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Original Article

ORIGINAL ARTICLE

Outcomes of kidney transplantation in patients with lysinuric protein intolerance

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ABSTRACT

Background. Lysinuric protein intolerance (LPI) is a metabolic disorder that leads to dysfunctional intestinal absorption and kidney clearance of cationic amino acids. Chronic kidney disease develops in many LPI patients and leads to end-stage kidney disease in at least 10% of patients. Since data on kidney transplants in LPI patients are limited, we analysed the outcomes of LPI patients after transplantation in Finland.

Methods. This retrospective cohort study includes all Finnish LPI patients who have received a kidney transplant. The data were collected from the Finnish Transplant Registry and electronic medical records from 2005 through May 2023 or patient death. The plasma amino acid profile was analysed before and after transplantation.

Results. Eight LPI patients (75% female, mean age at transplant 41.9 years) received a kidney allograft and two of the patients received a second transplant. Nine transplants were from deceased donors and one was from a living donor. Acute rejection occurred after four transplantations (two T-cell mediated and two antibody mediated). One patient died 6 months after transplantation due to alveolar proteinosis. Apart from lower citrulline and higher lysine concentrations, plasma amino acid levels showed no changes after transplantation. The 1-, 5- and 10-year graft survivals were 80%, 68.6% and 51.4%, and patient survivals were 88%, 86% and 50%, respectively.

Conclusions. Kidney transplantation is feasible in patients with LPI, although the acute rejection rate seems high and severe complications such as pulmonary alveolar proteinosis may occur. Transplantation led to changes in plasma citrulline and lysine concentrations.

Keywords: acute rejection, alveolar proteinosis, graft survival, lysinuric protein intolerance, transplantation

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KEY LEARNING POINTS

What was known:

- Some patients with lysinuric protein intolerance, a rare metabolic disorder, develop end-stage kidney disease.
- In these cases, kidney transplantation is often necessary.
- Data on kidney transplantation in patients with lysinuric protein intolerance are scarce.

This study adds:

- This is the largest reported cohort of patients with lysinuric protein intolerance undergoing kidney transplantation.
- It is the first long-term post-transplantation follow-up of lysinuric protein intolerance patients.

Potential impact:

- These novel findings could help clinicians assess the potential risks and benefits of kidney transplantation in LPI patients and help them inform patients about the decision to proceed to transplantation.

INTRODUCTION

Lysinuric protein intolerance (LPI) is a rare autosomal recessive disease that affects the transport of cationic amino acids through the basolateral membrane of the epithelial cells in the intestine and kidney tubules. More than 200 LPI cases from at least 25 countries are known worldwide [1]. One-third of them are from Finland, and the prevalence in Finland is 1/76 000 births [2]. Isolated clusters of patients have been reported in Italy and Japan [3], and sporadic cases are known worldwide. It is caused by a mutation in gene *SLC7A7* located in chromosome 14q11.2 [4]. All Finnish LPI patients share the same homozygous Finnish LPI founder mutation, 1181-2A>T. However, clinical presentation varies between patients and there does not seem to be a notable genotype–phenotype correlation.

LPI is characterized by increased kidney clearance and decreased intestinal absorption of the amino acids lysine, arginine and ornithine, leading to disturbances in the urea cycle [1]. Thus a high-protein meal can cause acute hyperammonaemia, especially in infants. However, infants often do not show symptoms because human milk has a low protein content. However, they may develop symptoms such as diarrhoea, vomiting, failure to thrive, hepatosplenomegaly and muscular hypotonia after weaning [5]. Patients often develop a spontaneous aversion to protein and in some cases might not be diagnosed until adulthood. Later symptoms of LPI include poor growth, osteoporosis, anaemia, leucopenia, thrombocytopaenia, hypercholesterolaemia and hypertriglyceridaemia [1]. The vague clinical presentation makes diagnosis difficult, and LPI is mainly diagnosed in countries where physicians are accustomed to it, particularly in Finland, Italy and Japan [2].

Diagnosis of LPI is done by urine and plasma amino acid analyses or, in recent years, increasingly by genetic testing. In plasma, lysine, arginine and ornithine concentrations are usually low and glutamine, alanine and glycine concentrations are high. The urinary concentrations of lysine, ornithine, arginine and orotic acid are high, often massive [6]. LPI is treated with a low protein diet, citrulline and lysine supplementation and nitrogen-binding medication such as sodium phenylbutyrate or sodium benzoate.

