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Plasma oxalate following kidney transplantation in patients without primary hyperoxaluria

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Abstract

Background. Patients with primary hyperoxaluria may need repeated kidney transplants due to damage from oxalic acid (oxalate) deposits. However, oxalate may also be potentially harmful in all transplant recipients. Determinants of oxalate following transplantation have not been well studied.

Methods. Two hundred and twelve recipients admitted for transplantation were included in the study. Blood samples for measurement of oxalate and other relevant laboratory parameters were collected at baseline and subsequently 10 weeks after transplantation. For oxalate determination, samples were obtained in 99, 167 and 54 patients out of the 212 at baseline, at follow-up and at both time points, respectively. We examined the bivariate association between plasma oxalate at transplantation and preemptive transplantation, time on dialysis, recipient age, creatinine, urea, phosphate, haemoglobin, PTH, albumin and calcium. Oxalate 10 weeks after transplantation was tested likewise including also laboratory parameters at baseline, primary non-function, rejection episodes, live *versus* deceased donor, donor age and GFR at follow-up.

Results. Median plasma oxalate concentration at transplantation was 35.0 $\mu\text{mol/L}$ [95% confidence interval (95% CI) = 10.4–93.9] and 98% of the values were above normal limits (2.6–11.0). Oxalate concentration after 10 weeks was 9.0 $\mu\text{mol/L}$ (4.0–25.5), still 37% being above the upper normal value. Multiple regression analysis re-

vealed established dialysis treatment ($P = 0.002$) and creatinine ($P < 0.000001$) as independent positive determinants of oxalate at transplantation. Oxalate at 10 weeks was negatively associated to ⁵¹Cr-EDTA absolute GFR ($P = 0.023$) and positively associated to donor age ($P = 0.027$) and plasma creatinine at 10 weeks ($P = 0.03$).

Conclusion. At transplantation, plasma oxalate was on average three times increased and above the upper normal limit in 98% of patients and were still above normal in 37% after 10 weeks. The reduction after 10 weeks is determined by GFR and donor age. Whether increased plasma oxalate following kidney transplantation may have long-term consequences needs further study.

Keywords: dialysis; end-stage renal failure; kidney transplantation; oxalate

Introduction

Primary hyperoxaluria (PH) includes two rare, well-characterized autosomal recessive diseases: primary hyperoxaluria type 1 (PH1) and primary hyperoxaluria type 2 (PH2). PH1 is caused by deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase and PH2 is caused by a deficiency of the cytosolic enzyme glyoxylate reductase/D-glycerate dehydrogenase [1]. Both

Table 1. Demographic and transplant data for 212 kidney transplant patients

Variables	
Number of patients	212
Recipient age, median in years (range)	51 (11–81)
Sex, male/female (%)	135/77 (64/36)
Donor age, median in years (range)	49 (1–77)
Live donor transplants (%)	118 (49)
Preemptive transplantation (%)	53 (25)
Dialysis time, median in months (range)	12.8 (0–369)
Non-primary function (%)	29 (14)

