ORIGINAL ARTICLE

Kidney graft survival of >25 years: a single center report including associated graft biopsy results

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SUMMARY

Only few centers have reported their observations on patients with very long-term kidney graft survival of more than 25 years. Eighty-six subjects were identified in our center with graft survival of >25 years. Donor age was 31.3 ± 18.5 years. Mean duration of transplantation was 30.3 ± 3.6 years. At last follow-up, the cystatin C clearance was 47 ± 23 ml/min. Transplant biopsies for cause were performed in 30 subjects at a median of 28.4 years (19.1–40.3) after transplantation. Acute or chronic active T cell-mediated rejection was present in five cases and histological characteristics of acute or chronic active humoral rejection in eight cases. More than 80% of biopsies had inflammatory infiltrates in nonatrophic or atrophic cortical areas. The number of HLA mismatches were higher in biopsied subjects (3.0 ± 1.8 vs. 2.2 ± 1.7 without biopsy). Immunosuppressive therapy was adapted in most biopsied subjects; impaired graft function and proteinuria was unchanged at last follow-up. Sixty percent of all subjects had hyperparathyroidism (iPTH of the whole group: 132 ± 157 pg/ml), which was predominantly secondary, as judged by serum calcium and graft function. Young donor age was certainly a prerequisite of longterm graft survival. Nonetheless, inflammation or rejection in most biopsied patients suggests an important role of alloreactivity even in this late course.

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Introduction

The first kidney transplantation was done by Murray in 1954 between twins [1]. Since then, kidney transplantation has evolved from experimental surgery to a standardized procedure. Discovery of drugs for immunosuppression, implementation of standardized protocols for induction therapy and maintenance immunosuppression, and therapeutic decisions based on standardized histological assessment of graft biopsies have contributed to a steady improvement of graft survival of over 90% at 5 years, mainly because of improvements in 1-year graft survival [2,3].

At Hannover Medical School, the first kidney transplantation was performed in 1968 and since then a total of 6601 kidney transplantations were performed during the observation period of this study until June 2014.

In this study, we were interested in clinical, laboratory, and histological characteristics of patients from our center with a very long graft survival time which

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was defined as more than 25 years. Graft biopsies were re-evaluated according to the most recent Banff classification [4].

Materials and methods

Subjects

All adult patients who are transplanted at Hannover Medical School, Germany, are transferred to our post-transplant care program [5]. The first contact with the outpatient clinic is made at the day of hospital discharge from transplant surgery. In the first three post-transplant months, the frequency of visits ranges between 2 and 6 weeks. After that, the intervals are increased to 3 months. After the first transplant year, regular visits usually occur every 6–12 months [5]. All patients transplanted at our institution agreed to use their clinical data for scientific analyses in an anonymous fashion. Data collection and use of data in this way was approved by the institutional Ethics board.

From all these patients, a group of 86 patients with a graft survival exceeding 25 years was identified. The 86 patients had been transplanted between November 1972 and March 1988. During that period a total number of 1513 transplantations had been performed. Fourteen patients were excluded; two with combined transplantation (liver/pancreas), and 12 patients with medical care afforded only by their local nephrologist or family physician, without sufficient available clinical information.

The 72 subjects with very long-term survival were regularly seen at least every year (median number of visits per year and patient: 1.4; 25/75th percentiles: 1.1/2.1). Besides taking the medical history including the current medication, body height and weight and blood pressure were documented and according to necessity, further physical examination was performed. Regular laboratory work-up included blood count, serum chemistry including creatinine and cystatin C clearance, intact parathormone, immunosuppressive drug levels and urine analyses. Cystatin C clearance, which has been shown to have higher accuracy than creatinine-based estimations of renal transplant function in transplant patients [6], was calculated according to [7]. Creatinine clearance (eGFR) was calculated by the Cockcroft and Gault formula. Protein excretion is given as total protein in mg/l. Donor-specific antibodies were measured with CDC and Luminex-based SPA. Graft biopsies were performed as described [8] either for unexplained functional impairment and/or proteinuria, defined by an increase in serum creatinine by more than 25% or proteinuria exceeding approximately 0.5 g/l. For this study, all biopsies were re-evaluated according to the criteria of the most recent Banff classification [4]. Last follow-up data were obtained in July 2014.

