Factors associated with health-related quality of life and psychosocial functioning in kidney transplanted children and adult patients

Thesisbook

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INTRODUCTION

End-stage renal disease (ESRD) is not compatible with life. On medical and technological development of the twentieth century ESRD patients can survive and their life can prolong significantly. Long lifespan suggests a number of questions about quality of life and demand to establishing the holistic and complex rehabilitation care. (Kovács, 2006)

To attend adult patients with chronic kidney disease is important to considering several factors: the social status of patient, psychological problems caused by the illness and the therapies, comorbid conditiones and their influences on quality of life together with micro and macro social effects given broken life (changes in family and work). In children above-mentioned factors are especially relevantes when in consequence of the chronic disease hole developing of children turns into atypical and the effects of familiar changes became more stressful. (Fukunishi, 1995)

Health related quality of life (HRQoL) is an independent predictor of mortality in several studies about chronic kidney patients. (Manu, 2001) Results of previous studies confirm relevant role of age, sex and social parameters of adult chronic kidney patients. Previous studies show that prevalence of depressive symptomes in adult chronic kidney recipients are associated with worse quality of life in different modalities of renal replacement therapies. (Kimmel, 1998; Patel, 2002; Vazquez, 2005; Molnár, 2005) Furthermore the different sleep disorders were associated with health related quality of life (Sanner, 2002; Molnár, 2007) because of their impression on well-being and general functioning. The prevalence of sleep disorders in chronic kidney patients is between 30-80%. (Iliescu, 2003) Level of health related quality of life can diverge – it depends on modalities of renal replacement therapies: the long-term influences of transplantation are betters (not only favorable survival but lower morbidity consequences) than dialysis outcomes. (Jofre, 1998; Rebollo, 2000; Valderrabano, 2001; Bohlke, 2009) Most of the previous studies compared non-selected patients on maintenance dialysis with transplanted patients and did not control for potentially important differences between the enrolled patient groups. (Dew, 1997) It is unknown the association between health related quality of life respectively survival parameters and graft survival of renal transplanted patients.

Health related quality of life of children with chronic renal failure is also significantly worse than in case of healthy counterparts. (Goldstein, 2006; Buyan, 2010) The majority of different studies emphasize the role of distress and depression (Bakr, 2007) and behaviour problems (Barney-Martinet, 2008). Moreover children with chronic kidney disease are at
increased risk for delays in neurocognitive development. Recent studies suggested that pediatric patients with chronic kidney failure had lower scores on intelligent quotients (IQ) and achievement tests compared to normal controls (Qvist, 2002; Madden, 2002; Duquette, 2007) or their sibling-controls (Bawden, 2004; Madden, 2003). The profile of intelligence conformation in studies shows that verbal skills are retained more than nonverbal/cognitive efficiency or thinking ability. (Falger, 2008)

AIMS AND HYPOTHESES

Health-related quality of life and mortality in adult kidney transplant recipients – prospective cohort study

In our study we wanted to assess the association between HRQoL and long-term clinical outcome in a large prevalent cohort of stable kidney transplant recipients using the KDQoL-SF (Kidney Disease Quality of Life–Short Form) questionnaire and we followed up patients for more than seven years.

We hypothesized that:
1. transplant patients with better HRQoL at baseline would have better survival;
2. after adjustment for depressive symptoms and several important clinical variables.

Comparison of health-related quality of life in patients on maintenance dialysis waiting for transplantation and kidney transplanted adult patients – cross-sectional study

In our Transplantation and Quality of Life-Hungary (TransQoL-HU) study we have compared the HRQoL of renal transplanted (Tx) outpatient population with dialysed patients on transplantation waiting list (WL). In this cross-sectional study we aimed to discover differences in dimensions of health related quality of life assessing the important sociodemographic and clinical parameters including sleep disorders and depressive symptoms.
We tested the following hypotheses:

1. health related quality of life is worse waitlisted patients compared to transplanted recipients;
2. after adjustment for clinical parameters, sleep disorders and depressive symptoms the differences in quality of life can be observed between the two groups mainly in kidney disease-specific domains.

**Cognitive and psychosocial function in kidney transplanted children**

We designed this cross-sectional study to determine the cognitive/intellectual skills and prevalence additionally characteristics of behavior problems of transplanted children and the associations with biomedical and psychosocial parameteres. We considered relevant to discover the aspect of children in conjunction with the parents’ opinion.

We hypothesized that:

1. the cognitive abilities are lower in transplanted children than in healthy controls;
2. the intellectual problems are associated with clinical and treatment related parameters;
3. the prevalence of depressive symptoms and behavioral problems is higher (in opinion of parents and children too) in transplanted children than in control group.