enzyme deficiencies result in an excess production of oxalic acid (oxalate), a metabolic end product that is excreted in urine. Oxalate binds to calcium forming calcium oxalate (CaOX) that is virtually insoluble at physiological pH. In PH1, progressive deposition of CaOX often leads to deteriorating kidney function and can result in end-stage renal disease [2]. The biochemical hallmark of PH is severe hyperoxaluria, but with deteriorating kidney function, hyperoxalemia develops. Kidney transplantation is not regarded as a successful treatment option in PH1 as, in most cases, the disease rapidly leads to oxalate deposits in the transplant and subsequent graft loss is common [2,3]. Therefore, combined liver and kidney transplant has emerged as therapy of choice since the metabolic defect is then also restored [3]. However, recurrence of deposits in the kidney is still a problem due to a high accumulation of oxalate stores which can result in high plasma levels of oxalate [4]. PH2 causes similar but usually milder symptoms. Non-hereditary elevated plasma oxalate due to increased enteric absorption may occur with diseases of the intestine and after bariatric surgery [5]. This may also lead to kidney oxalate deposition and eventually renal failure and may also cause graft loss after kidney transplantation [6]. Another major cause of oxalate retention is kidney failure *per se*, since the main excretion pathway of oxalate is glomerular filtration and secretion [7]. When end-stage renal patients are successfully treated with a kidney transplant, stored oxalate may be excreted by the graft and potentially harm the transplant as indicated in several biopsy studies [8–10]. The retention of oxalate in non-hyperoxaluria patients with end-stage renal failure has not been well studied [11]. We, therefore, initiated a prospective study and measured plasma levels of oxalate at the time of kidney transplantation and early post-transplant to assess the magnitude of hyperoxalaemia in a larger series of patients. We also aimed to address potential determinants of plasma oxalate.

Materials and methods

Study design

In this single-centre prospective study, we measured plasma oxalate at arrival in the transplant centre and also in a stable phase, on average, 10 weeks after transplantation in altogether 213 kidney recipients. The patients were recruited from February 2004 throughout May 2005. Due to lack of back-up for pre-analytical laboratory handling at all times, baseline samples could not be obtained in all cases. Samples for oxalate measurement that were not collected or stored correctly were excluded from the study (see ‘Plasma oxalate measurements’). Out of 213 patients, we received adequate oxalate samples at baseline for 100 patients and for 168

patients at 10 weeks. One patient with a plasma oxalate value of 157 $\mu\text{mol/L}$ at transplantation was later found to have PH1 and was excluded from the study, leaving 212 for observation in the present study. A test for homogeneity (ANOVA) was performed after sub-division into three separate groups (I = oxalate data obtained only at transplantation, $n = 45$; II = oxalate data obtained both at baseline and follow-up, $n = 54$; III = oxalate data only available at follow-up, $n = 113$). The test did not reveal any significant differences between these groups for all relevant demographic and laboratory parameters. To obtain meaningful analysis of determinants of oxalate at baseline and at follow-up, we examined only two groups, those with oxalate data at transplantation ($n = 99$) and those with oxalate data at follow-up ($n = 167$). Between these two groups, the only difference found was a higher proportion of live donor and preemptive transplants in the baseline cohort than those tested at 10 weeks, probably due to better availability of blood samples in these elective patients.

The patients generally received a triple-based immunosuppressive regimen comprising calcineurin inhibitor (cyclosporin A 80%, tacrolimus 20%), mycophenolate mofetil and prednisolone.

The demographic data of the overall cohort is shown in Table 1. All patients signed an informed consent form and the study was approved by the regional ethics committee.

Statistics

Univariate relationships were examined by means of Spearman's correlation coefficients. To ensure that continuous laboratory data were normally distributed before entering multivariate regression analyses (backward and forward procedures), values for plasma creatinine, urea, oxalic acid and PTH were log transformed. SPSS version 16 was used for statistical calculations. Two-tailed tests were applied, and significance level = 0.05 was adapted.

Plasma oxalate measurements

The plasma oxalate measurements were done on fresh samples of heparinized plasma. To avoid *in vitro* oxalogenesis (non-enzymatic conversion of plasma constituents into oxalate), resulting in falsely high plasma oxalate, efforts were made to ensure optimum pre-analytical conditions; after collection, the samples were centrifuged without delay and the plasma was assayed within 1 h or stored at -70°C for no longer than 1 week. All samples were assayed in duplicate. The oxalate was measured by means of solid-phase extraction followed by derivatization and liquid chromatography–tandem mass spectrometry as recently validated and described in detail [12].