Statistical analysis

Statistical analyses were done with IBM SPSS STATISTICS (Version 24). Graphs were prepared with GraphPad Prism (Version 4.00; San Diego, CA, USA). Continuous data are expressed as means with standard deviation and as median values with 25/75th percentiles. For correlation analysis, the nonparametric Spearman Rank correlation test was used. Group comparisons were made with the Kruskal-Wallis test and Mann-Whitney *U*-test. Statistical significance was assumed for $P < 0.05$.

Results

The 72 subjects included 39 males and 33 females with a graft survival of 26.4–41.7 years (mean 30.3 ±3.6) after transplantation (Table 1). The leading cause of end stage renal failure was glomerular disease, with 13 cases of biopsy-proven glomerulonephritis and 19 cases with suspected glomerulonephritis. Alport syndrome was diagnosed in six subjects and 10 subjects had congenital urogenital dysplasia. The mean age at transplantation was 29.4 ± 12 years. Sixty-six subjects received their first transplantation, five subjects their second, and one subject, the third. All kidney grafts were from Caucasian donors. In three cases, blood-related living donor transplantations were performed. The mean donor age was 26.9 ± 12.8, with a broad range from 3 to 57 years.

Clinical and laboratory data at the last follow-up visit are shown in Table 2. Type II diabetes was present in eight subjects. None of the subjects had Type I diabetes. Replicative hepatitis B had been diagnosed in six subjects and replicative hepatitis C in five subjects by nucleic acid testing. Mean systolic blood pressure was 128 ± 13 mmHg and diastolic blood pressure 78 ± 8 mmHg at last follow-up. Nineteen subjects had blood pressure results above the upper normal limit of 135/85 mmHg. Renal cell carcinoma in the transplanted kidney had been detected in two subjects, both with pT1 stage and without recurrence after R0 resection. On average, the body mass index was normal.

The median estimated GFR (eGFR) based on serum creatinine was 49 ml/min and the cystatin C clearance was 44 ml/min. Urinary protein excretion at the last follow-up visit was available in 70 subjects, with a

Table 1. Pretransplant and transplant data.

Total number of subjects	72
Age at transplantation (mean ± SD)	29.4 ± 12.0
Gender (male/female)	39/33
Underlying disease	
Suspected chronic glomerulonephritis	19 (26.4)
Glomerulonephritis	13 (18.1)
Pyelonephritis	12 (16.7)
Congenital anomalies of the kidney and urinary tract	10 (13.9)
Alport syndrome	6 (8.3)
Polycystic kidney disease	3 (4.2)
Unknown	3 (4.2)
Reflux nephropathy	3 (4.2)
Analgesics nephropathy	2 (2.8)
Nephronophthisis	1 (1.4)
Number of transplantations	
First	66 (91.7)
Second	5 (6.9)
Third	1 (1.4)
Panel reactive antibodies >0%*	14 (19)
Donor age (mean ±SD)*	26.9 ± 12.8
Cold ischemia time (h; mean ±SD)*	21.9 ±9.8
HLA mismatches on locus*	
A (0/1/2)	26/39/7 (36/54/10)
B (0/1/2)	25/36/11 (35/50/15)
DR (0/1/2)	29/28/4 (40/39/6)
Mean number on loci A, B, DR (mean ±SD)	2.57 ± 1.78

Percentages of cases are shown in brackets.

*Missing values: panel reactive antibodies; $n = 9$, donor age; $n = 5$, cold ischemia time; $n = 6$.

median of 70 mg/l (25/75th percentiles: 50/238). The cystatin C clearance correlated inversely with proteinuria ($r = -0.46$, $P = 0.002$; Fig. 1). The eGFR and cystatin C clearance were not correlated with the number of HLA mismatches on locus A, B, and DR (not shown). Also, the total number of mismatches was not linked with graft function (eGFR: $P = 0.97$, cystatin C clearance: $P = 0.94$). Likewise, protein excretion was not correlated with the number of HLA mismatches on locus A, B, and DR nor with the total number of mismatches ($P = 0.84$).

