as late as in 1965, and thus the knowledge of the natural progression of the disease is still limited. Newborns with LPI are usually asymptomatic until the amount of dietary protein increases. Later, the principal symptoms are nausea, vomiting, failure to thrive, growth retardation, hepatosplenomegaly, muscular weakness and osteoporosis. In addition, hypercholesterolemia, hypertriglyceridemia, hematologic abnormalities and deficient B cell function have been reported (Simell et al. 1975; Lukkarinen et al. 1999; Simell 2001; Tanner et al. 2010). Life-threatening complications include nephropathy, pulmonary fibrosis and alveolar proteinosis, the mechanisms of which are still unclear (DiRocco et al. 1993; Parto et al. 1994; Tanner et al. 2007).

Treatment of LPI consists of dietary protein restriction, oral L-citrulline supplementation to boost the urea cycle, L-lysine hydrochloride to correct lysine deficiency and, in some patients, sodium benzoate or sodium phenylbutyrate to scavenge ammonia (Simell 2001). Some patients may also require L-carnitine supplementation (Tanner et al. 2008).

In 2007, we reported (Tanner et al. 2007) that one third of the Finnish patients with LPI had signs of renal dysfunction, in some of them leading to end-stage renal disease (ESRD). The causes of this complication have remained unknown. In this study, we describe in detail the urine beta-2-microglobulin values, renal involvement, oral L-citrulline doses and plasma citrulline concentrations of all Finnish LPI patients in our cohort.

Patients and Methods

The follow-up of Finnish LPI patients is centralised to the Department of Pediatrics at the Turku University Hospital. The patients visit our outpatient clinic 1–2 times per year. The current study cohort consists of 41 patients (26 female). Mean age of the patients was 37.3 years (range 3 to 69 years), and six patients were under 18 years of age. Two patients died during the follow-up in 2007–2013 period.

In this study, we analysed retrospectively medical records and laboratory tests of the patients from 2007 to 2013. Hypertension, renal function tests, urinary protein and amino acid excretion, and plasma citrulline concentrations were the particular objects of interest. The development of renal dysfunction was investigated by observing changes in plasma creatinine, serum cystatin C and urine beta2-microglobulin levels over time.

Sitting blood pressure was measured annually after 15 min rest using average values of three consecutive blood pressure measurements from right arm using an oscillometric noninvasive blood pressure monitor (GE Dinamap Carescape V100 monitor). Size of the cuff was chosen according to the size of the right arm. All laboratory analyses were performed using standard clinical laboratory methods. Urine amino acids were measured from morning spot urine and plasma amino acids in fasting plasma with HPLC. Urine beta-2-microglobulin was analysed in morning spot urine using chemiluminescence detection. Proteinuria was measured from 24 h urine and also by using urine dipstick test (positive if proteins ++ or +++). Hematuria was defined using urine dipstick test. Glomerular filtration rate (GFR) was calculated using Cockcroft-Gault formula, 4-variable MDRD formula and CKD-EPI formula for adults and Schwartz formula for patients under 18 years of age. The data were analysed using IBM SPSS Statistics 22.0 software. Only adults were included in the statistical analyses of weight-based citrulline doses and fasting plasma citrulline concentrations. One patient had not used L-citrulline regularly and was excluded from these analyses. The patients with ESRD have been analysed separately.

This study was approved by the joint Ethics Committee of the University of Turku and Turku University Hospital.

Results

Characteristics of 41 patients with LPI are presented in Table 1. At the time of this study, 20 of the 36 patients (56%) had proteinuria (urine protein >0.1 g/24 h or urine albumin >30 mg/24 h) and nineteen of them (53%) had hematuria (positive urine dipstick test). Twenty-four hour urine was collected from 24 patients for protein excretion measurements. Seventeen of them (71%) had albuminuria, 46% had microalbuminuria (urine albumin 30–300 mg/24 h) and 25% had macroalbuminuria (urine albumin >300 mg/24 h). Plasma creatinine concentration was elevated in 48% and serum cystatin C in 62% of the patients. Urine beta2-microglobulin was measured from 31 patients and was elevated in 28 of them (90%). 4-variable MDRD formula (normal >60 ml/min/1.73 m^2), Cockcroft-Gault formula (normal >90 ml/min) and CKD-EPI formula (normal >90 ml/min/1.73 m^2) showed decreased GFR in 18, 28 and 25 patients, respectively. There was a correlation between beta2-microglobulin and GFR ($r = -0.69$, $P < 0.001$) (Tables 2 and 3). Table 4 shows that in some LPI patients, a rapid elevation of urine beta2-microglobulin preceded decrease of GFR. There was no correlation between urine beta2-microglobulin and urine albumin