GFR at 10 weeks was measured by plasma disappearance of ^{51}Cr -EDTA and normalized to 1.73 m^2 body surface. Haemoglobin was measured on a CELL-DYN 4000 automatic haematological analyser (Abbott Diagnostics, CA, USA). All other laboratory parameters were measured by standard procedures on Modular Automatic Analyser (Roche Diagnostics, Basel, Switzerland). Due to the vast variability in kidney function early after transplantation, urinary parameters were not assessed.

Results

Median plasma oxalate concentration at transplantation was $35.0\text{ }\mu\text{mol/L}$ [95% confidence interval (95% CI) = $10.4\text{--}93.9$] with 98% of the values above the upper normal value (reference = $3.0\text{--}11.0$) [12]. Almost two-thirds (61%) of the values were higher than $30\text{ }\mu\text{mol/L}$, which is considered to represent the saturation limit for CaOX [13]. After 10 weeks, oxalate concentration was significantly lower, with a median of $9.0\text{ }\mu\text{mol/L}$ (95% CI = $4.0\text{--}25.5$). Still, 37% of the values were above the upper normal limit. In the patients with elevated plasma oxalate at follow-up, a mean creatinine of $144\text{ }\mu\text{mol/L}$ (95% CI = $81\text{--}309$) was found *versus* those with plasma oxalate values within normal limits who had a mean creatinine of $108\text{ }\mu\text{mol/L}$ (95% CI = $57\text{--}187$).

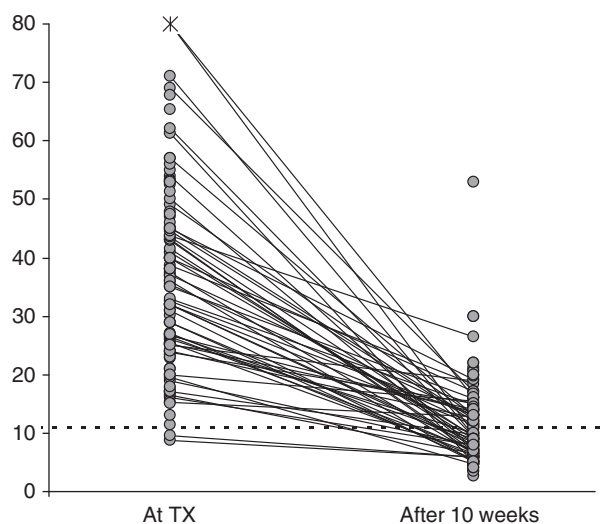


Fig. 1. Plasma oxalate measurements at transplantation ($n = 99$) and after 10 weeks ($n = 167$) (paired observations in the same patient are connected with lines), where the horizontal dashed line indicates the upper normal reference limit for plasma oxalate, and two exceptionally high values at baseline (124 and 156 $\mu\text{mol/L}$) are indicated by asterisks.

Two patients had extremely high oxalate values at transplantation that fell from 156 to 10 $\mu\text{mol/L}$ after 10 weeks in one and from 124 to 16 $\mu\text{mol/L}$ in the other.

All oxalate values are depicted in Figure 1. The laboratory and biochemical data at transplantation and after 10 weeks are shown in Table 2.

We examined univariate relationships between plasma oxalate at transplantation and corresponding values for creatinine, urea, phosphate, PTH, albumin, total calcium,

haemoglobin, preemptive transplantation, time on dialysis and recipient age. Oxalate at transplantation was found to be significantly correlated to both preemptive transplantation, phosphate and creatinine, but only preemptive transplantation and P-creatinine retained significance in a subsequent multivariate regression analysis: $\log [\text{oxalate at transplantation}] = -1.0471 + 0.8918 \times \log [\text{creatinine}] + 0.1136 \times [\text{preemptive transplantation; no} = 1; \text{yes} = 0]$; P -values for the regression coefficients were 0.0016, <0.0001 and 0.0021, respectively. Standardized results from the multivariate analysis are shown in Table 3. The relationship between plasma oxalate and plasma creatinine at the time of transplantation is shown in Figure 2. Patients who received preemptive transplantation and patients transplanted after start of dialysis are shown separately. The increase in plasma oxalate with increasing creatinine values is similar in the two patient groups although patients receiving dialysis had oxalate values about 6.5 $\mu\text{mol/L}$ higher than the preemptive patients.