With proper treatment, most LPI patients can live a nearly normal life, but complications such as chronic kidney disease and pulmonary alveolar proteinosis may develop [6, 7]. In addition to lung and kidney complications, LPI has been associated with aggravated viral infections, haemophagocytic syndrome, steatosis, autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, as well as cardiovascular complications including myocardial infarction and myocardial ischaemic change after exercise [8]. Kidney insufficiency is a major chronic complication of LPI; it has been reported to develop in the majority, and end-stage kidney disease in 10%, of the Finnish patients with LPI [9]. Additionally, LPI is associated with abnormal coagulation and enhanced fibrinolysis, which further contribute to kidney impairment and bleeds [10]. LPI patients commonly suffer from moderate bleeding tendency without spontaneous bleeds, but cases of fatal haemorrhage have been reported [10]. Data on the outcomes of kidney transplantation (KT) in LPI patients are scarce. To our knowledge only six KTs in LPI patients have been reported: five Finnish patients [11] (also included in this study) and one case report from the Netherlands [12]. However, detailed reports of the outcomes of these transplantations are included in only one case report [12]. We aimed to study the long-term outcome of 10 KTs in eight Finnish LPI patients. In addition, a case with therapeutic plasma exchange as treatment of antibody-mediated rejection and a case involving pulmonary alveolar proteinosis early after transplantation are presented in detail.

MATERIALS AND METHODS

A total of 43 patients alive with LPI are known in Finland, all of whom are followed up at the Department of Pediatrics of Turku University Hospital, regardless of age. Plasma amino acids have been annually collected and analysed by liquid chromatography and related laboratory values have been collected as well. All solid-organ transplantations in Finland are performed in the Helsinki University Hospital. Therefore, all patients who received KT in Finland due to LPI were included in this retrospective nationwide cohort study. After the operation, the follow-up is at the respective local regional or university hospital, and follow-up data are annually reported to a national transplant registry, required by law. In Helsinki, a combination of mycophenolate, steroids and cyclosporine or tacrolimus has been used for immunosuppression since 2004. Induction with basiliximab or anti-thymocyte globulin has been used only in patients with pre-existing human leucocyte antigen (HLA) antibodies, poor HLA match or retransplantation. Biopsy-proven acute rejections were graded according to the Banff classification [13]. Clinical and transplant-related data were collected from the transplant registry and electronic medical records. Data were collected from transplantation (2005) and follow-up of this cohort continued until May 2023 or patient death. All statistical analyses were performed with SPSS Statistics version 25 (IBM,

Armonk, NY, USA) or JMP Pro 17 (SAS Institute, Cary, NC, USA). Pre- and post-transplant amino acid concentrations were compared with paired *t*-tests. The study was approved by the institutional review board of the Helsinki University Hospital Abdominal Center (HUS/74/2023).

RESULTS

Whole cohort

A total of eight LPI patients underwent KT during 2005–2022 (Table 1). Two patients underwent KT twice, with the total number of transplanted kidneys being 10. All the patients shared the same homozygous Finnish LPI founder mutation, 1181-2A>T. Due to LPI, they followed a protein-restricted diet (≈1 g/kg/day). Of the eight patients, seven used citrulline (mean 90 mg/kg/day), four used lysine (mean 21 mg/kg/day) and six were on an ammonia scavenger (sodium benzoate and/or sodium phenylbutyrate) treatment. The patients developed the first signs of chronic kidney disease, i.e. increase in plasma creatinine or cystatin C concentration, on average 10 years (range 3–18) before transplantation. Seven had antihypertensive medication, usually an angiotensin-converting enzyme inhibitor or angiotensin type 2 receptor blocker, and seven were on statins due to hypercholesterolaemia.

Two transplantations were done pre-emptively and the others after 0.4–3.9 years of dialysis. Two patients received haemodialysis and six patients received peritoneal dialysis. No other significant comorbidities were reported in these patients pretransplantation. Nine of the ten transplants were from deceased donors. Three of the ten kidney grafts experienced delayed graft function. Acute rejection was seen in 4 of the 10 cases, of which 2 were T-cell-mediated rejections, and 2 antibody-mediated rejections (1 with pre-existing donor-specific HLA antibodies (DSAs) and 1 developed *de novo* DSAs). Complications such as infections were associated with all the transplantations and five of the eight patients showed coagulation dysfunction related to LPI. Unusual bleeding or extensive need for transfusions during transplantation surgery was not reported in any of these patients. Four grafts were lost 0.7–11.2 years post-KT. Reasons for graft loss were primary non-function (case 2), *de novo* focal segmental glomerulosclerosis in one and unknown in two patients (chronic slow deterioration of graft function without a specific aetiology evident in the graft biopsy). Two patients needed a second transplant and three patients died during the follow-up due to amino acid metabolism dysfunction related to LPI. The 1-, 5- and 10-year graft survivals were 80%, 69% and 51% and the 1-, 5- and 10-year patient survivals were 88%, 86% and 50%, respectively.