The immunosuppressive regimen included calcineurin inhibitors in 49 subjects, antiproliferative drugs in 39 subjects, including 13 subjects with mycophenolate mofetil, 14 with azathioprine, and 12 with sirolimus (Table 2). The majority of subjects ($n = 61$) were on a dual immunosuppression, nine subjects on a triple therapy and one subject each had only prednisolone or ciclosporin A. Subjects with an antiproliferative drug had a cystatin C clearance of 49 ±23 ml/min compared with 47±24 ml/min in subjects without (not significant). In 46 subjects, immunosuppressive therapy was constant over time with respect to dose and blood levels. Ciclosporin A trough levels were kept between 30 and 80 ng/ml, dependent on the additional immunosuppressive components and individual assessment. Changes in the immunosuppressive therapy were made mostly in subjects undergoing biopsy and are reported below.

A graft biopsy was performed for unexplained functional impairment and/or proteinuria in 30 subjects after a median time of 28.4 years (range 19.1–40.3) after transplantation, including two of the six retransplanted subjects. The median eGFR at biopsy was 42 ml/min (25/75th percentiles: 29/54) and unchanged at last follow-up (42 ml/min; 25/75th percentiles: 32/52) in these subjects (Fig. 2a). Median proteinuria was 135 mg/l (25/75th percentiles: 63/438) at biopsy and 110 mg/l (25/75th percentiles: 50-338) at last follow-up (Fig. 2b). HLA mismatches were higher in subjects who underwent biopsy (3.0 ±1.8 vs. 2.2 ±1.7 in subjects without biopsy; $P = 0.05$). As with the entire group of subjects, HLA mismatches on any HLA locus and the total number of mismatches were not associated with eGFR or with proteinuria (data not shown).

The results of the re-evaluation of the biopsies according to the criteria of the most recent Banff classification are shown in Table 3. Two subjects (one with a retransplant) had borderline T cell-mediated rejection (TCMR) and one subject, TCMR IA. Histomorphological characteristics of antibody-mediated rejection (ABMR) were present in eight subjects. Donor-specific antibodies (DSA) were detected in one case of active ABMR with glomerulitis against HLA class II antigens and in one case of chronic active ABMR against HLA class I and II antigens. The remaining subjects with ABMR had non-DSA HLA antibodies. Only two subjects fulfilled all criteria of chronic active TCMR and one of these was suspected to have additional ABMR, presenting with peritubular capillaritis, thrombotic microangiopathy, and non-DSA HLA antibodies. Notably, even without fulfilling the criteria of chronic active TCMR, interstitial inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA) was a frequent finding. In five subjects, the positive i-IFTA score was associated with recurrent urinary tract infection. Besides in the five subjects with TCMR and five of the subjects with ABMR, some degree of cortical interstitial inflammation (total i-score) was found in further 14 subjects. Regarding noninflammatory changes, all biopsies

Table 2. Clinical and laboratory data at last follow-up.

Morbidities	Mean ± standard deviation or number (%)	Median values with 25/75th percentiles
Hepatitis B (replicative)*	6 (8.3)	
Hepatitis B (nonreplicating)†	7 (9.7)	
Hepatitis C (replicative)‡	5 (6.9)	
Diabetes mellitus Typ II	8 (11.1)	
Previous renal cancer in the graft	2 (2.8)	
BMI (kg/m^2)	25.1 ± 6	24.4 (22.2; 28.1)
BMI > 25	30 (41.7)	
Systolic blood pressure (mmHg)	128 ± 13	130 (120; 135)
Diastolic blood pressure (mmHg)	78 ± 8	80 (70; 81)
Blood pressure > 135/80 mmHg	19 (26.4)	
Serum parameters		
Serum creatinine (µmol/l)	154 ±80	137 (97; 190)
eGFR (based on serum creatinine)	50.9 ± 20.8	48.7 (35.3; 63.4)
Cystatin C clearance (ml/min)	47.4 ± 2.7	43.5 (28.0; 66.8)
Calcium (mmol/l)	2.34 ± 0.15	2.34 (2.24; 2.43)
Phosphate (mmol/l)	1.08 ± 0.25	1.05 (0.90; 1.20)
Parathormone (pg/ml)	131 ± 157	103 (49; 149)
Alkaline phosphatase (U/l)	91.9 ± 11.9	70 (54.5; 92.8)
Immunosuppressive regimen		
Ciclosporin A	41 (56.9)	
Tacrolimus	8 (11.1)	
Azathioprine	14 (19.4)	
Mycophenolate mofetil	13 (18.1)	
Sirolimus	12 (16.7)	
Prednisolone	69 (95.8)	

BMI, body mass index.