**METHODS**

**Health-related quality of life and mortality in adult kidney transplant recipients – prospective cohort study**

All patients 18 years or older (n=1067) who were followed up regularly at a single kidney transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University were invited to participate in our prospective prevalent cohort study.
Baseline assessment was conducted between August 2002 and February 2003 Transplantation and Quality of Life–Hungary (TransQoL-HU) Study. Patients who refused to participate or had an acute rejection or infection within one month of data collection, had dementia were excluded. We recorded sociodemographic parameters and medical informations (medical history, medications) and laboratory datas. Patients were followed up for a median of 94 (25th-75th percentile, 76-95) months. The primary outcome variable was all-cause total mortality (including all deaths with a functioning transplant or after return to dialysis therapy). Secondary outcome measures were death-censored transplant loss and death with a functioning transplant and we analyzed these associations with quality of life. Death-censored transplant loss was defined as return to maintenance dialysis therapy.

HRQoL was assessed using the Kidney Disease Quality of Life–SF (KDQoL-SF) questionnaire. (Laupacis, 1992) For detecting depressive symptoms we used Center for Epidemiologic Studies- Depression (CES-D) questionnaire (Radloff, 1977) and with it we describe the severity of depressive symptoms.

Statistical analyses were carried out using SPSS 17.0 and the STATA, version 11.1. Data were summarized using proportion, mean (± standard deviation, or median 25th-75th percentile), as appropriate. Continuous variables were compared using Student’s t-test, Mann-Whitney U test, Kruskal-Wallis test, or analysis of variance (ANOVA), as appropriate. Categorical variables were analyzed using Chi-square test. In all statistics results were considered significant for p<0.05.

Because death with a functioning transplant and transplant loss are competing events, the association of different health related quality of life domains with these two outcomes was assessed using semiparametric competing-risks regression analyses. (Fine, 1999) The proportional hazard assumption was tested using Schoenfeld residuals. Variance inflation factors were used to assess colinearity between independent variables. The association between the different HRQoL domains and total mortality was assessed using Cox regression analysis and Kaplan-Meier plots with log-rank test.

**Comparison of health-related quality of life in patients on maintenance dialysis waiting for transplantation and kidney transplanted adult patients – cross-sectional study**

In our - above-mentioned - cross-sectional cohort study we examined the health related quality of life of 1067 adult kidney transplanted patients (Tx) participated in line with
214 patients on maintenance dialysis awaiting for transplantation (WL). Basic socio-demographic data were recorded and the most relevant clinical parameters were collected from patients’ charts and beyond that we discovered the quality of life, depressive symptoms and sleep disorders of these patients.

The health related quality of life of transplanted and waitlisted patients were measured with the modular Kidney Disease Quality of Life Questionnaire (KDQOL-SF). Depressive symptoms were assessed using the Centre for Epidemiologic Studies-Depression (CES-D) scale. The assessment of sleep disorders was also conducted using the three instruments: insomnia was screened with the Athens Insomnia Scale (AIS) (Soldatos, 2000), the risk for obstructive sleep apnea syndrome (OSAS) was measured with the Berlin Sleep Apnea Questionnaire (Netzer, 1999), and restless legs syndrome with RLS Questionnaire (RLSQ) (Allen, 2001).

The statistical analyses were performed using the SPSS 18.0 software. In case of categorical variables group-differences were analysed with Chi-square test, continuous variables were compared using student t-test, in case of non normal distribution we used Mann–Whitney U-test. For testing the independent relationship of quality of life domains, we used multivariate linear regression models.

Cognitive and psychosocial function in kidney transplanted children

All kidney transplanted children 6-18 years of age (n=40) who were regularly followed at the July of 2007 kidney transplant outpatient clinic at the Department of Transplantation and Surgery and the First Department of Pediatrics at the Semmelweis University, in Budapest, and also their parents were invited to participate in our case control study. Exclusion criteria were: current acute rejection (within the last 4 weeks), hospitalization, transplantation in the previous 3 months. The baseline assessment was conducted between September 2007 and December 2008 (Psychosocial Problems and Cognition in Kidney Transplanted Children (PPCKTC) Study. We asked for co-operate the patients’ parents, of the potentially eligible 40 children 3 (7%) parents refused to participate in the study and 2 (5%) patients were excluded (one child was transplanted within the previous 3 months and one had acute rejection within 4 weeks prior the study period). The control group was selected (1:1) by matching children from two primary and high schools in Budapest by gender and age (maximum 1 month difference). Children with any chronic
illness were ineligible to be selected for the control group. The enrolled population, therefore, included 70 persons: 35 patients and their parents and 35 healthy children and their proxy.

