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ORIGINAL ARTICLE

Lower quality of life in young men after pediatric kidney transplantation when compared to healthy controls and survivors of childhood leukemia—a cross-sectional study

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SUMMARY

Data about health-related quality of life (HRQOL) in adult recipients after pediatric kidney transplantation (KTx) are scarce. In this nationwide questionnaire-based study, HRQOL and social status in young adult men having undergone KTx during childhood (n = 29) were studied and compared to age- and gender-matched healthy controls (n = 56) and survivors of childhood acute lymphoblastic leukemia (n = 52) comprising controls with another chronic disease of childhood. Altogether 41% of the KTx recipients, 50% of the leukemia survivors and 80% of the healthy controls lived in a permanent relationship. When compared with leukemia survivors, the KTx recipients reported significantly more bodily pain and worse general health (RAND-36). Older age at time of study, longer duration of dialysis, multiple transplantations and diminished graft function correlated with lower scores. The KTx recipients had a significantly higher mean Beck Depression Inventory (BDI) score than the leukemia survivors (P = 0.000) or the healthy controls (P = 0.006). BDI scores were highest in patients who lived without a partner or children had lower educational level or were unemployed. KTx recipients had significantly lower HRQOL scores than their healthy and controls with childhood chronic disease. Early detection of psychosocial problems and poor physical functioning among these patients is warranted.

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Introduction

The long-term outcome of pediatric kidney transplant (KTx) patients has improved significantly during the last decades [1]. Despite better life expectancy, it is well recognized that chronic diseases in childhood [2,3] have a negative impact on quality of life (QOL) in adulthood. There is evidence showing that patients with a history of chronic disease [4] and exposure to cytotoxic medication are prone to secondary complications, mainly affecting hormonal function, the cardiovascular system, and neuropsychology [5–9]. The prevention of secondary complications and avoidance of the adverse effects of immunosuppressive medication have therefore become increasingly important.

There are an increasing number of studies reporting on QOL after pediatric transplantation [10–13]; however, in many of these reports, the results are only compared

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with healthy controls. In this study, we aimed to study health-related quality of life (HRQOL) and depression scale in a nationwide cohort of young men having undergone a pediatric KTx. We wanted to evaluate the influence of severe disease during childhood on HRQOL later in life, and therefore, the results were compared with age- and gender-matched leukemia survivors and healthy controls. We hypothesized that HRQOL and socioeconomic status would be worse in the KTx population compared to healthy controls but similar compared to survivors of childhood leukemia.

Materials and methods

Ethics and informed consent

The study protocol was approved by the Ethics Committee of Helsinki University Hospital. Written informed consent was obtained from all patients before the study commenced.

Study population

All solid organ transplantations in Finland are performed and the recipients followed up at the Helsinki University Hospital. The participants for this study were selected as described previously [14]. Briefly, all pediatric male KTx recipients operated between August 1983 and September 2011 were identified from our transplant database. The inclusion criteria were age over 18 years and a post-transplant follow-up time of at least 5 years at the time of the study. A total of 79 patients fulfilled the inclusion criteria. Patients with significant comorbidities [mental retardation ($n = 3$), severe psychosocial problems ($n = 11$), tetraplegia ($n = 2$), or recent lung transplantation ($n = 1$)] were excluded; thus, 62 eligible men were contacted. A total of 30 patients responded to the invitation and 29 (47%) completed the questionnaires. Plasma creatinine was measured from 22 study patients; for the remaining seven patients, recent laboratory results were acquired from The Finnish Registry for Kidney Disease. Estimated glomerular filtration rate (eGFR) was calculated using the formula by Modification of Diet in Renal Disease Study Group [15]. Two age-matched control groups were used. Firstly, altogether 52 leukemia survivors were interviewed as part of a larger study of male acute lymphoblastic leukemia survivors that assessed reproductive and bone health, related parameters, and overall well-being in adulthood, as previously described [16]. The other control group included 56 healthy, age-matched men with no history of malignancy or KTx. The healthy controls were recruited from occupational health services in the Helsinki municipality area and Helsinki University Hospital and all were employed.