Compared with pretransplant values, plasma citrulline concentration was lower and lysine was higher after transplantation (Table 2). Protein tolerance remained unaffected or was subjectively improved compared with the pretransplantation state.

Clinical synopses of two LPI patients with severe complications after KT are provided below.

Case 1 (patient 4)

A female LPI patient (age 41 years at transplantation) died 6 months after transplantation due to pulmonary alveolar proteinosis. She was sensitized before transplantation with a calculated panel-reactive antibody (cPRA) of 75% and had two DSAs at the time of transplantation (low-level HLA-B13 and -B44 antibodies). Haemodialysis was started 3 days post-KT due to delayed graft function. After transplantation, the coagulation system function tests showed abnormal factor VIII (328%) and fibrine D-dimer (108 mg/l) levels. Fibrinogen, activated partial thromboplastin time (APTT) and antithrombin III were within the normal range within 3 days post-KT. Symptoms of lower respiratory tract infection complicated the recovery. Nine days post-KT, pneumonia was diagnosed by chest X-ray. In addition, she simultaneously had a urinary tract infection, and both infection foci were treated with piperacillin/tazobactam. Two weeks post-KT, grade B oesophagitis was diagnosed and the patient was treated with antiviral medication. A kidney graft biopsy was taken due to slow graft recovery at day 17 post-KT. It showed mild interstitial inflammation, arteritis, capillaritis and C4d positivity, suggesting antibody-mediated rejection. Pulse steroid, intravenous immunoglobulin and anti-thymocyte globulin were given to the patient in an attempt to treat the rejection. Plasma exchange treatment of acute rejection was considered contraindicated due to the patient's coagulation dysfunction. Two months post-KT the patient was admitted to the intensive care unit (ICU) due to *Klebsiella pneumoniae* septicaemia and intra-alveolar haemorrhage. She also had deep vein thrombosis in her left leg. Four months post-KT she was readmitted to the ICU due to pneumonia and haemoptysis. Five months post-KT the patient suffered septicaemia of unclear microbial aetiology, severe metabolic acidosis and dyspnoea, which was treated with non-invasive ventilation. At this point, chest X-ray showed infiltrates suggestive of alveolar haemorrhage or alveolar proteinosis. Later, computed tomography showed interlobular septal thickening and a 'crazy paving' pattern typical of alveolar proteinosis. A sudden episode of haemoptysis led to the patient's death 6 months after transplantation.

Case 2 (Patient 6)

A female LPI patient (age 53 years at KT) underwent a pre-emptive KT. She was highly sensitized with cPRA of 96% and received a kidney through the Scandiatransplant Acceptable Mismatch Program without any pre-existing DSA. No dialysis was needed after transplantation, but the kidney graft function remained suboptimal. The first biopsy was taken on day 7 after transplantation, showing signs of acute tubular necrosis, without any signs of rejection. A second biopsy on day 13 post-transplantation showed acute tubular necrosis and additionally mildly positive C4d staining. A third biopsy at 19 days post-KT showed mild interstitial inflammation and glomerulitis suggestive of antibody-mediated reaction. The rejection was first treated with methylprednisolone, and after confirming the detection of *de novo* DSA (HLA-B51 with a mean fluorescence intensity of 7000), further treatment was evaluated to be necessary. Although previously considered contraindicated due to a lack of experience with plasma exchange in patients with LPI, after discussions with several experts, plasma exchange was initiated. Before the first plasma exchange, laboratory tests showed an abnormal coagulation profile: fibrinogen 0.8 g/l, fibrine D-dimer >128 mg/l, factor VIII 384%, antithrombin III 135% and APTT 23 s, and therefore the anticoagulation during the plasma exchange was performed with calcium citrate and unfractionated heparin. The first plasma exchange was unsuccessful due to acute haemolysis related to dysfunction of the coagulation system associated with LPI. By reducing the flow rate, 10 plasma exchange treatments were successfully carried out over 2 weeks. After the 10th treatment, the patient was given intravenous immunoglobulin and rituximab. The treatments did not markedly improve

Table 1: Characteristics of patients included in the study.