Demographic data, developmental information, and details of medical history were collected at enrollment and information about immunosuppressive drugs was obtained. Psychological problems were detected by three tests: Child Depression Inventory (CDI) (Rózsa, 1999), Beck Depression Inventory (BDI) (Beck, 1961) and Child Behavioral Checklist (CBCL) (Achenbach, 2000). The adapted and validated Hungarian (international) version of the Woodcock-Johnson Cognitive Abilities Test (WJIE) was used in this study. (McGrew, 2001)

Statistical analysis was carried out using the SPSS 17.0 software. Correlation analysis was performed using Pearson or Spearman correlation analysis, as appropriate. Continuous variables were compared using Independent-Samples T-test, the Mann-Whitney U Test or One-Way ANOVA. In case of categorical variables group-differences were analysed with Chi-square test or Fisher-Exact test, as appropriate. In all statistics results were considered significant for p<0.05.

RESULTS

**Health-related quality of life and mortality in adult kidney transplant recipients – prospective cohort study**

For 179 patients (17% of the cohort, n=1067), no quality-of-life data were available because of individuals declining to participate or not adequately completing the questionnaires. In addition, 9 patients were lost during follow-up. The final sample analyzed therefore consisted of 879 patients. Participants and nonparticipants were similar in age, male/female balance, serum albumin level, cumulative end-stage renal disease vintage, and estimated GFR (eGFR).

During follow-up of 94 months, 278 patients (32%) died, 230 (26%) patients died with a functioning transplant and 163 patients (18%) returned to dialysis therapy.

Almost all examined HRQoL domains were associated with total mortality in unadjusted models. However, this association disappeared for some HRQoL domains after adjusting for several potentially important confounders (age, sex, eGFR, serum albumin level,
CRP level, hemoglobin level, number of comorbid conditions, and total time with end-stage kidney failure) in our case-mix models.

Importantly, every 10-point increase in Physical Functioning score was still associated with 12% (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.83-0.94) in our fully adjusted model.

The association between Physical Functioning domain and total mortality is shown in Kaplan-Meier curve (next figure).

In the case of General Health Perception, every 10-point increase was associated with 9% lower mortality risk in the case-mix model (HR, 0.91; 95% CI, 0.86-0.97) and the risk difference decreased to 7% after adjusting for depression scores (HR, 0.93; 95% CI, 0.87-0.99). Every 10-point increase in Physical Functioning score (HR, 0.89; 95% CI, 0.83-0.96) and SF-36 Physical Composite Score (HR, 0.83; 95% CI, 0.70-0.97) were associated with 10% and 17% lower risks of death with a functioning transplant.

Similar results were seen when death-censored transplant loss was the clinical outcome in the analysis and in this case most HRQoL domains were associated with death-censored transplant loss in unadjusted and case-mix models, but the association was not significant after adjusting for depression in many subscales (shown in the next table).
## Comparison of health-related quality of life in patients on maintenance dialysis waiting for transplantation and kidney transplanted adult patients – cross-sectional study

Quality of life data were not available due to refusal or inappropriate completion of the questionnaires for 179 (17%) of the transplanted patients and 27 (13%) of the waitlisted patients (non-participants). The final sample analysed, therefore, consisted of 888 Tx and 187 WL patients. Transplant recipients had significantly longer cumulative ESRD “vintage” and higher serum albumin compared to the waitlisted group.

The differences in HRQoL domains between the Tx vs WL groups was significant in almost all of generic and disease-specific scales. Median scores were significantly higher for the Tx vs WL groups for all individual sub-scales assessed. The largest difference was seen in General Health Perceptions: Tx: med.: 50 (IQR: 40), WL: med.: 35 (IQR: 30), p<0,001; Cohen’s d: 0,65).