Immunosuppression protocol

The immunosuppression protocol of the KTx recipients consisted of triple medication. The most commonly used combination was cyclosporine A (CsA), azathioprine, and methylprednisolone (MP). Since the year 2000, basiliximab has been used at induction. Tacrolimus was a secondary choice used instead of CsA in the case of recurrent rejections, gradually increasing creatinine, cosmetic problems, or signs of calcineurin inhibitor toxicity. After KTx, MP was dosed daily, switching to alternate-day dosing at 3–6 months [14].

The leukemia survivors had received various combinations of prednisolone, vincristine, doxorubicin, cyclophosphamide, asparaginase, and 6-merkaptopurine during induction, consolidation, and maintenance therapy, and some of the patients were treated with irradiation therapy [16]. Primary leukemia treatment was 2–3 years, after which the patients did not receive any immunosuppressant drugs. None of the healthy controls or leukemia survivors were on immunosuppressive therapy.

Questionnaires

All KTx recipients, leukemia survivors, and controls filled a RAND-36 self-report questionnaire assessing physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perception. The questionnaire, consisting of 36 simple questions, has been developed to measure QOL. Each dimension is scored between 0 and 100, with a higher score indicating better health.

A Finnish version of the Beck Depression Inventory (BDI-21) questionnaire was used to detect depressive symptoms [17]. BDI is a self-administered test consisting of 21 items. Each item includes four statements that have a numerical value from 0 to 3. The questionnaire's total score ranges from 0 to 63. Scores of 10–18 indicate mild depressive symptoms and scores over 30 severe depression. All KTx recipients, leukemia survivors, and 55 healthy controls filled in the BDI questionnaire.

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Statistical analyses

SPSS statistics 22 (SPSS Inc., Chicago, IL, USA) was used for data analyses. We used nonparametric tests, and data between two subject groups were compared using Kruskal-Wallis test and Mann–Whitney *U*-test for continuous variables, and Pearson chi-squared test and Fisher's exact test for categorical variables. Spearman's rank correlation coefficient (r) was used to assess correlations. *P*-value less than 0.05 was considered statistically significant.

Results

Patient demographics

The majority of study patients were diagnosed with congenital nephrotic syndrome of the Finnish type (n = 10, 34%). Other diagnosis groups were urethral valve (n = 8, 28%), glomerulonephritis (n = 5, 17%) and other diagnosis (n = 6, 21%). The median age of the 29 KTx recipients at the initiation of renal replacement therapy (RRT) was 7.5 years (0.6–17.5 years) and the median age of transplantation 8.6 years (1.8–18.1 years). Median follow-up time was 18.7 years (6.4–33.2 years). Two-thirds of the patients had their first transplant. Median P-Creatinine in the KTx recipients was 168 μmol/l (IQR 132–261 μmol/l). The median blood pressure was 134/80 mmHg (IQR 127–146/75–89 mmHg). The median eGFR (n = 24) was 51.7 ml/min/1.73 m^2 (range 6.1–107.4 ml/min/1.73 m^2). In two patients (one of them on dialysis), the eGFR had declined below 20 ml/min/1.73 m^2. The KTx recipients were significantly shorter that the healthy controls (median 170.5 cm vs. 180.5 cm, $P < 0.001$) or leukemia survivors (median 170.5 cm vs. 176.0 cm, $P = 0.001$), but their BMIs (24.2 kg/m^2 vs. 25.2 kg/m^2 vs. 24.4 kg/m^2, respectively) were similar ($P > 0.05$) (Table 1). None of the study subjects were on growth hormone therapy at the time of the study. The median age of the leukemia survivors was 4.5 years (0.0–15.0 years) at the time of the leukemia diagnosis and the median follow-up time after diagnosis was 23.5 years (10.0–34.0 years) (Table 1). There was no statistically significant difference in the follow-up time between the KTx recipients and leukemia survivors.

Social characteristics

The majority of the KTx recipients did not have a partner (Table 2). The difference was significant when compared to the healthy controls ($P < 0.001$); however, comparison between the KTx and leukemia survivors did not reach statistical significance ($P = 0.456$). Only 10% of the KTx recipients and 21% of the leukemia survivors had at least one child ($P = 0.523$), while 43% of the healthy age-matched controls had fathered at least one child ($P = 0.002$).