Oxalate at 10 weeks was tested likewise, with all laboratory parameters at 10 weeks, but also including all laboratory parameters at baseline, primary non-function, rejection episodes, live *versus* deceased donor, donor age and GFR at 10 weeks. Phosphate, creatinine, albumin, urea and haemoglobin at 10 weeks, baseline PTH, recipient and donor age, rejection episodes and GFR were found to correlate significantly with oxalate at 10 weeks. In the subsequent multivariate regression analysis, only GFR, creatinine and donor age retained significance as determinants of oxalate: $\log [\text{oxalate at 10 weeks}] = 0.9277 - 0.4241 \times \log [\text{GFR}] + 0.002224 \times \text{donor age} + 0.3273 \times \log [\text{creatinine}]$; P -values = 0.12, 0.02, 0.028 and 0.032, respectively. See also Table 3.

Table 2. Laboratory data for 212 kidney transplant patients at transplantation and after 10 weeks

	At transplantation				After 10 weeks				Ref. interval
	<i>N</i>	Median	95% central interval	% below lower/above upper ref. limit	<i>N</i>	Median	95% central interval	% below lower/above upper ref. limit	
P-oxalate ($\mu\text{mol/L}$)	99	35	10.4–93.9	0/98	167	9	4.0–25.5	0/37	3–11
P-creatinine ($\mu\text{mol/L}$)	212				167				
♀ >15 years		597	284–968	0/100		95	54–163	0/60	50–90
♂ >15 years		619	252–1110	0/100		122	64–303	0/72	60–105
P-calcium (mmol/L)	212	2.38	2.01–2.78	10/18	167	2.41	2.05–2.83	5/23	2.15–2.51
P-phosphate (mmol/L)	212				167				
♀ >16 years		1.7	0.8–2.81	0/63		0.8	0.4–1.29	60/0	0.9–1.5
♂ 16–49 years		1.75	0.66–3.1	0/50		0.9	0.6–1.28	25/0	0.8–1.7
♂ ≥50 years		1.6	0.89–2.55	0/60		0.8	0.39–1.40	28/0	0.8–1.4
P-albumin (g/L)	211				167				
18–39 years		42	33.8–47	6/0		42	34.4–46.9	2/0	36–48
40–69 years		40.5	31–47	12/8		40	32.0–44.0	7/0	36–45
≥70 years		40	32–46	11/6		38	26.0–40	7/0	34–45
P-urea (mmol/L)	212				167				
♀ 18–49 years		22.5	9.16–45.6	0/100		8.55	3.5–15.9	0/61	2.6–6.4
♀ ≥50 years		17.9	7.5–34.1	0/100		9.35	3.20–23.10	0/65	3.1–7.9
♂ 18–49 years		19.2	8.72–36.8	0/100		8.45	2.75–16.17	0/54	3.2–8.1
♂ ≥50 years		19.3	5.88–36.58	0/96		11.9	3.83–31.24	0/70	3.5–8.10
P-PTH (pmol/L)	201	18.6	1.5–152	3/86	167	11.3	3.8–26.3	0/81	1.6–6.9
Hb (g/dl)	163				186				
♀ >11 years		12.0	8.81–14.50	32/2		11.45	9.15–14.35	56/2	11.7–15.3
♂ >11 years		12.7	9.90–15.60	46/1		12.20	9.70–15.60	78/0	13.4–17.0

Table 3. Multivariate regression analysis of oxalate at transplantation and after 10 weeks

Variables	At transplantation		After 10 weeks	
	Standardized coefficients	P-value	Standardized coefficients	P-value
Preemptive transplantation	0.243	0.0021		NS
Recipient age		NS		NS
Donor age		NA	0.167	0.028
Rejection		NA		NS
GFR		NA	-0.248	0.02
P-creatinine ^{a,b}	0.591 ^a	<0.0001	0.229 ^b	0.03
P-phosphate ^{a,b}		NS		NS
P-albumin ^b		NS		NS
P-urea ^b		NS		NS
P-oxalate ^a		NS		NS

NA, not applicable; NS, not statistically significant.

