

Factors associated with health-related quality of life in patients with chronic kidney disease

Ph.D. thesis - booklet

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INTRODUCTION

The symptoms and the frequent comorbidities, nevertheless the treatment of chronic kidney disease (CKD) have a significant negative impact on the everyday life of patients living with CKD. The burden of chronic disease cannot be fully assessed by conventional clinical parameters, therefore patient reported outcome (PRO) instruments are increasingly utilized to measure treatment efficiency and clinical outcomes. Health-related quality of life (HRQoL) as part of PROs, is a subjective parameter that reflects the opinion of the patient about his or her own health and treatment. In CKD populations HRQoL is independently associated with clinical outcomes, such as mortality or hospitalisation.

Devins et al. developed the theoretical model of illness intrusiveness, describing this as a mediator between the disease and HRQoL (Devins, 1994). Later on, the same group developed the Illness Intrusiveness Rating Scale (IIRS, Devins et al. 2001). The psychometric characteristics of the scale were excellent in different chronic disease populations. The IIRS is a reliable tool for measuring the burden of disease in various chronic medical conditions. Neither illness intrusiveness nor validated instruments measuring HRQoL have been utilized in Hungarian CKD patients prior to our studies.

Sleep disorders are important, potentially modifiable factors, associated with impaired HRQoL in CKD population. However, only few studies were performed to assess the impact of specific sleep disorders (found to be frequent in the target population, like restless legs syndrome or insomnia) on HRQoL in CKD patients.

Comparison of HRQoL of kidney transplant patients with patients on maintenance dialysis therapy lead to conflicting results. Although most experts consider the HRQoL of kidney transplant patients to be better, still, there is a lack of convincing evidence. Most of the studies used non-standard HRQoL tools or only generic instruments. Furthermore, the standard care and various components of the treatments have changed considerably since the last major studies on this field were conducted. 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. Furthermore, such comparisons can only be meaningfully interpreted in case of patients on dialysis who

are potentially eligible for transplantation. Recent publications demonstrated that the results of comparative HRQoL studies in this field are characterised by selection biases (Liem et al. 2009, Rosenberger et al. 2009). Only few studies compared transplanted patients to patients on waiting list, and even those trials involved only a limited number of participants and assessed only a few co-variables, nevertheless, they used only generic HRQoL tools (Fujisawa et al., 2000; Overbeck et al., 2005; Rosenberger et al., 2009).

OBJECTIVES, HYPOTHESES

The psychometric evaluation of Illness Intrusiveness Rating Scale (IIRS) Hungarian version

There was a lack of standard Hungarian questionnaire to assess illness intrusiveness. Our goal was to translate this short, practical questionnaire (the IIRS), to test its psychometric properties, and to assess the burden of disease using the Hungarian version among patients on maintenance dialysis in Budapest. Furthermore, since several North-American assessments occurred with IIRS in patients on dialysis, we aimed to compare the results of those studies to ours by means of simultaneous confirmatory factor analysis.

Hypotheses:

- 1) The Hungarian version is reliable.
- 2) The results of the Hungarian and North-American IIRS assessments in patients on maintenance dialysis are comparable.

Health-related quality of life and related psychosocial factors among Hungarian patients on maintenance dialysis, focusing on sleep disorders

There is a lack of HRQoL assessment using standard methods among Hungarian CKD patients. Although sleep disorders are important, potentially modifiable factors modulating HRQoL, there are only a few studies focusing on this topic in CKD population. Our aim was to assess the relationship between sleep disorders and HRQoL in chronic dialysis patients. Basic sociodemographic and clinical parameters, assumed to be related to sleep disorders and/or HRQoL, were also assessed.

We tested the following hypotheses:

- 1) The percentage of patients on maintenance dialysis suffering from sleep disorders is high and these patients are characterised by worse HRQoL data. The poorer HRQoL scores can be observed both at the level of generic and kidney disease-specific domains.
- 2) Restless legs syndrome is associated with worse HRQoL independently of the presence of insomnia.

Cross-sectional comparison of health-related quality of life in kidney transplanted patients versus patients on maintenance dialysis waiting for transplantation

In our cross-sectional study we aimed to compare the HRQoL of renal transplanted (Tx) outpatient population with dialysed patients on transplantation waiting list (WL). The study was designed to avoid the selection bias of previous similar studies. Our study is remarkable for its large sample-size, the comparable patient populations and for using modular HRQoL instrument. The assessment of important sociodemographic and clinical parameters including sleep disorders and depressive symptoms is also remarkable.