*Hepatitis B DNA positive.

†Hepatitis B DNA negative.

‡Hepatitis C RNA positive.

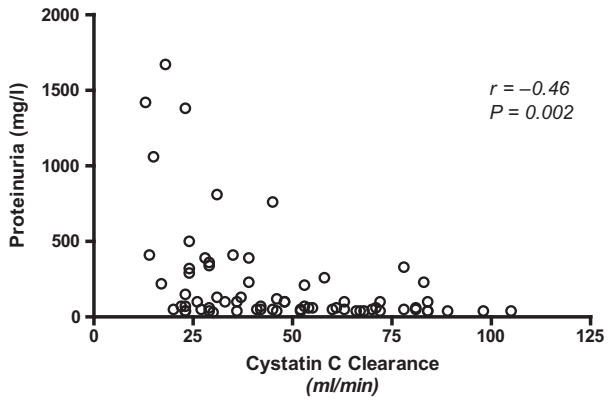

Figure 1 Correlation between graft function and proteinuria.

showed some degree of arteriolar hyalinosis. Four cases with hyalinosis grade ah3 were associated with a diagnosis of type 2 diabetes. Fifteen of the biopsied subjects had calcineurin inhibitor therapy and showed hyalinosis grade ah3 in 10 cases, while subjects without calcineurin inhibitor had 12 cases with ah3. Systolic and diastolic blood pressure was not correlated with the degree of arteriolar hyalinosis ($P = 0.93$). In two of the five cases with focal and segmental glomerulosclerosis the cause of end stage renal failure was unknown and in the remaining cases other diseases than focal and segmental glomerulosclerosis were causative.

An inferior graft function at the time of biopsy was associated with IFTA, with a median eGFR of 46, 32, and 41 ml/min (grade I, II, III, respectively) compared with 60 ml/min in the absence of IFTA ($P = 0.02$). Similarly, i-IFTA was associated with lower graft function, with a median eGFR of 40, 32, and 44 ml/min (grade 1, 2, 3, respectively), compared with 60 ml/min in the absence of i-IFTA ($P = 0.048$). The median eGFR in cases with TCMR or ABMR was 40 ml/min, which was

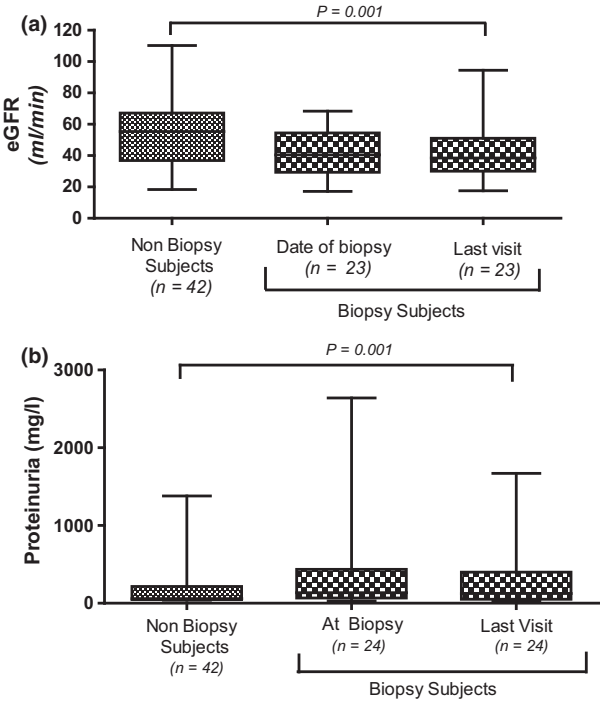

Figure 2 Graft function (a) and proteinuria (b) of patients with and without graft biopsy. Median, lower and upper quartiles, and extreme values are given. Graft function is expressed as creatinine-based estimated GFR.

not significantly different from cases without rejection (44 ml/min; $P = 0.963$).

Proteinuria tended to be lower in cases with acute tubular injury compared to cases without this finding (median: 85 vs. 305 mg/l; $P = 0.15$). A positive total i- score was linked with higher proteinuria, with 100 mg/l for ti1 and 925 mg/l for ti2, compared with 70 mg for ti0 ($P = 0.036$). Regarding i-IFTA, only cases with grade 3 had higher proteinuria (430 mg/l compared to all other cases (80 mg/l; $P = 0.018$). Also, ABMR and TCMR cases had higher proteinuria (405 vs. 77 mg/l; $P = 0.05$). At last follow-up visit, proteinuria appeared to be stably elevated in these subjects compared to subjects without rejection (315 vs. 63 mg/l; $P = 0.026$).

