Long-term Outcomes of Kidney Transplantation in Fabry Disease

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Background. Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutations in the α-galactosidase A gene that obliterate or markedly reduce α-galactosidase A activity. This results in the systemic accumulation of its glycosphingolipid substrates in body fluids and organs, including the kidney. Fabry nephropathy can lead to end-stage renal disease requiring kidney transplantation. Little is known about its long-term outcomes and the overall patient survival after kidney transplantation. **Methods.** Here, we report 17 Fabry patients (15 male and 2 female subjects) who received kidney transplants and their long-term treatment and follow-up at 4 specialized Fabry centers. **Results.** The posttransplant follow-up ranged to 25 years, with a median of 11.5 (range, 0.8-25.5] years. Graft survival was similar, and death-censored graft survival was superior to matched controls. Fabry patients died with functioning kidneys, mostly from cardiac causes. In 2 male subjects 14 and 23 years posttransplant, the grafts had a few typical FD lamellar inclusions, presumably originating from invading host macrophages and vascular endothelial cells. **Conclusions.** We conclude that kidney transplantation has an excellent long-term outcome in FD.

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Fabry disease (FD), a rare X-linked lysosomal storage disorder, is caused by mutations in the α-galactosidase A gene (*GLA*).[1] The mutations result in markedly decreased or absent α-galactosidase A (α-Gal A) enzymatic activity and the accumulation of its major substrate, globotriaosylceramide (Gb3), and its deacylated derivative, globotriaosylsphingosine (Lyso-Gb3)[2] in the fluids and cellular lysosomes throughout the body. Progressive Gb3 accumulation causes major organ damage, most frequently of the kidneys and heart.[1]

There are 2 major subtypes: the "classic" and "later-onset" phenotype. Classic male subjects have little or no residual α-Gal A activity; have prominent vascular endothelial cell glycosphingolipid accumulation; and have childhood or adolescence onset of severe acroparesthesias, angiokeratoma, hypohidrosis, and corneal and lenticular opacities that, with age, progress to early demise primarily due to cardiac and renal involvement.[3,4] Male subjects with the later-onset phenotype have residual α-Gal A activity; have no vascular endothelial cell glycosphingolipid accumulation; lack the childhood/adolescent hallmark symptoms; and predominantly experience progressive nephropathy, cardiomyopathy, and cerebrovascular disease in adulthood.[5-7] Heterozygous female subjects also can be affected by the disease; however, their FD manifestations are variable and typically milder because of random X-chromosomal inactivation.[8,9]

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This means that Fabry nephropathy can lead to end-stage renal disease (ESRD) requiring dialysis or transplantation (KTx) in male subjects and severely affected heterozygotes with both phenotypes.[4,10,11] The first kidney transplant in an FD patient was conducted in 1967 in Basel, Switzerland.[12] Initial reports advised against KTx in FD because of infectious and other complications and early transplant demise.[13] Limited information is available about the long-term outcome of KTx in FD, particularly posttransplant survival.[14-16] Later studies showed good survival rates, but mortality rates were high compared with non-Fabry recipients, mainly because of cardiovascular events.[16] The longest previously reported graft survival was 10 years,[14-18] and most patient outcome studies were conducted before the introduction of enzyme replacement therapy (ERT)[14-17] or did not include data on the duration of and the number of patients undergoing ERT.[15,16] Moreover, previous studies, most of which were registry analyses, did not report *GLA* mutations of recipients to confirm the FD diagnosis and determine the phenotypic subtype nor were systematic transplant biopsies performed.[14-18] The impact of posttransplantation ERT was also unclear. Because the normal endogenous α-Gal A activity in the graft should be sufficient for graft health, the recently reported European Best Practice Guideline on Fabry nephropathy recommended that ERT should be continued for nonrenal indications.[19] Some early reports, particularly before the advent of ERT, found Gb3 deposits in kidney transplants, albeit in host macrophages or vascular endothelial cells that infiltrated the allograft.[20-23] To further document the effects of renal transplants in FD, we conducted a long-term observational study that included follow-up of KTx grafts for up to 25 years in 17 Fabry patients, who were regularly treated and followed at 4 specialized FD centers.

MATERIALS AND METHODS

We investigated the FD patients that were transplanted and followed in Zurich, Bern, and Lausanne, Switzerland, and in Berlin, Germany. This study was conducted in accordance with the Declarations of Helsinki and Istanbul and approved by the respective center's ethics committee (KEK-ZH-Nr. 2014–0534, PB_2016–00360, and EKNZ 2015–403). All living patients provided written informed consent.

Patient Selection, Characteristics, and Follow-up

The databases of all participating centers were screened for patients with FD and kidney transplantation, and all identified patients were included in the study. The patients (15 male and 2 female subjects) were all regularly treated between 1979 and March 2017 at the 4 specialized FD centers in Zurich (patients 1-9), Bern (patients 10-12), Lausanne (patient 17), and Berlin (patients 13-16). The clinical data were extracted from medical records. Phenotyping was determined as reported previously.[24] Separate annual follow-ups were carried out in the Fabry and transplant centers. ERT was initiated according to the written local guidelines. Accordingly, ERT was indicated in all male subjects, independent from age, phenotype, and symptoms. In heterozygotes, ERT was indicated if they had proteinuria of more than 300 mg per day, Fabry-typical kidney biopsy findings, signs of Fabry cardiomyopathy such as left ventricular hypertrophy or arrhythmia, stroke or transient ischemic attack, persistent FD-related neuropathic pains despite conventional analgetic therapy, and/or gastrointestinal symptoms. ERT was prescribed at the licensed dose of either 0.2 mg/kg body weight of recombinant agalsidase-alpha (Replagal) or 1 mg/kg body weight agalsidase-beta (Fabrazyme) and given intravenously every 14 days.