Our hypotheses were:

- 1) Both generic and kidney disease-specific HRQoL is better in transplanted patients compared to WL patients.
- 2) After adjustment for psychosocial parameters, the difference in HRQoL can be observed mainly in kidney disease-specific domains and not in generic subscales.

METHODS

The psychometric evaluation of the Hungarian version of the Illness Intrusiveness Rating Scale (IIRS)

The translation of IIRS from English to Hungarian was performed according to standard procedure (Bonomi et al., 1996). The linguistic validation was carried out with the inclusion of 15 hemodialysed patients. After the linguistic validation the final version of the scale was assessed among 399 patients on maintenance hemodialysis in eight dialysis centres of Budapest. A subset of the sample (58 participants) was asked to complete the IIRS repeatedly after a three-four weeks period to verify test-retest reliability of the

instrument. The internal consistency of IIRS was tested by calculating Cronbach's alpha coefficient. IIRS scores of Hungarian patients were compared to data of North-American assessments in patients on dialysis with simultaneous confirmatory factor analysis (SCFA). The thirteen items of the IIRS were grouped in three factors similarly to the original (English) factor-structure. The fit of factors to our data was evaluated by SCFA using the EQS structural equations modelling program.

Health-related quality of life and related psychosocial factors among Hungarian patients on maintenance dialysis, focusing on sleep disorders

In our cross-sectional study 257 patients receiving maintenance dialysis therapy in Fresenius Medical Care dialysis centres in Budapest were enrolled. In addition, 214 patients on chronic dialysis who were waitlisted for kidney transplant, were also included in the survey. We collected the most important sociodemographic factors and clinical parameters. The HRQoL was measured with the modular Kidney Disease Quality of Life Questionnaire (KDQOL-SFTM) (Hays et al., 1994) validated previously by our workgroup. Sleep disorders were assessed: restless legs syndrome by using the Restless Legs Syndrome Questionnaire (RLSQ; Allen, 2001); insomnia with Athens Insomnia Scale (AIS, Soldatos et al., 2000). Patients were considered having RLS if all diagnostic criteria for RLS were met. The psychometric properties of these instruments were tested by our group in the target population with good results.

Cross-sectional comparison of health-related quality of life in kidney transplanted patients versus patients on maintenance dialysis waiting for transplantation

In our cross-sectional cohort study entitled **Transplantation and Quality of life-Hungary Study (TransQoL-HU Study)**, conducted between 2002 and 2003, 1067 adult kidney transplanted patients (Tx) participated from the Department of Transplantation and Surgery Semmelweis University, Budapest. At the same time, 214 patients on maintenance dialysis awaiting for transplantation (WL) were enrolled from 9 dialysis centres in Budapest. Basic socio-demographic data were recorded, and the most relevant clinical parameters were collected from patients' charts. The HRQoL was measured with the

modular Kidney Disease Quality of Life Questionnaire (KDQOL-SFTM). Depressive symptoms were assessed using the Centre for Epidemiologic Studies-Depression (CES-D) scale (Radloff, 1977). The psychometric testing of CES-D scale was previously carried out by our workgroup. The assessment of self-reported sleep disorders was also conducted using the following instruments: insomnia was screened with the Athens Insomnia Scale (AIS), restless legs syndrome with the above mentioned RLS Questionnaire (RLSQ), the high risk for obstructive sleep apnea syndrome (OSAS) was measured with the Berlin Sleep Apnea Questionnaire (Netzer et al., 1999).

Statistical analysis

The statistical analyses were performed using the SPSS (version 13) software. In all analyses two-sided tests were used, and results were considered statistically significant when alpha was fewer than 5%. In descriptive statistics, for non-normally distributed variables, median and interquartile range was used, normally distributed variables are presented by their mean and standard deviation. For correlation analyses Spearman-rank correlation or Pearson-correlation were applied. In case of categorical variables group-differences were analysed with Chi-square test. Continuous variables were compared using student t- test, analysis of variance (ANOVA) with Bonferroni-correction, Mann–Whitney U-test or Kruskal–Wallis test, as appropriate. For testing the independent relationship of HRQoL sub-scales, we used multivariate linear regression models.

RESULTS

The psychometric evaluation of Illness Intrusiveness Rating Scale Hungarian (IIRS) version

The Cronbach's alpha of the Hungarian IIRS version showed good internal consistency ($\alpha = 0.80$). The Cronbach's alphas for the three IIRS subscales were of moderate strength: *Relationships and personal development* $\alpha = 0.67$; *Intimacy* $\alpha = 0.66$; *Instrumental* $\alpha = 0.64$.