^aAt transplantation.

^bAfter 10 weeks.

Discussion

This is the first study of a larger cohort of patients addressing plasma oxalate in kidney failure patients before and after transplantation. This is also the first study to address the determinants of plasma oxalate in these patients. The data confirm earlier more limited observations of very high levels of oxalate in patients with end-stage kidney failure [11]. The increase was 7-fold compared with healthy persons. The independent determinants of oxalate in multivariate regression analysis were creatinine and established dialysis treatment, supporting the hypothesis of increasing values with declining kidney function. It has previously been shown that oxalosis, the deposition of CaOX in tissues, can be a complication of chronic renal failure. CaOX crystals have been found both in kidneys and myocardium of these patients at autopsy [14]. Super-

saturation of CaOX in plasma occurs when plasma oxalate level rises beyond 30 $\mu\text{mol/L}$ [13]. Almost two-thirds of our patients had values beyond this limit at admission for kidney transplantation despite the fact that many had preemptive transplantation, implying some residual capacity for renal excretion of oxalate. It was interesting to note that, at the time of transplantation, two of the patients had oxalate concentrations in the same range as found in the patient who was later diagnosed with PH. In one of these patients, the elevated plasma oxalate might have been due to enteric hyperoxaluria. Distal parts of the ileum and caecum had been removed due to accidental thrombosis 25 years before transplantation and she developed several kidney stones and was transplanted with a live donor a year after the start of dialysis. The other patient with grossly elevated plasma oxalate at transplantation had no history of gastrointestinal disease or gastrointestinal surgery and had a clinical diagnosis of nephrosclerosis. However, at 10 weeks follow-up, the two non-PH patients had oxalate values at or slightly above the upper reference limit, while the PH patient still had oxalate values three times the upper reference limit (results not shown).

The severity of oxalosis has also been found to be related to the duration of renal insufficiency [14]. However, we could not demonstrate that plasma oxalate concentration at the time of transplantation was significantly associated with the time on renal replacement therapy. Our results might have been biased in patients who had started regular dialysis treatment since it is well recognized that plasma oxalate is readily removed by dialysis [15] and is thus reduced after each treatment session and increases by refilling from extra-vascular stores until the next dialysis session. Therefore, the time elapsed since the last dialysis session may have influenced the results. We have limited information on the time elapsed from the last dialysis session to the time of blood sampling at admission for transplantation. However, analysis of data from preemptive patients revealed the same relationship between oxalate