Endpoint Evaluation

Cumulative patient and graft survival and death-censored graft survival were determined. Transplant function was regularly monitored at the respective FD and transplant centers. If a patient died outside the Fabry center, the date of death was obtained from the patient's general practitioner, family, or home care nurse administering ERT. All events were prospectively recorded and coded. The follow-up time was based on the date of the patient's death, graft loss, or the end of the study (March 31, 2017). Graft survival analysis was used to estimate the probability of a functioning graft at the study end. Graft failure was defined as graft loss or patient death, whichever came first. In addition, death-censored graft survival was used to estimate the probability of graft loss irrespective of death. For this purpose, the date of death in patients who died with a functioning graft was defined as the last follow-up.[25]

Control Group and Matching Algorithm

Data from non-FD KTx recipients were from the kidney transplant registry of the University Hospital Basel Switzerland and served as the control group.[26] This registry contains detailed information on more than 2220 kidney transplant patients, grouped according to immunosuppression era, as previously published by Wehmeier et al., 2016, and classified as follows: first period 1967 to 1980, second period 1981 to 1997, third period 1998 to 2004, and fourth period 2005 to 2015.[26]

To compare graft survival and overall patient survival between FD and matched non-FD KTx controls, each FD recipient was best matched and blinded to the outcome in a 1:1 ratio. The matching algorithm is shown in Table 1. The FD and non-FD KTx recipients were matched for sex, number of transplants, similar age with a maximum of –2/+4 years, and KTx year ±3 years, similar number of human leukocyte

TABLE 1.

The matching algorithm of FD and non-FD recipients

Parameter	Deviation
Sex	—
↓	
Year of transplantation	±3 years
↓	
Age at transplantation	–2/+4 years
↓	
Number of transplants	—
↓	
Presence of DSA	—
↓	
HLA mismatches	±2
↓	
Immunosuppression era	±1
↓	
Immunosuppression drugs	max. 1 drug

DSA, donor-specific anti-HLA antibodies; HLA, human leukocyte antigen; max, maximum.

antigen (HLA) mismatches ±2, same status of donor-specific antigens (DSAs), belonged to the same immunosuppression period (when possible), and similar immunosuppression regime with a maximum of 1 drug difference (Table 2). A 1:1 matching ratio was preferred to 1:2 or 1:3 as it would have required further expansion of the matching criteria to find several matches for 1 patient.

KTx Outcome and Gb3 Depositions

The latest value of serum creatinine (μmol/L), estimated glomerular filtration rate (eGFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[27] urinary protein/creatinine (mg/mmol), and albumin/creatinine (mg/mmol) ratios were used to assess KTx function. An eGFR below 15 mL/min per 1.73m^2 was considered a transplant failure. Recurrence of Gb3 deposits in kidney transplants was assessed using electron microscopy (EM) and/or histological analysis of kidney tissue from biopsies or autopsies.

Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges. Kaplan-Meier analysis and log-rank test of survival distributions were calculated. The statistical analyses were performed using the SPSS/PC software package (version 23.0; SPSS Inc., Chicago, IL). All statistical tests were 2 sided, and $P<0.05$ were considered significant.

RESULTS

Patients

The patients' demographics, renal data, and KTx-related information are presented in Table 2, and detailed clinical information, *GLA* genotypes, phenotypes, age at death, and

TABLE 2.

Demographics, donor type, baseline immunogenic risk, and clinical outcomes in FD recipients and matched non-FD controls