Table 1 A summary of the follow-up data of the 41 patients with LPI at Turku University Hospital in 2007–2013

Patient number	Sex	Age at study	Proteinuria	Hematuria	Hypertension (RR > 140/90 mmHg)	Estimated GFR			Elevated serum cystatin C	Elevated urine beta2-microglobulin	Bicarbonate supplementation	Phospate supplementation	ESRD[b]
						4v-MDRD[a]	Cockcroft-Gault	CKD-EPI					
1	F	3				162							
2	M	10				289				+			
3	F	10				250				+			
4	F	16		+		104				+			
5	F	16				109				+			
6	F	17				112			+	+			
7	F	18	+			74.7			+	+	+	+	
8	F	20				111	116	126		+			
9	F	21	+	+		31	32	34	+	+	+	+	
10	M	22	+	+		46	43	47	+		+	+	
11	F	24	+	+		60	74	69	+	+		+	
12	F	28				80	79	93		+			
13	F	29	+		+	79	64	93			+		+
14	M	29	+	+	+	32	38	35	+	+		+	+
15	M	30				79	109	90		+			
16	F	32			+	84	159	99	+	+		+	
17	F	33	+	+		46	51	52	+	+			
18	M	36		+	+	99	81	111					
19	M	38		+	+	77	99	87		+			
20	F	39		+		82	102	96		+			
21	F	39	+	+		8	9	8	+	+			+
22	F	40				72	61	83	+	+			
23	M	41	+	+	+	59	85	66	+	+			
24	F	43				29	32	32	+		+		
25	M	44	+	+	+	122	116	115					
26	M	45	+	+	+	20	25	21	+	+	+		
27	F	46	+	+	+	71	68	81		+			
28	F	46	+	+	+	45	44	50	+	+			
29	F	47	+	+		36	48	39	+	+			
30	M	48			+	32	50	34	+	+			
31	M	49	+	+		79	71	78		+			

(continued)

Table 1 (continued)

Patient number	Sex	Age at study	Proteinuria	Hematuria	Hypertension (RR > 140/90 mmHg)	Estimated GFR			Elevated serum cystatin C	Elevated urine beta2-microglobulin	Bicarbonate supplementation	Phospate supplementation	ESRD[b]
						4v-MDRD[a]	Cockcroft-Gault	CKD-EPI					
32	F	49	+		+	59	57	66	+	+	+	+	+
33	M	50	+		+	66	76	73	+	+			
34	F	53	+		+	68	52	76	+				
35	M	55	+	+	+	11	11	11	+	+	+		+
36	F	57	+	+		38	53	41	+	+			
37	M	58			+	87	69	94					
38	F	58	+		+	41	34	44	+	+			
39	F	60	+	+	+	7	8	7	+			+	+
40	F	62	+	+	+	74	61	80	+	+			+
41	M	69	+	+	+	55	61	56		+			

[a] <18 years old with Schwarz formula
[b] Five of the patients with ESRD had received a kidney transplant

Table 2 Urine beta2-microglobulin, GFR and urine albumin in LPI patients: correlations between urine beta2-microglobulin, GFR and urine albumin

	Urine beta2-microglobulin	GFR[a]
GFR[a]	−0.69[b]	
Urine albumin	0.09	−0.12

[a] GFR was calculated using CKD-EPI formula
[b] Correlation is significant at the 0.01 level

Table 3 Urine beta2-microglobulin, GFR and urine albumin in LPI patients: correlations between urine beta2-microglobulin and GFR in 2011–2013

		GFR[a] in		
		2011	2012	2013
Urine beta2-microglobulin in	2011	−0.61[b]	−0.50[c]	−0.54[c]
	2012		−0.57[b]	−0.56[c]
	2013			−0.69[b]