All the KTx and leukemia survivors and healthy controls had completed the 9-year compulsory education; however, the final educational level differed between the groups (Table 2). Most of the KTx survivors (62%) had finished either upper secondary education or upper secondary vocational education. One (4%) KTx survivor,

Table 1. Clinical characteristics of 29 kidney transplant (KTx) patients, 52 acute lymphoblastic leukemia (ALL) survivors, and 56 healthy controls.

	KTx	ALL	Controls	*P*-value*	*P*-value†
Age at time of study, years	27.1 (19.0–41.8)	28.5 (25.0–38.0)	30.0 (24.0–36.0)	0.291	0.123
Anthropometrics‡					
Height, cm	170.5 (155.5–188.3)	176.0 (163.0–193.5)	180.0 (167.5–194.0)	0.001	<0.001
Weight, kg	72.6 (44.8–96.4)	75.8 (48.5–132.0)	82.5 (58.0–114.0)	0.064	<0.001
Body mass index, kg/m^2	24.2 (16.2–35.4)	24.4 (18.3–36.2)	25.2 (19.4–34.8)	0.522	0.381
Age at first dialysis or ALL diagnosis, years	7.5 (0.6–17.5)	4.5 (0.0–15.0)			
Follow-up time, years	18.7 (6.4–33.2)	23.5 (10.0–34.0)			

Data presented as median (range). *P*-values from the Mann–Whitney *U*-test.

**P*-value between KTx patients and leukemia survivors.

†*P*-value between KTx patients and controls.

‡Clinical data missing for two controls and two leukemia survivors.

Table 2. Social demographics of 29 kidney transplant (KTx) patients, 52 acute lymphoblastic leukemia (ALL) survivors, and 56 healthy controls.

	KTx	ALL	Controls	*P*-value*	*P*-value†
Relationship status					
Married/cohabitating	12 (41%)	26 (50%)	45 (80%)	0.456	<0.001
Single/divorced	17 (59%)	26 (50%)	11 (20%)		
Biological children	3 (10%)	11 (21%)	24 (43%)	0.217	0.002
Highest education					
Comprehensive school (9 years)	5 (17%)	2 (4%)	3 (5%)	0.056	0.006
Upper secondary or vocational school (12 years)	18 (62%)	35 (69%)	20 (36%)		
Lower tertiary education (15 years)	5 (17%)	7 (14%)	23 (41%)		
Higher tertiary education (min 17 years)	1 (4%)	7 (14%)	10 (18%)		
Employment					
Employed/student	22 (76%)	47 (90%)	56 (100%)	0.105	<0.001‡
Unemployed	7 (24%)	5 (10%)	0 (0%)		

Data presented as number of subjects (%). *P*-values from the chi-squared or Fischer's exact test, as appropriate.

**P*-value between KTx patients and leukemia survivors.

†*P*-value between KTx patients and controls.

‡$P = 0.091$ when compared to the population norms.

seven (14%) leukemia survivors, and 10 (18%) of the controls had graduated from university. The difference in final educational level was significant ($P = 0.006$) between KTx recipients and healthy controls but not between the KTx and leukemia groups ($P = 0.056$).

Seventy-six percent of the KTx recipients, 90% of the leukemia survivors, and all the healthy controls ($P < 0.001$) were employed at the time of study. The difference between the KTx and leukemia survivors was not statistically significant ($P = 0.105$).

Quality of life

The KTx recipients scored lower in all RAND-36 categories when compared to the healthy controls (Table 3). Significant differences between these groups were found in role limitations due to physical health problems (72 vs. 89, $P = 0.026$), vitality (62 vs. 72, $P = 0.008$), mental health (76 vs. 82, $P = 0.009$), bodily pain (72 vs. 86, $P = 0.031$), and general health subscales (53 vs. 81, $P < 0.001$). The KTx recipients also scored lower when

Table 3. Health-related quality of life according to RAND 36-Item Health Survey in 29 kidney transplant (KTx) patients, 52 acute lymphoblastic leukemia (ALL) survivors, and 56 healthy controls.