Cause of ESRD	Sex	Age at KTx	Year of KTx	Donor type	Number of HLA mismatches	Presence of DSA	Baseline immunosuppression	Graft loss	Death
FD (1)	m	24	2005	Living	5	No	M, P, C	No	No
Interstitial nephropathy		26	2002	Living	3		M, P, C	No	No
FD (2)	m	40	1995	Deceased	3	No	A, P, C	No	Yes
Extracapillary glomerulonephritis type II		41	1993	Living	3		A, P, C	Yes	No
FD (3)	m	45	1993	Deceased	4	No	A, P, C	No	No
Polycystic kidney disease		45	1994	Living	3		A, P, C	No	No
FD (4)	m	61	2007	Deceased	4	No	M, P, C	No	No
Hypertensive nephropathy		61	2007	Deceased	4		M, P, T	No	No
FD (5a)[a]	m	44	1999	Deceased (first)	3	No	M, P, C	Yes	Yes
Diabetic nephropathy		46	1999	Living (first)	3		M, P, C	Yes	No
FD (5b)[b]	m	56	2011	Deceased (second)	2	Yes	M, P, C	No	Yes
Polycystic kidney disease		57	2010	Deceased (second)	3		M, P, T	No	No
FD (6)	M	44	2011	Deceased	4	No	M, P, C	No	No
Malignant nephrosclerosis		42	2010	Deceased	5		M, P, T	Yes	No
FD (7)	m	17	1991	Living	2	No	A, P, C	Yes	No
Chronic pyelonephritis		18	1990	Living	2		A, P, C	Yes	No
FD (8)	m	35	1993	Deceased	4	No	P, C	No	Yes
Chronic pyelonephritis due to VUR		34	1993	Deceased	3		A, P, C	Yes	No
FD (9)	m	33	1979	Deceased	4	No	A, P	No	Yes
Polycystic kidney disease		35	1977	Deceased	5		A, P	Yes	No
FD (10)	m	28	1990	Deceased	3	No	A, P, C	No	Yes
Chronic pyelonephritis due to VUR		28	1992	Living	2		A, P, C	Yes	Yes
FD (11)	m	44	2014	Living	2	No	M, P, T	No	No
Diabetic nephropathy		42	2014	Living	1		M, P, T	No	No
FD (12)	m	27	1998	Deceased	3	No	M, P, C	No	No
Chronic pyelonephritis		28	1997	Living	3		M, P, C	Yes	No
FD (13)	m	53	2006	Living	3	No	M, P, C	No	No
Hypertensive nephropathy		52	2004	Living	3		M, P, C	No	No
FD (14)	f	56	2016	Living	4	No	M, P, T	No	No
Polycystic kidney disease		57	2015	Living	5		M, P, T	No	No
FD (15)	m	16	2013	Living	3	No	M, P, T	No	No
Congenital anomalies of the kidney		20	2011	Living	3		M, P, T	No	No
FD (16)	f	45	2015	Deceased	0	No	M, P, T	No	No
Unknown		44	2015	Deceased	1		M, P, T	No	No
FD (17)	m	59	2002	Deceased	3	No	M, P, C	No	Yes
Chronic glomerulonephritis		56	2002	Deceased	2		M, P, C	Yes	Yes

[a]First and [b]second transplant in the same FD recipient. A, azathioprine; C, cyclosporine; DSA, donor-specific anti-HLA antibodies; ESRD, end stage renal disease; FD, Fabry disease; f, female; HLA, human leukocyte antigen; KTx, kidney transplant; m, male; M, mycophenolate; P, prednisone; T, tacrolimus; VUR, vesicoureteral reflux.

TABLE 3.

Demographics, genetic, and clinical information and patient outcome in FD recipients

Patient and sex	Phenotype	*GLA* mutation; predicted amino acid change	Latest age, yr	Year of KTx	Year of ERT start	Type of ERT	Biweekly ERT dose (mg/kg)	Cumulative post-KTx ERT dose (g)	Overall survival (yr)	Deceased (+/–) Year	Cause of death
1 (m)	Classic	c.125 T > C;p.M42 T	35	2005	2004	α	0.2	3.4	11.2	-	
2 (m)	Classic	c.1033 T > C; p.S345P	60	1995	2001	α	0.2	5	19.6	2015	Septic endocarditis
3 (m)	Classic	c.1033 T > C;p S345P	61	1993	No	-	0	0	15.4	2009	Unknown
4 (m)	Later-onset	c.902G > A; p.R301Q	70	2007	2001	β/α	1.0/0.2	β:6.2/ α:2.2	9.4	-	
5a (m)	Classic	c.899 T > A;p.L300H	59	1999	2004	β	1.0	13	15.2	-	
5b (m)	Classic	c.899 T > A;p.L300H		2011	2004	β/α	1.0/0.2	β:3.5/ α:0.4	15.2	2014	Cardiac arrest
6 (m)	Classic	c.613C > T;p.P205S	49	2011	2004	α	0.2	2.1	5.3		
7 (m)	Classic	c.370-2A > G;Cons. Splice Site	42	1991	2001	α	0.2	4.4	25.5		
8 (m)	Classic	c.1167dupT;p.V390CfsX9	58	1993	2001	α	0.2	4.8	22.6	2016	Suicide
9 (m)	Classic	c.1167dupT; p.V390CfsX9	47	1979	No	-	0	0	13.8	1993	Cardiac arrest, Hepatitis B
10 (m)	Classic	c.1167dupT; p.V390CfsX9	40	1990	No	-	0	0	11.6	2002	Brainstem compression by basilar artery aneurysm
11 (m)	Classic	c.744_745delTA; p.F248LfsX7	46	2014	2005	α	0.2	0.9	3	-	
12 (m)	Classic	c.370-2A > G; Cons. Splice Site	46	1998	2001	α	0.2	4.8	18.8	-	
13 (m)	Classic	IVS6-10G > A; Alternative Splicing	63	2006	2006	β/α/β	1.0/0.2/1.0	β:16.7/ α:0.3	10.8	-	
14 (f)	Later-onset	c.416A > G;p.N139S	57	2016	2013	β	1.0	1.4	0.8	-	
15 (m)	Classic	c.638A > G;p.K213R	19	2013	2013	α	0.2	1.1	3.6	-	
16 (f)	Later-onset	c.109G > A; p.A37T	46	2015	2008	α	0.2	0.5	1.3	-	
17 (m)	Classic	Not available[a]	69	2002	2001	α	0.2	3.2	10.6	2012	Cardiac arrest

α, agalsidase-α; β, agalsidase-β; α/β or β/α, switch of the ERT; f, female; m, male; 5a, first transplant; 5b, second transplant.