Following biopsy, immunosuppression was intensified in the case with acute TCMR IA and in one case each with borderline TCMR and chronic active TCMR, in six out of eight subjects with ABMR, and in six subjects with positive i-IFTA and total i- scores. Intensification of immunosuppression was tailored individually and included steroid boli, switching from a dual to triple therapy and exchanging ciclosporin A for tacrolimus. The calcineurin inhibitor was reduced or terminated in nine cases with severe acute tubular injury or isometric vacuolization and in one case with severe IFTA.

Hyperparathyroidism was observed in 43 subjects (59.7%) according to the upper normal limit of 65 pg/ml for intact parathormone (iPTH). Serum calcium levels were normal in almost all subjects with a mean of 2.34 ±0.15 mmol/l, as well as serum phosphate levels (Table 1). There was no correlation of parathormone values with serum calcium (Fig. 3). iPTH values correlated weakly with alkaline phosphatase activity (Fig. 4, $r = 0.245$; $P = 0.046$). In individual subjects, alkaline phosphatase activity was remarkably stable over time with the exception of three subjects who showed a steady increase. One of these subjects with high alkaline phosphatase activity was hypocalcemic and had an iPTH value of 1120 pg/ml, and one had an iPTH of 291 pg/ml and serum calcium close to the upper normal limit. In one subject who had a low iPTH and normal serum calcium, high alkaline phosphatase activity was associated with increased liver enzymes. iPTH values were inversely correlated with graft function (Fig. 5, $r = -0.39$, $P = 0.001$). Vitamin D analogues were given to 46 of the 72 subjects. Bone fractures without a history of significant trauma were not observed.

Discussion

Very long survival of kidney transplants for more than 25 years has been rarely reported [9–11]. We identified 86 subjects with functioning kidney transplants exceeding 25 years. We had to exclude 14 subjects, mainly because of lacking sufficient clinical information because of lost to follow-up.

The 72 subjects presented in this report differ in several aspects from patients transplanted in more recent years at our center [12]. The mean age of our patient group at transplantation was 29 years, compared with 50 years in recent years, and is similar to other reports on patients with long-term graft survival [9,11]. Leading causes of end stage renal failure in our cohort were glomerulonephritis or suspected glomerulonephritis (44.4%), compared to only 22% in recent reports from the European countries [13]. Currently leading causes of end stage renal failure were absent like diabetes or present with low prevalence such as cystic kidney disease [12]. Nonetheless, eight of the 72 subjects developed diabetes in their post-transplant course. Retransplants were prevalent with only 8%.

The patients with long-term graft survival appear to have a better general health status than average patients transplanted in the last two decades. Only one quarter had hypertension compared with >90% in our recent report and similarly, diabetes after transplantation was

Table 3. Histopathomorphological findings in the 30 renal graft biopsies.

Diagnosis/BANFF scores	Number of cases	Additional information
Acute TCMR		
Borderline rejection	2	All three cases with IFTA grade II, ti-score 2,
TCMR grade IA	1	and i-IFTA grade I
Chronic active TCMR (Grade IA)	2	One case suspicious of acute ABMR
Active ABMR	2	One case with glomerulitis and DSA
		One case with peritubular capillaritis and TMA
Chronic active ABMR	6	c4d1 *n* = 3
		c4d2 *n* = 1
		c4d3 *n* = 2
Acute tubular injury	8	In six cases as primary diagnosis
Isometric vacuolization	12	Six cases had a calcineurin inhibitor at biopsy
Arteriolar hyalinosis		
ah1	3	
ah2	5	
ah3	22	
IFTA		
None	4	Acute tubular injury as primary diagnosis in
I	11	all four cases without IFTA
II	13	
III	2	
Total i-score		
0	6	
1	15	TCMR *n* = 1, ABMR *n* = 4
2	9	TCMR *n* = 4, ABMR *n* = 1
i-IFTA score		
0	4	
1	8	
2	5	Recurrent UTI present in *n* = 1
3	13	Recurrent UTI present in *n* = 4
Transplant glomerulopathy		
cg1	7	Chronic active ABMR in *n* = 4
cg2	1	Chronic active ABMR in *n* = 1
Transplant vasculopathy		
cv1	3	Chronic active ABMR in *n* = 3
Other specified lesions		
IgA nephropathy	1	CAKUT as primary renal disease
Focal segmental glomerulosclerosis (FSGS)	5	None with primary renal disease of FSGS
Diabetic glomerulopathy	3	Only one case with established diabetes
Nephrocalcinosis	1	Serum calcium of 2.54 mmol/l
Ascending nephritis	9	UTI present in *n* = 5