Subscale	KTx	ALL	Controls	*P*-value*	*P*-value†
Physical functioning (SD)	87.2 (23.7)	91.5 (18.0)	97.8 (5.2)	0.908	0.050
Role limitations due to physical health problems (SD)	72.3 (42.1)	83.8 (29.8)	89.3 (27.3)	0.193	0.026
Role limitations due to personal or emotional problems (SD)	84.5 (38.2)	81.4 (32.6)	92.9 (18.8)	0.539	0.434
Vitality (energy/fatigue) (SD)	61.7 (20.9)	67.4 (19.3)	72.3 (16.4)	0.178	0.008
Mental health (SD)	75.5 (14.2)	75.4 (17.0)	82.1 (12.4)	0.652	0.009
Social functioning (SD)	82.8 (25.8)	87.3 (18.1)	92.4 (14.8)	0.527	0.061
Bodily pain (SD)	71.5 (30.0)	83.5 (21.7)	85.7 (17.6)	0.043	0.031
General health (SD)	52.8 (24.2)	72.6 (20.1)	81.3 (16.4)	<0.001	<0.001

SD, standard deviation.

Data presented as mean. *P*-values from the Mann–Whitney *U*-test.

**P*-value between KTx patients and leukemia survivors.

†*P*-value between KTx patients and controls.

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compared with the leukemia survivors on the bodily pain (72 vs. 84, $P = 0.043$) and general health subscales (53 vs. 73, $P < 0.001$).

Older age at the time of the study correlated with lower scores in RAND-36; however, age at the initiation of the first dialysis period or at the time of the first KTx did not correlate with any of the measured QOL parameters. The time spent on dialysis correlated inversely with emotional well-being and feeling of pain (Table 4). An increasing number of transplants correlated with increased limitation due to physical ($P = 0.046$) and emotional problems ($P = 0.026$), and lower mental health ($P = 0.040$) scores. Patients with multiple transplantations scored lower on all RAND-36 subscales compared to the KTx recipients who still had their first transplant. Estimated GFR correlated positively with vitality ($P = 0.014$), feeling of pain ($P = 0.045$), and general health ($P = 0.039$) scores among the KTx men.

Depression scores

The mean BDI score was higher among the KTx recipients (3.9, SD (standard deviation) 4.3) than among the leukemia survivors (2.4, SD 3.9, $P = 0.006$) or the healthy controls (1.8, SD 4.7, $P < 0.001$). BDI scores were the highest in patients who lived without a partner or children, had lower educational level, or were unemployed. The BDI scores exceeded the level of ten, thus pointing at increased depressive symptoms, in three (10%) KTx survivors, four (8%) leukemia survivors, and two (4%) healthy controls.

Higher BDI scores correlated with decreased QOL in all RAND-36 categories including vitality ($P < 0.001$), mental health ($P = 0.049$), social functioning ($P = 0.001$), and general health ($P = 0.031$). Among KTx recipients, age at KTx, number of KTx, length of dialysis, age at time of study or GFR at the time of study, or final height had no correlation with the BDI score.

Discussion

The survival of pediatric patients with end-stage kidney disease has improved dramatically thanks to successful kidney transplant programs. Despite better life expectancy, it is well recognized that chronic diseases in childhood have a negative impact on QOL in adulthood [8]. There are an increasing number of studies reporting on QOL after pediatric transplantation [10–13]; however, in many of these reports, the results are only compared with healthy controls. In the present nationwide

Table 4. Correlation between clinical characteristics and RAND-36 subscale scores in 29 kidney transplant (KTx) patients.