Patient no.	1	2	3	4	5	6	7, first	7, second	8, first	8, second
Gender	Female	Female	Female	Female	Male	Female	Male		Female	
Donor	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Live
Pretransplant dialysis duration (years)	0.4	1.4	1.3	3.6	2.6	Pre-emptive	0.4	3.9	2.8	Pre-emptive
Age at KT (years)	53	55	47	41	58	53	21	35	24	35
cPRA at KT (%)	0	0	0	75	16	96	1	0	0	0
Acute rejections	None	None	None	ABMR 17 days post-KT	None	ABMR 21 days post-KT	TCMR 12 days post-KT	None	TCMR 11 days post-KT	None
Treatment of acute rejection	N/A	N/A	N/A	Steroid, ATG, IVIG	N/A	Steroid, IVIG, plasma exchange, rituximab	Steroid	N/A	Steroid	N/A
Complications (days post-KT)	Haematoma at KT, tuberculosis (247)	Septicaemia (1, HZV (1254), CMV (2658), pneumonia (2660), EBV (2661)	Diabetes (578), CMV (602)	Urosepsis, pneumonia (9)	Wound infection (9), CMV (28)	Diabetes (43)	Parvovirus (342)	CMV (81), urosepsis (463)	CMV (50)	Urinary bladder tamponade (1), CMV (8), CMV (201)
Coagulation status	Abnormal	Normal	Abnormal	Abnormal	Normal	Abnormal	Abnormal	Abnormal	Normal	Normal
Early outcome	EGF	DGF	DGF	DGF	EGF	Non-function	EGF	EGF	EGF	EGF
Long-term outcome	Graft lost 3 years post-KT, deceased 8 years post-KT	Deceased 8 years post-KT with functioning graft	Alive with functioning graft 10.2 years post-KT	Deceased 6 months post-KT with functioning graft	Alive with functioning graft 1.5 years post-KT	Alive, primary non-function	Alive, graft lost 11 years post-KT	Alive with functioning graft 3 years post-KT	Alive, graft lost 11.2 years post-KT	Alive with functioning graft 3.3 years post-KT
Last eGFR (ml/min)	N/A	85	22	18	50	N/A	N/A	67	N/A	92

ABMR: antibody-mediated rejection; TCMR: T-cell-mediated rejection; IVIG: intravenous immunoglobulin; ATG: anti-thymocyte globulin; HZV: herpes zoster virus; CMV: cytomegalovirus; EBV: Epstein–Barr virus; EGF: early graft function; DGF: delayed graft function; eGFR: estimated glomerular filtration rate as calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 2: Pre- and post-transplant amino acid concentrations of the current LPI cohort.

Amino acid	Reference values (μmol/l), mean	Before transplantation (μmol/l), mean	After transplantation (μmol/l), mean	*P*-value
Ornithine	22–115	33	38	0.22
Lysine	115–289	125	162	0.02
Arginine	15–183	44	53	0.11
Citrulline	0–53	120	49	0.02
Glutamine	324–781	744	788	0.35
Glycine	145–356	725	574	0.19
Leucine	70–232	60	76	0.07
Valine	136–385	117	151	0.08
Alanine	231–580	436	497	0.21

allograft function, although no signs of rejection were detected in follow-up biopsies and the DSA became undetectable after the plasma exchange treatment. Creatinine levels remained at pretransplant levels and eventually dialysis treatment was initiated 8 months after the pre-emptive transplantation, with no evidence of proper graft function at any time point after transplantation.

DISCUSSION

This largest cohort of LPI patients with kidney transplantation so far showed that KT can be an effective treatment for end-stage kidney disease in LPI patients. However, the graft and patient survival rates were somewhat lower than in other patient groups and infectious and immunological complications were frequent. As previously reported [14], we also found that, compared with pre-transplantation levels, the plasma level of citrulline was lower after transplantation and plasma lysine was higher, possibly reflecting better lysine reabsorption in the transplanted kidney, but there were no differences in ornithine, arginine, glutamine, glycine, alanine, leucine and valine values. Protein tolerance remained subjectively unaffected or improved slightly.

Kidney insufficiency usually develops rather slowly in LPI. In our cohort, the average time from initial chronic kidney disease diagnosis to KT was 10 years and it varied from 3 to 18 years. Most patients were in their 40s or 50s at the time of transplantation, but some LPI patients may develop end-stage kidney failure in their second or third decade. The ultimate cause of kidney failure in LPI remains unknown, although damage due to the accumulation of cationic amino acids or nitric oxide within epithelial cells has been postulated. Urine β2-microglobulin might be the first sign of kidney impairment in LPI [11]. However, to date, no regimen for the prevention of kidney impairment is available apart from anti-proteinuric treatment and routine antihypertensive and hyperlipidaemia therapies.