[a] GFR was calculated using CKD-EPI formula
[b] Correlation is significant at the 0.01 level
[c] Correlation is significant at the 0.05 level

Table 4 Urine beta2-microglobulin, GFR and urine albumin in LPI patients: urine beta2-microglobulin and changes in GFR in LPI patients in 2011–2013

Patient number	Urine beta2-microglobulin[a]			GFR[b]		
	2011	2012	2013	2011	2012	2013
19	0.004	1.64	2.20	88	95	87
20	1.40	2.28	5.50	102	106	96
22	7.96		6.90	93	105	83
27	7.08	2.44	8.49	98	99	81
33	0.58	2.13	13.7	96	78	73

[a] Normal value <0.25 mg/l
[b] GFR was calculated using CKD-EPI formula

(Table 2). Base excess (BE) was measured from twenty-six patients, and it was decreased (<−2.5) in 21 of them (81%). Nineteen patients (46%) had elevated blood pressure, and 16 of them were treated with antihypertensive drugs. Twelve patients have received treatment with ACE inhibitors. Twelve patients (29%) needed oral supplementation of bicarbonate, phosphate or both (Table 1). Eight patients needed specific phosphate supplementation due to tubular wasting of phosphate.

During this follow-up, 29 of the 41 patients (70%) had developed renal dysfunction (i.e. proteinuria, decreased GFR, hypophosphatemia and/or decreased bicarbonate level); two of them were children. A total of seven patients (18%) have progressed to end-stage renal disease (ESRD, GFR <15 ml/min/1.73 m^2), two of them already in their early twenties. In 2007, only one patient was treated with peritoneal dialysis, and three had received a kidney transplant. In 2013, two patients were in peritoneal dialysis, and a total of five patients had received a kidney transplant at mean age of 39.4 years (range 20–55 years) (Table 5). Most of the renal transplantations were initially successful (first one in 2005). However, three patients experienced episodes of graft rejection, and one patient lost her transplant. The reason of rejections is still obscure. Allograft biopsies were not routinely performed because of patients' bleeding tendency. Also, plasma concentrations of the immunosuppressive drugs of one of the patients remained below the therapeutic level though the dosage was increased. After the transplantations, anaemia and recurrent or chronic infections have remained a problem. Four patients had proteinuria since transplantation. GFR (CKD-EPI) remained normal in only one patient. Other recipients had decreased GFR (MDRD, range 32–57; Cockcroft-Gault, range 38–64; CKD-EPI, range 35–93). One patient lost her transplant three years after the operation, was subsequently treated with peritoneal dialysis and died 8 years after transplantation from sequelae of kidney failure at the age of 60 years. In addition, one patient with renal dysfunction died of the complications of the disease at the age of 16 years.

We were also interested in L-citrulline doses and plasma citrulline concentrations (Table 6). The amount of L-citrulline supplementation depended on individual protein intake. Therefore, daily doses varied widely, i.e. from 28 to 229 mg/kg. Mean adult dose was 82.9 mg/kg (including all adults), while children had higher mean weight-adjusted citrulline dose (122.7 mg/kg). Mean adult L-citrulline dose was 79.5 ± 29.2 mg/kg in patients with decreased renal GFR (CKD-EPI) and 82.4 ± 21.9 mg/kg patients with normal GFR ($p = 0.619$). Mean daily L-citrulline dose was 94.3 ± 29.2 mg/kg in patients with ESRD. Fasting plasma citrulline concentration was analysed in 20 adult patients. Mean concentration was 76.3 μmol/l (range from 38 to 118 μmol/l), 80.3 ± 20.1 μmol/l in patients with decreased GFR and 64.8 ± 23.0 μmol/l in patients with normal GFR ($p = 0.362$). Fasting plasma citrulline concentration was analysed in one patient with ESRD, and it was 62.0 μmol/l.