[a]The original genetic report of this patient, who died in between, was no longer available. The classic phenotype has been confirmed by clinical symptoms: cardiomyopathy, nephropathy, cornea verticillata, and hypohidrosis.

cause are presented in Tables 3 and 4. There were 14 affected classic male subjects and 1 male subject with the later-onset phenotype who were diagnosed with FD at median ages of 34 (21-43) and 49 years, respectively. In addition, there were 2 severely affected heterozygotes, both from classically affected families, who were diagnosed at ages 38 and 54 years. The 15 male and 2 female patients were treated and followed for up to 25 years, with a median patient age of 53 (45-60) years as of March 31, 2017, or at death. In the majority, nephropathy was first diagnosed at ESRD, which then led to the diagnosis of FD. Diagnosis of nephropathy in the classically affected male subjects was made at the median age of 31 (21-43) years, in the later-onset male subject at 49 years, and at 25 and 42 years in the 2 heterozygotes. Chronic dialysis was initiated at a median age of 33 (22-43) years in the classically affected male subjects and at 38 years in 1 heterozygote and continued for a median time of 1 (0.25-3.7) years before KTx was undertaken at the median age of 44 (28-47) years. Eleven patients received 12 kidneys from deceased and 6 patients from living donors. The living donors were 2 healthy fathers (both to male recipients), 1 mother (who was diagnosed with FD after donating the kidney to her undiagnosed son), 1 stepmother, and 2 spouses. Immunosuppression was prescribed according to local transplantation guidelines of the respective period.[26] In this cohort, 5 patients were siblings belonging to 2 families with the classic phenotype. Recipients in family 1 included males 7 and 12 and family 2 included males 8, 9, and 10.

Enzyme Replacement Therapy

Fourteen of the transplanted FD patients had ERT: 9 patients started before and continued after KTx (4 agalsidase-α, 5 agalsidase-β) and 6 started after KTx (5 agalsidase-α, 1 agalsidase-β). Patient 5, who received 2 transplants, was counted in both categories. Their individual estimated cumulative agalsidase doses after KTx are indicated in Table 3. Patient 9 died in the pre-ERT era. Patient 10 died shortly after ERT became available. ERT was not provided to patient 3 because of the patient's frailty and dementia.

Patient and Graft Survival

During the median overall follow-up time of 11.5 years (range, 0.8-25.5), 11.6 years (7.6-17.1) for classic male subjects, 9.4 years for the later-onset male subject, and 0.8 and 1.3 years for the 2 heterozygotes. Seven classic male subjects died with functioning renal grafts (Table 3). The median age at death was 59 (47-61) years. Four of the 7 male deaths resulted from cardiac arrest secondary to hypertrophic cardiomyopathy and ventricular arrhythmias (in 2 cases, most likely triggered by septic endocarditis or hepatitis B), 1 died from a brain stem compression due to a large basilar artery aneurysm, 1 committed suicide, and 1 cause remains unknown (presumably cardiac due to known arrhythmias). The cumulative FD patient survival with KTx is shown in Figure 1. Cumulative graft survival in FD patients was similar to that of matched controls (Figure 2). Two kidney transplants were lost because of chronic transplant failure, (patients 5 and 7 after 9 and 22 years, respectively). Patient 5 was retransplanted at 9.1 years, and patient 7 was on the transplant waiting list at the end of this study. However, cumulative death-censored graft survival in FD patients was better than that of matched controls (P=0.03; Figure 3). As noted previously, FD patients mainly died from cardiac events but with functioning grafts. Overall patient and graft survival is shown in Table 5. There were 10 patients who had functioning grafts 10 years post-KTx that were all classic male subjects. Of the 10 patients who had functioning transplants at 10 years post-KTx, the median survival was 14.6 (11.1-20.2) years.

TABLE 4.

Transplant-related information in the FD recipients

Patient	Age at KTx, yr	Year of KTx	Survival of KTx, yr	Donor type and HLA mismatches		Immunosuppression at baseline	at last	eGFR (mL/min)[a]	Serum creatinine (μmol/L)[a]	Pro/C ratio (mg/mmol)[a]	Alb/C ratio (mg/mmol)[a]	AT1-/ACE-inhibitors[a]
1	24	2005	11.2	Living *(step mother)*	5	M, P, C	M, T	60	132	91	53.2	0
2	40	1995	19.6	Deceased	3	A, P, C	M, C	56	120	31	n/a	0
3	45	1993	15.4	Deceased	4	A, P, C	A, C	56	97	20	n/a	1
4	61	2007	9.4	Deceased	4	M, P, C	M, C	18	295	21	11.5	0
5a	44	1999	9.1	Deceased (first)	3	M, P, C	M, C			*anuric*		0
5b	56	2011	3.2	Deceased(second)	2	M, P, C	M, C	42	154	22	9.3	0
6	44	2011	5.3	Deceased	3	M, P, C	M, C	77	99	no	4.3	1
7	17	1991	21.8	Living *(father)*	2	A, P, C	P			*anuric*		1
8	35	1993	22.6	Deceased	4	P, C	P, C	43	152	45	18.9	1
9	33	1979	13.8	Deceased	1	A, P	A, P	n/a	n/a	n/a	n/a	n/a
10	28	1990	11.6	Deceased	3	A, P, C	A, P, C	27	282	109	n/a	1
11	44	2014	3	Living *(father)*	3	M, P, T	M, T	55	132	7	0.8	1
12	27	1998	18.8	Deceased	2	M, P, C	M, C	49	147	9	2.4	0
13	53	2006	10.8	Living *(wife)*	3	M, P, C	M, P, T	63	101	no	0.4	1
14	56	2016	0.8	Living *(husband)*	4	M, P, T	M, P, T	74	77	9.2	0.3	1
15	16	2013	3.6	Living *(mother)*	3	M, P, T	M, T	98	96	9.8	0.8	1
16	45	2015	1.3	Deceased	0	M, P, T	M, P, T	49	115	7.8	0.2	0
17	59	2002	10.6	Deceased	3	M, P, C	M, C	68	96	29	1.1	1