Theoretically, the transplanted kidney should be able to correctly process cationic amino acids, resolving their excess excretion and thus improving LPI symptoms. However, intestinal absorption of cationic amino acids remains deficient even after KT. A dichotomic amino acid imbalance with increased non-essential amino acids and decreased essential amino acids contributes to disturbances of basic cellular metabolism [15]. A case report from the Netherlands showed that KT improved one patient's LPI symptoms: plasma levels of ornithine, lysine and arginine improved to the normal range and she could increase her protein intake to a normal level and stop citrulline supplementation [12]. Five Finnish LPI patients who received KT have been previously reported [11]. In these cases, however, KT was not associated with a marked improvement in LPI symptoms. There was no change in the patients' dietary protein intake after transplantation and the citrulline dose remained unchanged. The differences in the outcomes of the Finnish and Dutch patients could be explained by different LPI mutations, although this remains to be proven.

Graft survival at 1, 5 and 10 years was 80%, 68.6% and 51.4%, respectively. Thus the outcome of KT in LPI patients is worse than in other patient groups; one study found 3-, 5- and 10-year graft survival after deceased donor kidney transplants in Finland to be 89%, 82% and 63%, respectively [16]. Acute rejections were seen more frequently (40% of transplantations) compared with kidney transplants in patients without LPI (10–15% of transplantations). In some other metabolic diseases, such as methylmalonic acidaemia (MMA), transplant outcomes in terms of rejections seem to be similarly poor compared with patients without metabolic disease; a case of a single MMA patient without acute rejection [17] and a case of a single MMA patient with an acute rejection have been reported [18], as well as a study of four MMA patients, two of which suffered from acute rejection after KT [19]. In Finland, to our knowledge only one combined liver and kidney transplantation has been performed in an MMA patient. Whereas in the case of LPI, KT alleviates symptoms of the metabolic disorder in only some patients, all aforementioned MMA patients receiving a kidney transplant saw marked improvements in metabolic function. Firm conclusions on the risk of acute rejection in patients with these metabolic disorders compared with other patient groups cannot be drawn due to the small sample size. Of the five patients with coagulation dysfunction, one of whom received two transplants, two died and three grafts were lost. Of the three patients who did not have coagulation dysfunction, one of whom received two transplants, one died and the other lost the graft. Therefore, coagulation dysfunction does not seem to be associated with worse graft survival or shorter life expectancy. However, coagulation dysfunction might be an underlying cause of haemolysis during plasma exchange in our patient. It may be speculated that LPI patients' blood is more susceptible to haemolysis and haemorheological stress during plasma exchange is tolerated poorly. However, the findings in this study are limited by the small cohort size and the fact that all patients have the same nationality and the same Finnish LPI founder mutation. An additional limitation is that exact information from the onset or diagnosis of chronic kidney disease was not available.

In summary, KT is a viable treatment for end-stage kidney disease associated with LPI. However, based on our data, outcomes seem somewhat inferior to the transplant population without LPI. Plasma exchange treatment of acute transplant rejection in LPI patients with coagulation dysfunction is viable but the conditions, especially flow rate, need to be carefully controlled. Moreover, the possibility of pulmonary alveolar proteinosis, which is a well-known complication of LPI, should be suspected if a patient with LPI presents with worsening respiratory symptoms before or after KT. A decrease in plasma citrulline concentrations and an increase in lysine concentrations can occur after transplantation. Protein tolerance remained unaffected or was subjectively improved after transplantation.

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AUTHORS' CONTRIBUTIONS

T.R. was the primary researcher and was responsible for data collection, data analyses and manuscript preparation. K.A. was responsible for study planning, data analyses and manuscript preparation. H.N. and S.K. were responsible for amino acids analyses and long-term follow-up of LPI patients. M.L. was responsible for study planning and project management. F.O. was responsible for study planning, analyses and manuscript preparation. I.H. was responsible for study planning, data collection, analyses and manuscript preparation. In addition, all authors participated in the final revision of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

I.H. has received research funding from Hansa Biopharma and MSD and has ongoing consultancy agreements with AstraZeneca, Hansa Biopharma, MSD and Sandoz. K.A. receives lecture fees from Hansa Biopharma and Astellas. F.O. has consultancy agreements with Vifor, Takeda, GSK, MSD and Stada and receives lecture fees from AstraZeneca and Astellas. M.L. receives lecture fees from Astellas and is a board member of Scandiatransplant. S.K. receives support for attending meetings and/or travel from Novo Nordisk, Amicus and Kyowa Kirin.

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