Urine amino acids were measured from 33 patients. Urine arginine was elevated in 31 patients (94%). Mean urine arginine was 149.7 ± 132.4 μmol/mmol creatinine (normal range 0–5 μmol/mmol creatinine). Mean urine citrulline was 55.2±78.4 μmol/mmol creatinine (normal

Table 5 A summary of the data of the five LPI patients with a renal transplant

Patient number	Sex	Age			Complications after the transplantation				Immunosuppressive drugs	
		At study	At start of dialysis	Transplantation	Infections	Anaemia	Graft rejection	Graft loss	After the transplantation	At study
13	F	29	20	24	+	+	+		CsA	TAC, MPA
14	M	29	20	20	+	+	+		MPA, TAC	CsA
32	F	49	45	46	+	+			CsA, MPA	CsA, MPA
39	F	60	51	52	+	+	+	+	CsA, MPA	–
40	F	62	53	55	+	+			CsA, MPA	CsA, MPA

CsA cyclosporin, *MPA* mycophenolic acid, *TAC* tacrolimus

Table 6 Oral L-citrulline doses in LPI patients with or without nephropathy in 2013

	Normal GFR		Decreased GFR[a]		
	N (female)	Mean ± SD	*N* (female)	Mean ± SD	*P*-value[b]
Age	8 (4)	36 ± 12	20 (12)	42 ± 13	0.055
GFR[c]	8 (4)	103 ± 13	20 (12)	57 ± 20	<0.001
Weight-based citrulline dose (mg/kg)	8 (4)	82.4 ± 21.9	19 (11)	79.5 ± 29.2	0.619
Fasting plasma citrulline (μmol/l)	4 (2)	64.8 ± 23.0	15 (10)	80.3 ± 20.1	0.362

[a] Patients with ESRD were not included
[b] *P*-value by using non-parametric tests: independent samples
[c] GFR was calculated using CKD-EPI formula

Table 7 Correlations between urine arginine, urine citrulline, urine amino acids, plasma citrulline and weight-based citrulline dose

	Urine arginine	Urine citrulline	Urine amino acids	Plasma arginine	Plasma citrulline
Urine citrulline	0.64[a]				
Urine amino acids	0.41[b]	0.49[b]			
Plasma arginine	0.40[b]	0.35	0.13		
Plasma citrulline	0.07	0.18	0.15	0.06	
Citrulline dose	0.15	0.07	−0.19	0.29	−0.18

[a] Correlation is significant at the 0.01 level
[b] Correlation is significant at the 0.05 level

range 1–15 μmol/mmol creatinine). Plasma arginine was measured from 32 patients, and mean plasma arginine was 26.4 μmol/l ± 11.5 (normal range 15–185 μmol/l). There was no correlation between urine citrulline or urine arginine and weight-based oral citrulline doses (Table 7).

Discussion

Renal insufficiency in Finnish patients with LPI was first reported in 2007. At that time, 10% of Finnish LPI patients had ESRD and 59% had impaired renal function (Tanner

et al. 2007). Since then, renal dysfunction has become more frequent in LPI patients: 18% of the patients had ESRD and 70% impaired renal function despite regular follow-up and careful treatment. At the time of the study, almost all patients over 45 years of age had developed renal problems, and only twelve patients had normal renal function.

Beta2-microglobulin is a component of the major histocompatibility class I molecule (MHC I) and is presented in all nucleated cells (Creswell et al. 1974). It is eliminated by glomerular filtration and is, thus, elevated in renal dysfunction. Muscle mass, body weight and gender do not affect its plasma concentrations. It has been shown that serum beta2-microglobulin increases more and earlier than serum creatinine (Bianchi et al. 2001). Therefore, it might represent an ideal marker of GFR in patients with renal diseases (Wibell et al. 1973; Trollfors and Norrby 1981; Acchiardo et al. 1989; Shea et al. 1981; Bianchi et al. 2001). Furthermore, beta2-microglobulin is reabsorbed almost completely in renal tubules, and therefore, increased urinary excretion is a sign of decreased tubular reabsorption and damage of tubular structures (Gauthier et al. 1984). In our study, urine beta2-microglobulin was elevated in 90% of the patients. In some patients, it started to elevate before any changes in GFR were detected and while plasma creatinine and serum cystatin C were still within the reference range. We feel that it is currently the most sensitive early marker of renal disease in subjects with LPI.