[a]At the end of follow-up time or latest available results. A, azathioprine; Alb/C, albumin/creatinine; C, cyclosporine; M, mycophenolate; P, prednisone; Pro/C, protein/creatinine; T, tacrolimus.

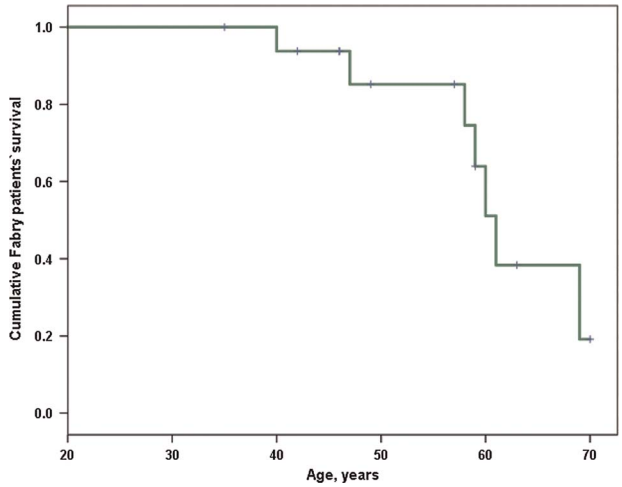

FIGURE 1. Cumulative survival of FD patients after KTx. Cumulative patient survival (Kaplan-Meier estimates) is shown for all FD patients after kidney transplantation (n = 17). The median age at the end of the study was 53 (45-60) years. Seven patients, all classic male subjects, died at a median age of 59 (47-61) years.

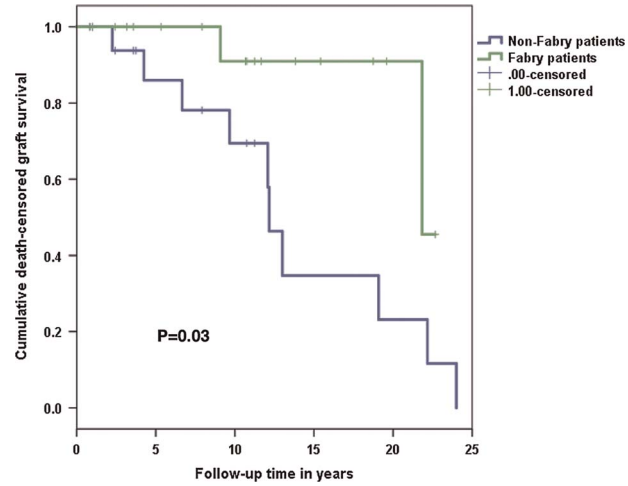

FIGURE 3. Death-censored graft survival in FD patients and matched controls. Cumulative death-censored graft survival is shown in FD patients and matched controls. Death-censored graft survival analysis is shown to be superior in Fabry patients, who mainly died with functioning kidneys, mostly from cardiac causes.

Kidney Transplant Biopsies

Twenty KTx biopsies were performed in 11 patients (Table 6). There were 4 patients with graft biopsies after at least 10 years (patients 7-10; biopsy after 11.6-22.6 years). There was no evidence of glycosphingolipid deposits in the transplanted kidneys with 2 exceptions among these patients (patients 8 and 9). A few electron-dense lamellar inclusions were identified in vascular endothelial cells in a classic male 14 years posttransplant (Figure 4, patient 9).[28] The invasion of vascular endothelial host cells into the graft endothelium can occur.[23] This recipient was not on ERT as he died before it was available. The deceased donor of this recipient was a 35-year-old unrelated man. The other transplant recipient with ultrastructural deposits appearing as "zebra bodies" was the younger brother of the above patient (patient 8). He was transplanted 14 years before ERT was available; subsequently, he received ERT for 9 years, after which EM showed a few myelin figures, most likely originating from host histiocytes (Figure 5). In contrast, patient 7 (no ERT for 10 years, biopsy after 21.8 years) and patient 10 (no ERT at all, biopsy after 11.6 years) had no Gb3 deposits. Also in the other biopsies, no FD-specific changes were found on light and/or EM.