<table>
<thead>
<tr>
<th>HRQoL domain</th>
<th>Unadjusted</th>
<th>Case-Mix Adjusted</th>
<th>Case-Mix &amp; CES-D Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHR (95% CI)</td>
<td>p</td>
<td>SHR (95% CI)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>0.97 (0,91-1,03)</td>
<td>0.441</td>
<td>0.94 (0,88-1,01)</td>
</tr>
<tr>
<td>General Health Perceptions</td>
<td>0.91 (0,85-0,97)</td>
<td>0.007</td>
<td>0.91 (0,84-0,98)</td>
</tr>
<tr>
<td>Energy-Fatigue</td>
<td>0.90 (0,84-0,95)</td>
<td>0.001</td>
<td>0.90 (0,84-0,96)</td>
</tr>
<tr>
<td>Emotional Well-being</td>
<td>0.92 (0,86-0,98)</td>
<td>0.011</td>
<td>0.93 (0,86-0,99)</td>
</tr>
<tr>
<td>Symptoms/Problems List</td>
<td>0.88 (0,80-0,95)</td>
<td>0.003</td>
<td>0.88 (0,80-0,98)</td>
</tr>
<tr>
<td>Effects of Kidney Disease</td>
<td>0.95 (0,89-1,00)</td>
<td>0.082</td>
<td>0.94 (0,89-1,01)</td>
</tr>
<tr>
<td>Burden of Kidney Disease</td>
<td>0.94 (0,86-1,01)</td>
<td>0.133</td>
<td>0.97 (0,89-1,06)</td>
</tr>
</tbody>
</table>

Note: Case-Mix Adjusted models that included quality-of-life domain score plus age, sex, estimated glomerular filtration rate, serum albumin level, Ln-transformed C-reactive protein level, hemoglobin level, number of comorbid conditions, and Ln-transformed total time with end-stage kidney failure.

* SHRs are shown per 10-point increase in HRQoL domain score. **CI: confidence interval.
In all case of disease-specific domains transplanted patients had significantly higher points than recipients in WL group. The largest difference was shown in Effects of Kidney Disease (Tx: med.: 87 (IQR: 25), WL: med.: 69 (IQR: 28), p<0.001; Cohen’s d: 0.70), Burden of Kidney Disease (Tx: med.: 75 (IQR: 38), WL: med.: 50 (IQR: 38), p<0.001; Cohen’s d: 0.90). In three domains of the four specific subscales was 10 point or more the difference between groups that is significant not only in statistical analysis, but it has clinical importance too.

In the fully adjusted model (associate variables, sleep and CES-D points) the different modalities had significant correlation with the following subscales: General Health Perception (beta: 0.158; p<0.001), Burden of Kidney Disease (beta: 0.219; p<0.001) and Effects of Kidney Disease (beta: 0.182; p<0.001).

**Cognitive and psychosocial function in kidney transplanted children**

Most variables (age, male, maternal education) of main characteristics of the 35 participant kidney transplant children (Tx) and 35 controls (Co) were similar, mean age was nearly 13 years (Tx: 160 months, Co: 161 months). 59% of Tx recipients and 60% of control children were male. Kidney disease children were 9 years old in the beginning of dialysis treatment and 10 years old when they had the transplantation. 4 children (12%) had retransplantation. The median of duration of dialysis therapy were 9 months (IQR: 14) and the time of the last transplantation were 28 months (IQR: 40).

We found association between prevalence of depressive “risk” and “symptom” of the different groups: in transplanted group this proportion was higher in all case. In CBCL’s parental view of transplanted children the Total Score (med. 61 (IQR: 12) versus 53 (IQR: 18) point, p<0.01) and in Internalizing Problem Scale (med. 62 (IQR: 13) versus 52 (IQR: 14) point, p<0.01) were significantly higher than in control group, but in Externalizing Problem Scale (med. 57 (IQR: 14) versus 51 (IQR: 15) point, p=0.13) we did not found any difference between groups. Furthermore in transplanted group parents with higher maternal education level signed higher points in behavioral problems than mothers with lower education. This difference was significant in the following subscales: Anxious/Depressed („low”: med. 55 (IQR: 8), „high”: med. 70 (IQR: 9), p<0.01), Internalizing Problems („low”: med. 58 (IQR: 14), „high”: med. 67 (IQR: 12), p=0.03) and Total Score („low”: med. 59 (IQR: 8), „high”: med. 65 (IQR: 10), p=0.05). Prevalence of Internalizing Problem presented by parents was
significantly higher in chronic ill group than in healthy group (41% versus 11%, p<0.01). Results of children were similar but they did not detect so serious their own problem: in transplanted group 6.5% of children recorded 65 points or higher, while in control group there were not a single value higher than 65 points (p=0.13). Children of parents with depressive symptoms (parents with high BDI scores) showed less depressive symptoms.

Transplanted patients had significantly worse scores on all sub-scales of the Woodcock-Johnson Cognitive Ability Test compared to controls: Verbal Ability (97±25 vs. 110±13), Thinking Ability (88±28 vs. 107±10), and Cognitive Efficiency (82±25 vs. 103±13), respectively, p<0.01 for all comparisons. The Full Scale Intellectual Abilities score was 85±26 vs 107±10 for the Tx vs Co groups, respectively; p<0.001.