ABMR, antibody-mediated rejection; CAKUT, congenital anomalies of the kidney and urinary tract; DSA, donor-specific antibodies; IFTA, interstitial fibrosis and tubular atrophy; i-IFTA, inflammation in areas of IFTA; TCMR, T cell-mediated rejection; UTI, urinary tract infection.

less prevalent with 11% compared with 15% [12]. Noteworthy, one report on long-term graft survival of 19 to 29 years showed a relatively high incidence of type II diabetes of 23% post-transplant [10]. Different to the actual low numbers of replicative hepatitis (7%; [12]), subjects with long-term graft survival had a higher rate of 15%, similar to other reports on patients with long-term survival (11–48%) [10,11].

Hypertension is an important factor for graft survival [14]. In our patient group, three quarters had normal blood pressure values at last follow-up, and graft function was not correlated with blood pressure values (data not shown). There was no difference in graft function between subjects with and without an antiproliferative drug in the maintenance immunosuppression. Graft function calculated as creatinine-based eGFR was highly

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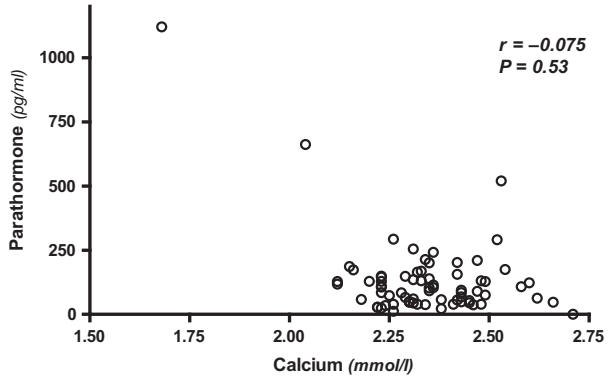

Figure 3 Correlation between serum levels of intact parathormone and calcium.

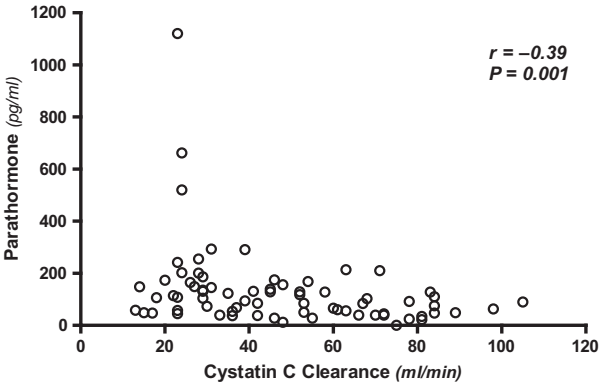

Figure 5 Correlation between serum levels of intact parathormone and graft function.

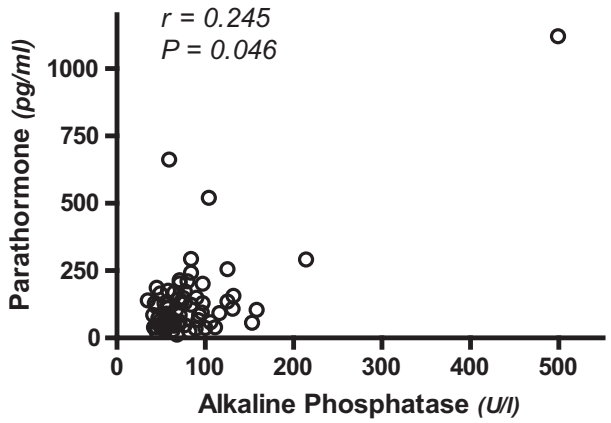

Figure 4 Correlation between serum levels of intact parathormone and alkaline phosphatase activity. The subject with liver disease and elevated liver enzymes was excluded from the graphical depiction.

variable in our patient group at last follow-up, ranging from 18 to 110 ml/min, with a median of 49 ml/min. Subjects who underwent a biopsy had a lower eGFR at biopsy and at last follow-up (median 42 ml/min at both time points).