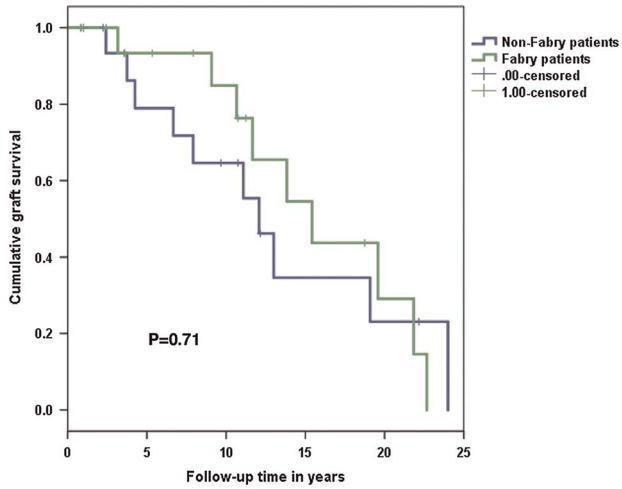

FIGURE 2. Cumulative graft survival in FD patients and matched controls. Cumulative graft survival is shown in FD patients and matched controls. Graft survival analysis was censored at graft loss or patient death, whichever came first. Graft survival is shown to be similar in FD patients and matched controls.

DISCUSSION

In this study, we found similar overall and superior death-censored graft survival in the FD patients compared with non-FD matched controls. To our knowledge, these data describe the longest reported experience with KTx in FD—up to 25 years. All of the KTx recipients in our cohort who died were classic male subjects (median age at death, 59 years), who had functioning grafts, their deaths mainly due to cardiac events. Therefore, these findings highlight the importance of cardiovascular protection and ERT in this population. ERT should be beneficial in the long-term outcome of KTx patients, by treating the heart and clearing other host cells that can migrate into the graft including macrophages, histiocytes, and vascular endothelial cells.[29] The recipients' survival rates were similar to non-FD recipients. Importantly, our high-risk population of predominantly classic male subjects, with most on ERT, survived longer (median age at death, 59 years) than reported for an FD male population without ERT (mean age at death, 49.9 years).[3]

TABLE 5.

Patient and graft survival at 5, 10, 15, 18, and 20 years

Follow-up time, yr	Number of patients	Number of grafts	Patient survival	Graft survival
5	13	14	100% (13/13)	93% (13/14)
10	11	12	100% (11/11)	92% (11/12)
15	9	10	67% (6/9)	60% (6/10)
18	9	10	44% (4/9)	40% (4/10)
20	8	9	25% (2/8)	22% (2/9)

TABLE 6.
FD patients with kidney transplant biopsies

Patient	Number of biopsies	Kind of microscopy		Transplant age at last microscopy in months	No ERT after KTx, yr	FD-specific changes	Other histological changes
		light	electron				
1	1	Yes	No	0.3	0	No	Rejection Banff 1B
2	3	Yes	Yes	4	5.5	No	Intima fibrosis, acute interstitial nephritis
3	2	Yes	Yes	0.3	15.4	No	Intima proliferation
4	2	Yes	Yes	8	0	No	Rejection Banff 2A
5a	2	Yes	No	68	4.5	No	Interstitial fibrosis, tubular atrophy
5b	3	Yes	Yes	12	0	No	Chronic glomerulitis, interstitial fibrosis, tubular atrophy
6	1	Yes	No	12	0	No	Acute tubular necrosis
7	2	Yes	Yes	262	10	No	Rejection Banff 2A, papillary renal carcinoma
8	1	Yes	Yes	272	8.4	Single concentric inclusions in a migrated host tissue macrophage and an intercalating histiocyte	Capillaritis with C4d positive staining
9	1[a]	Yes	Yes	166	13.8	Abandoned vascular endothelial Gb3 deposits, most likely migrated from host	Not reported
10	1	Yes	Yes	140	11.6	No	Mild lymphoplasmacellular interstitial infiltration and arteriolohyalinosis
15	1	Yes	No	0.1	0.25	No	Limited focal lymphocytic infiltration at cortex/medulla region without tubulitis, no vasculitis, no C4d staining, no signs of rejection

[a]Autopsy. ERT, enzyme replacement therapy; FD, Fabry disease; KTx, kidney transplant.

FIGURE 4. Electron microscopy of a kidney transplant 14 years without ERT. Formalin fixed and refixed in glutaraldehyde. Vascular endothelial cells showing numerous lamellar bodies in a patient with the mutation p.V390CfsX9. (EM x 3700, inset x 83 700). Previously published in Gantenbein et al., 1995 (Recurrence of Fabry's disease in a renal allograft 14 years after transplantation. Nephrol Dial Transplant. 1995;10(2):287-9), with permission.[28]

Several case reports of KTx in FD (Table 7) and a few registry studies[14,16,18] have been published in the last 40 years, but all had shorter follow-up periods. With findings similar to ours, previous studies[14-16] show patient and graft survival comparable to non-FD patients and found cardiac and cardiovascular events as major causes of mortality in FD patients. However, patient and graft survival rates in our patients were superior to the rates reported in studies from the pre-ERT era: the 10-year patient and graft survival in the present study exceeds 90%, previous studies report 67% to 76% patient and 56% to 67% graft survival.[14,15]