All part of cognitive test had significant correlation with maternal education level. Verbal Ability (r=0.55, p<0.01), Thinking Ability (r=0.47, p<0.01), Cognitive Efficiency (r=0.40, p<0.05) and Full Scale too (r=0.49, p<0.01). The total time on dialysis and the first time on dialysis showed significant correlation with all of the standard points of intellectual skills. In transplanted group children with more chronic hospitalization and worse comorbid condition had significantly lower IQ.

Linear regression analysis was used to determine the independent association between the presence of cognitive deficits and the following variables: the total time on dialysis, cumulative hospitalization and maternal education level. In our model (R square was 0.486) the independent and significant predictors were the maternal education (beta=0.39, p=0.010) and the hospitalization time (beta=-0.51, p=0.002).

**CONCLUSIONS**

**Health-related quality of life and mortality in adult kidney transplant recipients – prospective cohort study**

In our prospective cohort study of 879 stable prevalent kidney transplant recipients, HRQoL predicted mortality. After adjusting for depressive symptoms and relevant clinical variables of the seven quality of life dimension two proved significant. Moreover, several HRQoL domains were significant predictors of death-censored transplant loss in case-mix-
adjusted models. Our results represent that HRQoL domains were associated independently with increased mortality risk and death-censored graft-loss in kidney transplant recipients. Previous studies have shown a strong association between depression and quality of life in patients with end-stage kidney disease; however it is remarkable that in our study the association between mortality and the two HRQoL subscales (General Health Perceptions and Physical Functioning) and SF-36 Physical Composite Score remained significant after extensive adjustment for case-mix variables and depressive symptoms.

These results confirm that measuring HRQoL may add useful information to the assessment of kidney transplant recipients.

**Comparison of health-related quality of life in patients on maintenance dialysis waiting for transplantation and kidney transplanted adult patients – cross-sectional study**

We reported that several dimensions of HRQoL were significantly better in a large sample of kidney transplant recipients compared to a well-matched group of WL haemodialysis patients. Quality of life points measured in generic scales showed higher values in transplanted group.

General health perception domain signed in all models significant association with the different modalities. The most substantial difference between the two groups was seen in kidney disease targeted subscales of the KDQoL-SF questionnaire.

These results confirm that kidney transplantation is associated with better HRQoL compared to dialysis. We also demonstrated the complexity of HRQoL assessment and emphasize the need of using multifaceted approach when comparing HRQoL data between groups of patients treated with different treatment modalities.

**Cognitive and psychosocial function in kidney transplanted children**

In Hungary our pilot study is the first to examine the cognitive function of renal transplanted children. Our results demonstrated that the intellectual abilities of transplanted children are significantly lower than cognitive skills of healthy pairs. We found behavior and emotional problems of children and their parents, typically in chronic illness patients.
Cognitive skills of transplanted children standed under the normal range and the associative (maternal education, total time on dialysis, hospitalization time) and emotional (internalizing problems) factors seems to be relevant in this population. Prevalence of parental depressive symptoms demonstrated important factor of transplanted patients’ relatives.

This results confirm that kidney transplanted children have severe cognitive, behavioral and emotional problems compared to healthy population.
PUBLICATIONS

Publications associated with the dissertation

Original articles - international journals:

   IF: 5.242
   DOI szám: 10.1053/j.ajkd.2011.03.028

   IF: 3.564
   DOI szám: 10.1093/ndt/gfq476

Abstracts - international journals:

1. **Vargáné Molnár M**, Reusz Gy, Sallay P, Pászthy B, Novák M: The link between ESRD and learning disabilities
   14th Congress of International Pediatric Nephrology Association 31 Aug-04 Sep 2007, Budapest, Hungary

Chapters:

1. **Vargáné Molnár M**, Sinkó E, Tóth A: Az egészségkárosodás és a krónikus betegségek kapcsolata a tanulási korlátok különböző formáival

Abstracts - Hungarian journals:


Tudat-Valóság-Identitás, Magyar Pszichiátriai Társaság XV. Vándorgyűlése, 2009. január 28-31., Debrecen


Publications not associated with the dissertation

Abstracts - international journals:

10th Congress of the European Federation for Research in Rehabilitation 09 Sep – 12 Sep 2009, Riga, Latvia
Original articles - Hungarian journals:


2. Vargáné Molnár M, Paulik E, Tróznai T, Kullmann L: A DIS-QOL életminőség vizsgáló eljárás adaptálásának hazai eredményei értelmi fogyatékos személyek körében
   In: Gyógypedagógiai Szemle, 2011; 39(2) p. 142-152.