Subscale	Physical functioning	Role/physical	Role/emotional	Vitality	Mental health	Social functioning	Bodily pain	General health
Age at time of study	−0.220 (0.250)	−0.080 (0.686)	−0.242 (0.215)	−0.125 (0.518)	−0.170 (0.377)	−0.055 (0.776)	−0.006 (0.976)	−0.143 (0.458)
Age at first dialysis	−0.039 (0.840)	0.120 (0.543)	0.210 (0.284)	0.141 (0.466)	0.003 (0.988)	0.052 (0.788)	0.178 (0.356)	−0.086 (0.659)
Dialysis duration	−0.293 (0.123)	−0.357 (0.062)	−0.420 (**0.026**)	−0.132 (0.495)	−0.194 (0.312)	−0.244 (0.202)	−0.398 (**0.033**)	−0.076 (0.694)
Age at first KTx	−0.034 (0.861)	0.069 (0.728)	0.147 (0.454)	0.116 (0.548)	−0.002 (0.992)	0.053 (0.786)	0.102 (0.598)	−0.067 (0.730)
Number of KTx	−0.436 (0.180)	−0.380 (**0.046**)	−0.421 (**0.026**)	−0.203 (0.292)	−0.383 (**0.040**)	−0.369 (0.049)	−0.278 (0.144)	−0.222 (0.247)
GFR	0.394 (0.063)	0.319 (0.148)	−0.074 (0.745)	0.504 (**0.014**)	0.022 (0.920)	0.287 (0.184)	0.422 (**0.045**)	0.433 (**0.039**)
BDI score	−0.327 (0.083)	−0.361 (0.059)	−0.362 (0.058)	−0.714 (<**0.001**)	−0.368 (**0.049**)	−0.591 (**0.001**)	−0.261 (0.171)	−0.402 (**0.031**)

GFR, glomerular filtration rate; BDI, beck depression inventory.
Data presented as Spearman correlation coefficient (*P*-value; significant in bold).

questionnaire-based study, we evaluated social status, marriage and paternity, educational level, QOL, and general well-being in Finnish adult males with a history of KTx during childhood. The control groups comprised healthy age-matched controls and age-matched leukemia survivors who had a history of severe chronic disease during childhood but no need for therapies during the recent years. According to our findings, the KTx recipient's results were in many aspects inferior when compared to those of the age-matched healthy controls and leukemia survivors. They scored lower on the general health, physical functioning, and mental health subscales and were less frequently employed than the leukemia survivors but shared the decreased probability of getting married and fathering a child with the leukemia survivors.

In the present study, we did not find a significant correlation between the RAND-36 scores and the age at the initiation of the RRT or the age at transplantation in the KTx recipients. This is contrary to the leukemia survivors in whom younger age at the time of the leukemia diagnosis was positively correlated with HRQOL [2]. This finding may be due to the different nature of these two clinical conditions. Long-term survivors after childhood leukemia do not have any permanent medication while KTx patients are bound to lifelong immunosuppression which may strengthen the feeling of having a chronic illness. In addition, most KTx recipients are aware of the fact that the graft function may decrease, leading to uremia and reoperation. It is of note that our KTx population was relatively heterogeneous. Most of the patients had their first graft; however, 34% of the patients had undergone additional transplantations. There was also variation in the graft function in the KTx group, including two uremic patients. According to our results, HRQOL was significantly influenced by both the number of transplants and eGFR, which may also explain differences in HRQOL between the KTx patients and the leukemia survivors.

Successful KTx permits the recipients to attend school without any significant restrictions [18]. However, according to many reports, the academic achievements of KTx recipients are lower in comparison with their healthy peers [19]. The lower educational level of the KTx recipients in the present study supports this observation. All KTx recipients had completed their compulsory education but only 38% attended secondary school, which was a lower proportion when compared to the leukemia survivors (45%) or healthy controls (59%). We have previously reported lower neuropsychological scoring in the verbal and visuospatial domains among pediatric KTx recipients compared to normal population [20]. Neuropsychological problems may partly explain the poorer academic achievement among KTx recipients in the present study, lending further support to appropriate neurocognitive testing and optimized education opportunities among patients with end-stage renal disease [21].

According to previous studies, the employment level of pediatric solid organ transplantation survivors varies between 21% and 86% [10–13,19]. In the present study, 76% of the KTx recipients were employed, which was lower than among the leukemia survivors (90%). The relatively high employment level in our KTx cohort is partly explained by patient selection. KTx recipients with significant neurological or psychiatric conditions were excluded from this study. The lower employment level compared to the leukemia survivors may be due to lower academic achievements and lower scores in physical and mental well-being among the KTx recipients. Comparison to healthy controls was not possible as they were recruited from occupational health services.