Alloimmunity obviously had a role in a substantial proportion of the 30 subjects who underwent a biopsy. Thirteen of the 30 subjects fulfilled the histomorphological criteria of T cell-mediated or antibody-mediated rejection. Only two subjects with antibody-mediated rejection had DSA, however non-DSA HLA antibodies were present in six further cases with antibody-mediated rejection. Lacking detection of DSA in these cases could be because of the imprecision of tissue typing in former years, particularly for DRB1, and missing of class II antigens DQB1 and DPB1 so that it remains open whether these non-DSA antibodies were directed against the graft or other, non-HLA antibodies [15] were involved. Also, some mismatches may be of greater importance for developing DSA, e.g. HLA DRß1 [16]. Another important observation is the high prevalence (>80%) of inflammation in nonatrophic or atrophic tubulointerstitial cortical areas in subjects without a specific diagnosis of T cell-mediated or antibody-mediated rejection. Inflammatory infiltrates in atrophic areas (i-IFTA) are, after excluding other causes like urinary tract infection, one of the key features in chronic T cell-mediated rejection [4]. In patients of the DeKAF study, late biopsies for cause showed positive i-IFTA scores in 69%, which was clearly associated with a higher risk of graft failure [17]. In another study, i-IFTA was associated with a higher number of HLA mismatches and patients with this finding had higher proteinuria like in our subjects [18]. A similar high i-IFTA prevalence of more than 70% at 15 years after transplantation was reported in combined kidney/pancreas transplanted patients, which was associated with inferior graft function [19]. In that study, tacrolimus treatment was associated with a lower prevalence of i-IFTA. Tacrolimus was given to few subjects in our study.

Arteriolar hyalinosis was observed in all subjects and was severe in most cases. It was not specifically linked with calcineurin inhibitor therapy, diabetes, or hypertension, like in our previous study [20] that identified age of the graft as the main factor.

The immunosuppressive treatment was almost exclusively changed in subjects who were biopsied. As median eGFR and proteinuria at the time of biopsy were similar to the last follow-up visit, therapeutic decisions that had been made were probably adequate in most subjects.

High pre- and post-transplant parathormone levels have been reported as risk factors for graft failure and death [21,22]. Nearly 60% of subjects of this study had an elevated serum parathormone level. Only three subjects had hypercalcemia consistent with tertiary hyperparathyroidism. The observed inverse correlation of

parathormone with eGFR indicates parathormone induction secondary to an impaired graft function. Analysis of serum alkaline phosphatase revealed rather low or moderate activities in most subjects, with weak correlation with iPTH values. The optimal iPTH value in renal transplant patients is unknown [23]. Responsiveness of the bone to parathormone may be impaired in patients with reduced kidney function [24]. Also, the biological activity of parathormone may be reduced in patients with chronic renal insufficiency, for instance by oxidation of the molecule [25,26]. The intact parathormone assay used in this study may be insufficiently informative for bone metabolism and calcium homeostasis as PTH fragments besides the 1–84 peptide that are not detected by the assay may reduce the effects of the 1–84 peptide or may have counter regulatory effects via own signaling pathways [27]. Based on these considerations and the observed normal serum calcium values and alkaline phosphatase activity in most patients, elevated iPTH values were most likely an adaptive response to maintain calcium and bone homeostasis in the presence of reduced kidney function.

Our study has relevant limitations. Our center has no reliable data on overall patient and graft survival from the era in which the reported patients were transplanted. Because it was impossible to retrieve the clinical files from patients who were transplanted in the same era and lost their graft earlier, factors that favor long graft survival could not be identified in a comparative fashion. Certainly, the reported younger donor and recipient age and lacking or few comorbidities are a prerequisite of very long graft survival.

Authorship

BK: wrote the paper, analyzed data, collected data, performed research, designed research. IS, JHB and MH: analyzed data. NR: contributed important reagents. KHH: collected data. FL: contributed important reagents. JK: contributed important reagents. WG: analyzed data, performed research, designed research, wrote the paper.

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Conflicts of interest

The authors have declared no conflicts of interest.

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