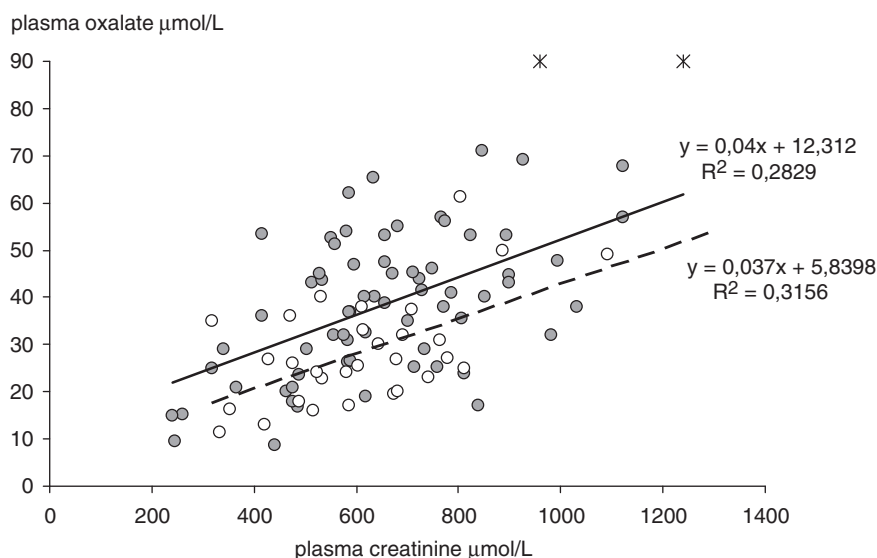


Fig. 2. Variation of plasma oxalate with plasma creatinine at the time of transplantation is shown (filled circles, patients on dialysis, open circles, preemptive patients), with trend lines (solid for dialysis and dashed for preemptive), and formulae and corresponding correlation coefficients, while two exceptionally high oxalate values (124 and 156 $\mu\text{mol/L}$) are indicated by asterisks.

and creatinine, substantiating that increasing retention of oxalate occurs with declining kidney function.

Median plasma oxalate at 10 weeks was 9 $\mu\text{mol/L}$, indicating some 75% reduction of plasma oxalate compared with the values at admission for transplantation. This finding was not surprising, but has not been previously reported in the literature. Interestingly, more than one-third of the patients still had values above the upper reference limit for healthy controls and three had a value at or beyond the supersaturation level of 30 $\mu\text{mol/L}$. This is in contrast to findings in a previous small study of eight patients undergoing living related kidney transplantation [11] where plasma oxalate was found to be in the normal range 3 days post-transplant although a tendency for higher oxalate levels was observed when compared with controls. The lack of statistical significance might be attributed to the inter-individual variability and the fact that the above-mentioned study only comprised eight patients. Episodes of kidney stones were not recorded in any patient. Episodes of urinary tract obstruction were caused by lymphocele or urethral necrosis; in no case was obstruction caused by stone in the transplant urinary tract.

We demonstrated that kidney function at 10 weeks as measured by plasma $^{51}\text{Cr-EDTA}$ GFR (and also plasma creatinine) and donor age were the only determinants of oxalate in multivariate regression analysis. Baseline level of oxalate was not a predictor for the reduction at 10 weeks, indicating that the plasma load of oxalate at the time of transplantation is not important for the subsequent reduction in plasma oxalate. By contrast, the establishment of adequate kidney function for excretion of the excess oxalate load is obviously of importance. However, we could not find that primary non-function of the kidney transplant was of importance as long as an acceptable function was established within the first few weeks.

The measurement of oxalate in biological fluids has been challenging, especially due to *in vitro* oxalogenesis, leading to erroneously high plasma oxalate from the auto-oxidation of ascorbate into oxalate after sampling and even during assay [16]. Thus, to obtain reliable quantitative results, samples for oxalate determination must be processed expeditiously.

We found that 37% of the patients studied had plasma oxalate above the upper reference limit after 10 weeks. This could at least theoretically have been attributed to oxalogenesis, if sample collection and pre-treatment had not been standardized. However, all samples included in this study have been handled according to protocol. The few samples that had not been correctly treated (e.g. left at room temperature after collection, etc.) were excluded from the present analysis.

Strengths of the study

The study was prospectively performed and the analyses are well validated [12]. This is the first study of a larger cohort of patients with kidney failure measuring plasma oxalate before and after transplantation. This is also the first study of the determinants of plasma oxalate in these patients.

Limitations

The plasma concentrations of oxalate may not be representative of the tissue damage observed in biopsy and autopsy studies. The importance of hyperoxalaemia in these patients remains obscure and follow-up studies of clinical endpoints or simultaneous protocol biopsies addressing oxalate deposits in the kidney transplants are needed.

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Conflict of interest statement. None declared.

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