Our results confirmed that the results obtained with the Hungarian and North-American version of IIRS are comparable. The simultaneous confirmatory factor analysis confirmed that the three-factor structure of the English version remained applicable also in the Hungarian version. Fit indices indicated very good to nearly excellent model fit in SCFA analysis of Hungarian and English data (the χ^2 /df was < 2.5 , the fit indices /goodness of fit index, comparative, non-normed fit index/ were higher than >0.88 and the SRMR was <0.10).

The majority of the residual correlations were below 0.1, which further supports the good fit of the three-factor model in the two groups. We have found factorial invariance across the two populations with cultural differences.

Health-related quality of life and related psychosocial factors among Hungarian patients on maintenance dialysis, focusing on sleep disorders

The prevalence of restless legs syndrome was 14% in our sample. Insomnia was twice as prevalent among patients suffering from RLS compared to patients not having RLS symptoms. Patients with RLS scored significantly higher on the insomnia scale (median AIS score = 8 versus 4, $p < 0.01$). We built a multivariate regression model to analyse the relationship between RLS and those quality of life domains that had been shown to be valid. Our multivariate model was adjusted for parameters that showed significant correlation with HRQoL in univariable models: age, gender, education, financial status, serum albumin level and number of co-morbidities. All HRQoL domains that showed significant negative relationship with the presence of RLS in univariate analysis (*Physical function, Pain, Emotional well-being, Sleep, Burden of kidney disease and Symptoms of kidney disease*) remained in a significant association with RLS even after adjustment for the aforementioned co-variates. In order to evaluate whether the relationship between RLS and worse HRQoL is independent from sleep-related problems, insomnia was introduced in our model as an independent variable. After adjustment for the AIS score, RLS remained a significant, negative predictor of most HRQoL domains. Our results

demonstrate that RLS impairs HRQoL both via sleep-related and also via sleep-independent mechanisms, like pain, anxiety, discomfort or restlessness.

Cross-sectional comparison of health-related quality of life in kidney transplanted patients versus patients on maintenance dialysis awaiting for transplantation

The valid and psychometrically sound KDQOL- SFTM domains were included in our analysis. The renal transplant patients scored significantly higher on most of the generic and all of the kidney-disease specific domains of KDQOL- SFTM. No difference was observed between the two groups in case of *Pain* and *Role function- physical* sub-scales. The difference between the HRQoL of Tx and WL patients was more than 10 points, which was shown by previous publications performed in dialysis population to be clinically significant. The effect size was notable in case of *Burden of kidney*, *Effects of kidney disease* and *General health perceptions* (Cohen's $d=0.65-0.90$). Generic sub-scales showed smaller effect size than kidney disease-targeted dimensions. We performed multivariate regression analysis to study the relationship of HRQoL domains and renal replacement modality (Table 1). In the first model (Table 1, first block) only modality was included as independent variable. All three generic (*Physical function*, *Energy/fatigue/fatigue*, *Emotional well-being*, *General well-being*) and all kidney disease-targeted domains (*Sleep*, *Burden of kidney disease*, *Effects of kidney disease* and *Symptoms of kidney disease*) had positive correlation with transplant-modality. Modality, however explained only 0.5-10% of HRQoL domain-variance. In the second model (Table 1, second block), besides the modality, the co-variables related to HRQoL were also involved: age, gender, haemoglobin level, serum albumin level, number of co-morbidities, time since diagnosis of end-stage renal disease, education, financial situation. The R-square was notably higher than in first step (0.09–0.2). The most significant R-square increase was observed in case of *Physical function* domain, but was not negligible in case of kidney disease-targeted sub-scales, either. In this latter case, the renal replacement modality had significant relationship only with one generic (*General health perceptions*) and all four disease-specific HRQoL domains. In the third model (Table 1, third block), additionally to all independent variables already included in our model, sleep disorders (high risk for presence of insomnia, RLS and

OSAS) were introduced. This model explained higher portion of variance of each HRQoL domain than any of the previous models, and not surprisingly the relationship between modality and Sleep HRQoL domain became insignificant. Finally, CES-D score was included in the model (Table 1, fourth block). After adjustment for depression, a 20-40% relative R-square increase was observed for each HRQoL sub-scale. In this final model, renal replacement modality showed significant, independent relationship with only three HRQoL domains: *Burden of kidney disease*, *Effects of kidney disease* and *General health perceptions*. Our final models explained around half of generic HRQoL sub-scale-variances (Energy/fatigue 48%, Emotional well-being 51%). The percentage of variance explained by our final models in case of kidney disease-targeted sub-scales were 31% (*Burden of kidney disease*) to 46% (*Sleep*).