Kidney transplant recipients are known to be less frequently married or have a partner than their healthy peers. In previous studies, 27–50% of the KTx recipients had a spouse or lived with a partner [10,11,13,19]. In the present study, 41% the KTx recipients, 50% of the leukemia survivors, and 80% of the healthy controls lived in a permanent relationship. Relations with other people are strongly influenced by emotional and social competence. The RAND scores measuring mental and physical health were significantly lower in both KTx recipients and leukemia survivors, which may have an adverse influence on marital status. A previous study on liver transplant recipients showed that especially male recipients have internalization and behavioral problems [18]. Problems with social skills and achieving independence from parenteral care [22] may further aggravate the inability to have close relationships.

Only three of the 29 (10%) KTx recipients and 11 (21%) of the leukemia survivors had biological children. These numbers were significantly lower than that of the healthy controls (43%). According to a previous report on male patients, at a mean age of 31 years, 8% of pediatric KTx recipients had fathered at least one child [19]. There is previous evidence on smaller adult testicular volumes and lower total sperm counts in comparison with control populations [14]. These observations may indicate decreased fertility after KTx, possibly due to gonadotoxicity or psychosocial factors.

The questionnaire-based physical functioning of our KTx recipients was significantly poorer when compared

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to the leukemia survivors or the healthy controls. The KTx recipients also scored significantly worse on the questions concerning general health and bodily pain. Similar poor physical functioning has previously been reported in liver transplantation survivors [12,23] and adolescent KTx recipients [24]. Weakness, slow walking, and low physical activity combined with self-reported exhaustion and small muscle mass are criteria of the frailty phenotype, commonly described in the elderly. The prevalence of frailty is known to be increased among patients with chronic kidney disease [25]. The present observation suggests that poor general health and decreased physical functioning persist also into adulthood after pediatric KTx and may be associated with the high prevalence of fatigue among KTx recipients reported before [26]. As previously mentioned, the range of eGFR among the KTx patients was wide, which may also have influenced the physical functioning in this patient group. Further research is needed to detect risk factors for poor physical functioning among long-term survivors of KTx.

The KTx recipients reported more depressive symptoms than their healthy controls or leukemia survivors and scored significantly lower on the mental health and social functioning subscales. Patients with a history of two or more transplants scored particularly low in these domains. They also felt more limitations due to emotional problems than patients with their first graft. Final body height did not correlate to depressive symptoms. Our observations suggest that 10% of KTx recipients had depressive symptoms. In general, the rates of self-reported depressive symptoms were very low among all three groups. Even though the KTx group had a higher mean score, this mean score did not indicate clinically significant symptoms of depression.

The major limitations of the present study are the small sample size and low participation rate. We have compared the clinical data between the participants and nonparticipants finding no significant differences between the groups [14]. We therefore believe that our study group is well representative of the male pediatric KTx recipients in Finland. In addition, most of the KTx patients had congenital nephrosis and had undergone nephrectomy before their renal function had been impaired. Thus we could not take into account the duration of CKD in our analysis. Another limitation of this study was that the healthy control group was recruited from occupational health services, and all were employed. The employment data of the KTx recipients could therefore only be compared to leukemia survivors. The strengths of the present study are the long follow-up time and evaluation of pediatric KTx cohort in adulthood. Information on adult social and educational surveillance could be combined with HRQOL and depression scales in a nationwide cohort. The comparison groups represented both age-matched healthy controls and chronic childhood disease survivors.

In conclusion, despite the relatively good graft function, the long-term KTx recipients showed significantly lower HRQOL scores and higher depression scores than their age- and gender-matched healthy and chronic disease controls. Early detection of learning difficulties, psychosocial problems, and poor physical functioning among these patients is warranted to improve the long-term outcome and QOL in patients with pediatric KTx.

Authorship

KE: wrote the paper and performed data analysis. JT: collected data. JT, TJ and KE: wrote the paper. TJ, HJ and KJ: designed the research.

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Conflict of interest

The authors declare that they have no conflict of interests.

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