Pathogenesis of renal disease in LPI is still poorly understood. Histological data are limited, but immune complex-mediated glomerulonephritis has been detected in some patients, and glomerular lesions have been similar to those in systemic lupus erythematosus (SLE). Also, antinuclear antibodies have been measured in some patients (Parto et al. 1994; Kamoda et al. 1998). However, renal insufficiency may perhaps be a part of natural progression of the LPI disease, but the role of L-citrulline therapy has also been considered (Zager et al. 1983). L-citrulline is used to improve the function of the urea cycle and, subsequently, protein tolerance. As a neutral amino acid, it uses a different transport route than arginine and ornithine and is readily absorbed, causing high peak plasma concentrations (Rajantie et al. 1980b, 1981). The Finnish patients were originally treated with arginine monohydrochloride during years 1965–1976 and subsequently with more effective and better tolerated L-citrulline supplementation (Awrich et al. 1975). However, it seems that renal problems have become more common in LPI patients during the citrulline therapy, and even children with nephropathy have been observed during the last three decades. Nephropathy in children was not seen during the arginine therapy (Lukkarinen et al. 2006). One must, however, remember that natural history of untreated LPI is yet very poorly characterised, and it is possible that in the past many patients have died before renal involvement was detected.

We found no difference in weight-based L-citrulline doses and plasma citrulline concentrations between the patients with normal and decreased renal function. However, in theory, it is possible that high citrulline concentrations might have a role in the development of nephropathy. High concentrations of especially cationic amino acids are nephrotoxic in animals (Zager et al. 1983). Large amounts of citrulline increase the intracellular synthesis of arginine, which may cause damage and apoptosis in tubular, glomerular and mesangial cells via increased production of nitric oxide (Sebastio et al. 2011; Alderton et al. 2001; Mori 2007; Morris 2007; Ogier de Baulny et al. 2012). On the other hand, patients with citrullinemia have very high citrulline concentrations but have not been reported to have renal problems. One of our patients with ESRD neglected citrulline therapy for many years, but his renal function still decreased rapidly. However, due to equivocal role of citrulline in renal function in LPI, we have during the last few years deliberately slightly reduced L-citrulline doses of the patients to minimise the possible risks. At the beginning of the 2000s, mean weight-based oral citrulline dose was up to 110 mg/kg, but it has recently been reduced to 80–90 mg/kg. Many LPI patients use sodium benzoate and/or sodium phenylbutyrate to increase nitrogen excretion and thus reduce the need of L-citrulline.

In conclusion, renal insufficiency has become more common in Finnish LPI patients. We suggest that urine beta2-microglobulin is the most sensitive early marker of renal problems, and it should be monitored regularly in LPI patients. Urine beta2-microglobulin was elevated in 90% of our patients. We also calculated GFR with three different formulas, and of those, the CKD-EPI formula seems to be the most reliable in LPI patients who typically have low muscle mass. In this study, we did not find significant correlations between weight-based L-citrulline doses and renal function. However, due to possible role of citrulline in renal problems, we have slightly reduced L-citrulline doses and monitored plasma citrulline concentrations regularly. More investigation is clearly needed in this issue. In Finland, a total of six LPI patients have been treated with peritoneal dialysis and five of them have received a kidney transplant. One patient lost her transplant. Considering the overall situation, the prognosis after transplantation has been satisfactory.

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Synopsis

Urine beta-2-microglobulin is an early marker of renal complications affecting the majority of Finnish LPI patients.

Compliance with Ethics Guidelines

Conflict of Interest

Mari Kärki declares that she has no conflicts of interest.

Laura M. Tanner declares that she has no conflicts of interest.

Harri Niinikoski declares that he has no conflicts of interest.

Kirsti Näntö-Salonen declares that she has no conflicts of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Details of the Contributions of Individual Authors

Mari Kärki has been responsible for collecting and analysing the data and writing the manuscript.

Laura M. Tanner has been responsible for planning the present study design as well as drafting the manuscript.

Harri Niinikoski has been responsible for examining and treating the study subjects as well as drafting the manuscript.

Kirsti Näntö-Salonen has been responsible for examining and treating the study subjects, planning the present study design as well as drafting the manuscript.

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