KTx remains an important therapeutic option for Fabry nephropathy because ERT, when initiated late in the disease course, only slows progression.[24,30,31] Germain et al. reported that patients who initiated treatment at older ages or had advanced renal disease or both experienced faster disease progression.[32] The mean slope for eGFR for the 20 older patients (median age, 38 years) with urinary protein/creatinine ratio of greater than 0.5 g/g or 50% or greater sclerotic glomeruli was –6.82 mL/min per 1.73m^2/year.[32] In contrast, the mean slope for eGFR for the 32 younger patients (median age, 25 years) with urinary protein/creatinine ratio of less than 0.5 g/g or 50% or less sclerotic glomeruli was –1.89 mL/min per 1.73 m^2/year. In addition, the 3- to 5-year survival rate of FD patients on chronic dialysis was less than that of the general dialysis population.[33,34] Unfortunately, there are no comparative age-matched Fabry data for our sample from Switzerland and Germany that could serve as the denominator. The survival data of our transplanted Fabry patients can be compared with those of Fabry patients who underwent renal dialysis approximately 20 to 25 years ago. Thadhani et al.[34] (2002) analyzed 137 FD patients in 2 cohorts, 1985 to 1993 (93 patients) and 1995 to 1998 (42 patients). Although not age matched, the overall 3-year survival rate for the 1985 to 1993 and 1995 to 1998 groups was 63% and 53%, respectively. Tsakiris et al.[33] (1996) reported that the

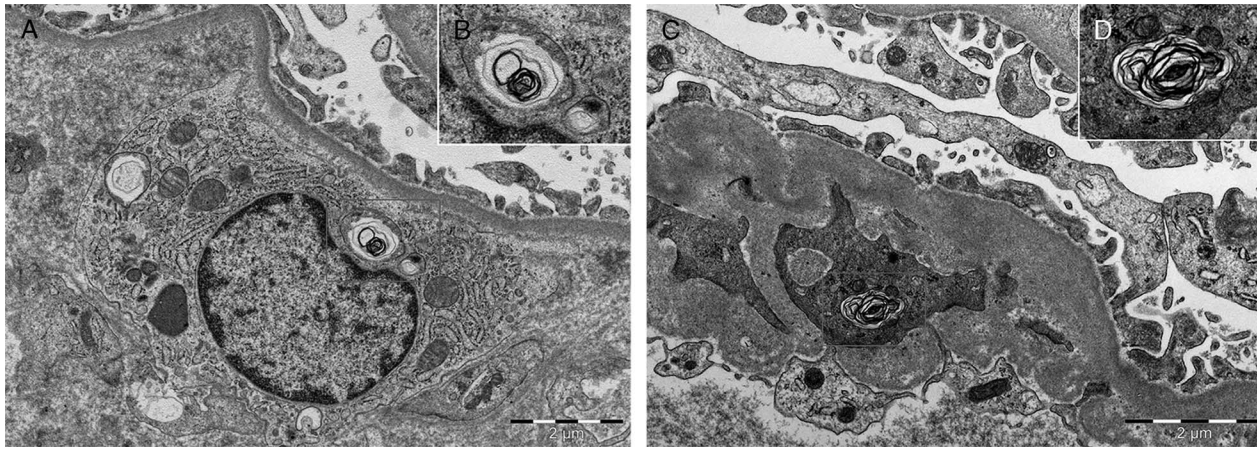

FIGURE 5. Electron microscopic findings of a kidney transplant biopsy in a recipient with FD 14 years without ERT. Single inclusions with lamellated structures—myeloid body—in a histiocyte, migrated into the graft vascular endothelium (A) (TEM, × 2800) and in a histiocyte, intercalated into a graft podocyte (C). B and D, Higher magnification of the myeloid bodies showing the included storage material.

5-year survival rate of 83 Fabry dialysis patients reported to the European Registry, who initiated dialysis from 1985 to 1993, was only 41%. Our findings that transplantation offers longer survival rates would support the recommendation that all transplantable patients with suitable donors (living-related or histocompatible) should be transplanted when possible.

In our cohort, only 2 grafts in classic male brothers had renal lysosomal substrate inclusions on EM. Lamellar lysosomal inclusions were present in vascular endothelial cells of the older brother 13.8 years post-KTx (pre-ERT era), presumably because of the endothelial cell invasion from the host into the graft.[23] In his younger transplanted brother who began ERT 14.3 years posttransplant and was biopsied 22.7 years after KTx, biopsy showed isolated inclusions in histiocytes, which also migrated into the transplant from the host. In contrast to these patients, 2 other patients, who were also not under ERT for a long time (10 and 11.6 years) and were biopsied after 11.6 and 21.8 years had no lysosomal inclusions by light and EM.