Table 1: Multivariate linear regression analysis of quality of life domains (Ln transformed scores) to assess the association with renal replacement modality.

Shown in the cells are the parameters of the independent variable: waiting list vs transplantation, highlighted with bold, when the results are significant. Independent variables entered into the model: **Block 1:** modality; **Block 2** (Clinical and socio-demographic): age; gender; education; self reported financial situation; serum albumin; hemoglobin; number of co-morbid conditions; ESRD vintage; **Block 3** (Sleep disorders): self-reported restless legs syndrome, obstructive sleep apnea, insomnia; **Block 4:** depressive symptoms (CES-D score).

HRQoL domains	A: modality			B: A+ Block 2			C: B+ Block 3			D: C+ Block 4		
	beta	p value	adjusted R square	beta	p value	adjusted R square	beta	p value	adjusted R square	beta	p value	adjusted R square
Physical function	0.068	0.04	0.004	0.036	0.3	0.198	0.019	0.6	0.258	0.005	0.9	0.309
General health perceptions	0.225	<0.001	0.050	0.195	<0.001	0.175	0.173	<0.001	0.228	0.158	<0.001	0.290
Energy-fatigue	0.110	0.001	0.011	0.082	0.2	0.116	0.057	0.09	0.222	0.027	0.3	0.479
Emotional well-being	0.065	0.5	0.003	0.059	0.09	0.109	0.033	0.3	0.193	-0.001	0.9	0.510
Kidney disease (KD) specific HRQoL domains												
Symptoms of KD	0.124	<0.001	0.014	0.092	0.008	0.144	0.067	0.05	0.214	0.038	0.1	0.321
Burden of KD	0.321	<0.001	0.102	0.263	<0.001	0.180	0.241	<0.001	0.233	0.219	<0.001	0.364
Effects of KD	0.230	<0.001	0.052	0.228	<0.001	0.148	0.200	<0.001	0.222	0.182	<0.001	0.313
Sleep	0.117	<0.001	0.013	0.095	0.008	0.092	0.042	0.2	0.361	0.024	0.4	0.455

CONCLUSION, SUMMARY OF NEW FINDINGS

We demonstrated that the Hungarian version of Illness Intrusiveness Rating Scale is reliable, and it allows the assessment of disease-burden and its relationship with HRQoL in Hungarian patients. After further validation in different chronic disease populations, the scale could be used for comparison of disease burden in patients with various chronic diseases. Factorial invariance was also observed between the Hungarian and English versions, therefore the North-American data can be compared to the Hungarian results, providing further information on dialysis outcomes.

In our second cross-sectional survey we assessed the relationship of sleep disorders and HRQoL in chronic dialysis population using validated and reliable instruments. Until this time no similar study had been performed in Hungary. Our study is notable for the assessment of several important co-variables, like sociodemographic and clinical parameters. The RLS was related to clinically significant insomnia and worse sleep-quality. The RLS was related to worse HRQoL in case of several generic and kidney disease related sub-scales even after adjustment for co-variables. The independent relationship between HRQoL and RLS remained significant even after adjustment for insomnia. This result indicates that worse HRQoL scores are related not only to sleep- related symptoms and complaints of RLS, but also to non-sleep related issues.

We conceptualized and carried-out our third cross-sectional study by avoiding the selection bias and other limitations of previous similar comparative surveys. Our study is notable for the large sample size, for the comparable patient populations (kidney transplanted patients and patients awaiting for kidney transplantation), we used modular HRQoL questionnaire that was validated in both cohorts (Tx and WL patients), we assessed several important sociodemographic and clinical parameters, we assessed the important modifiable psychosocial problems such as sleep disorders and depressive symptoms with validated scales. Our results demonstrate that the difference of HRQoL between the two renal replacement modalities is more prominent in kidney disease-targeted sub-scales. Importantly, our results demonstrated that the worse HRQoL observed in patients on dialysis is related mainly to psychosocial parameters, and not to the modality itself.

LIST OF PUBLICATIONS

LIST OF PUBLICATIONS RELATED TO Ph.D. THESIS

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