An important differential diagnosis in the interpretation of the myelin figures and zebra bodies found in renal biopsies are drug-induced phenocopies of FD[1]—ultrastructural changes that appear morphologically similar to those due to FD.[40-43] Certain cationic amphiphilic drugs and their derivates are inhibitors of α-Gal A and can cause renal inclusions which appear similar to FD inclusions and are reversible after discontinuation[40]: (hydro)-chloroquine[43-45] and amiodarone[46,47] are direct inhibitors of α-Gal A, and gentamicin,[40] ranolazine,[48] pentamidine,[49] and macrolide[50] also cause the phenotype. Silicosis results in inclusions that mimic those in FD, and thus, similar observations were made in silica-induced nephropathy.[1,51]

Early studies reported increased levels of plasma α-Gal A activity post-KTx[20,52] which were later shown to be due to increased α-N-acetylgalactosaminidase (α-Gal B) activity, an enzyme evolutionarily related to α-Gal A,[53,54] that is assayed using the same fluorogenic substrate. Thus, the increased α-Gal A activity was an artifact. Subsequently, one of the authors (R.J.D.) showed that plasma α-Gal B activity was increased because of the immunosuppression medications (R.J.D., unpublished data, 1973).

TABLE 7.

Case reports of kidney biopsies from the pre-ERT era

Year of publication	Authors	Time point of microscopy	Histological findings
1972	Clarke et al.[20]	7 months (autopsy)	EM: intracellular multilamellar bodies, epithelium was normal; no accumulation of glycolipids
1973	Bühler et al.[12]	17 months (autopsy)	No deposits
1981	Faraggiana et al.[21]	6 months	LM: glomerular, tubular and interstitial deposits EM: few inclusions on the vascular endothelium
1982	Clement et al.[35]	15 months (autopsy)	LM and EM: normal
1982	Bannwart et al.[36]	12 yrs	LM and EM: normal
1986	McMahon et al.[23]	4 yrs	Accumulation in endothelial cells leading to narrowing and occlusions
1987	Friedlaender et al.[22]	8 yrs	LM: no abnormalities EM: occasional small myelin figures in the vascular endothelium
1987	Popli et al.[37]	5.5 yrs	donor was heterozygous sister LM and EM: FD typical changes
1991	Mosnier et al.[38]	11 yrs (autopsy)	LM: normal EM: sphingolipid inclusions in the vascular endothelium
1995	Gantenbein et al.[28]	14 yrs (autopsy)	LM: no abnormalities EM: massive tubular, interstitial and endothelial deposits of Gb3
1998	Erten et al.[39]	10 yrs	LM and EM: normal

EM, electron microscopy; FD, Fabry disease; LM, light microscopy.

Importantly, FD does not recur in kidney transplants, in contrast to other renal diseases.[55] Among hereditary systemic diseases, primary hyperoxaluria type 1 or adenine phosphoribosyl transferase deficiency have high recurrence rates of renal disease in the transplant.[55,56] In cystinosis, cysteine-laden cells were occasionally observed in the grafts but were found to be without clinical relevance.[55] In Alport syndrome, antiglomerular basement membrane antibodies were occasionally found.[55] Primary renal diseases that recur in the transplant include membranoproliferative glomerulonephritis (approximately 30% in type 1, 80% in type 2),[55] focal segmental glomerulosclerosis (30%-50%),[57] and IgA nephropathy (50%).[55] This is not the experience in FD: if the graft is healthy, it can function well for at least 25 years as documented here.

Specific challenges of KTx in FD should be noted. Recipients or donors might have undiagnosed FD because FD is not part of the routine pretransplant workups.[58] Individuals with unrecognized FD may donate their kidneys to non-Fabry patients (e.g.,[58]), which can lead to early graft dysfunction and chronic kidney disease in the living donor and recipient.[33] Living kidney donations can occur within families with unrecognized FD relatives.[37,59] Thus, it is important to perform genetic testing for FD where there is clinical suspicion of FD or an unclear nephropathy.

A limitation of this report is the size of the patient sample. This is an inherent limitation in rare diseases. Moreover, we might be analyzing survivor advantage, as Fabry patients may not reach transplantation, especially in the era of late diagnosis. Furthermore, we have no way to determine, if all Fabry patients were diagnosed pretransplant. There could have been unrecognized Fabry patients with kidney transplantation in whom the diagnosis of FD was not made. However, and in contrast to previous KTx reports,[14,16,18] most patients had a graft biopsy, and the majority had biopsy or autopsy EM to exclude Gb3 deposits in the graft. EM was not conducted in some of the donor kidneys because the deposits were generally considered unlikely in a non-FD kidney. On the other hand, light microscopy can identify FD-related kidney changes.[11] The strengths of the study are that it was a multicenter design, had no dropouts to follow-up, and applied regular multidisciplinary patient assessments; the study also included the complete collection of clinical, biochemical, genetic, and phenotypic information; data on the immunogenic pretransplantation risk; and regular and serial KTx biopsies. These advantages were frequently lacking in other studies. Importantly, this study used a well-matched non-FD control group that was also exposed to the same environmental conditions because of medical treatment and geographic and cultural proximities of the FD and non-FD recipients. As Fabry patients requiring transplantation are generally younger than the overall transplant patient population and, on that basis, might be expected to have better outcomes, we have used an age-matched control group to avoid this potential bias. Because it is not sufficient to match age and sex to reach an equal start line, we also matched according to the immunosuppression era, number of transplants, and presence of DSA and HLA mismatches.

CONCLUSIONS

In conclusion, the study shows similar graft survival and superior death-censored graft survival in FD patients compared with non-FD matched controls. ERT may improve patient survival and protect kidney grafts from invasion of host cells containing Gb3 deposits. Finally, the study data further support KTx in FD only using a screened-negative donor for FD.

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