Perceived Health Status after Kidney Transplantation

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Contents

CHAPTER 1

Introduction

1.1. Chronic kidney disease

A substantial number of patients with end-stage renal disease require lifelong renal replacement therapy. In Europe as a whole, 70-150 incident patients per million inhabitants started renal replacement therapy in 2003, with an overall prevalence of 500-1200 patients per million inhabitants, causing a heavy burden to public health resources [1]. Two distinct approaches to patients with kidney failure are possible today: dialysis (hemodialysis and peritoneal dialysis) and transplantation either from a cadaver or a living donor. Hemodialysis was used for the first time by Kolff in 1943 for treatment of acute renal failure [2]. It is an intermittent extracorporal elimination method in which blood is passed through a dialyser which contains a biocompactible artificial membrane where diffusion and convection of molecules from and to blood take effect. Patients in a chronic hemodialysis program usually undergo 4- to 5-hour long sessions three times a week. Peritoneal dialysis is a continuous intracorporal elimination method which uses the patient's own peritoneal membrane as a dialyser. Diffusion and osmosis are the main principles of elimination in peritoneal dialysis. Dialysis fluid is usually exchanged four times a day by the patient or several times during the night by an automatic cycler. Both dialysis methods are equal in effectivity and thanks to them patients with kidney failure can survive for more than 20 years today. However, patients are dependent on dialysis throughout their lives and withdrawal from it causes the patients to die. On the other hand, kidney transplantation is a treatment method in which a kidney is transplanted into a patient, restoring all its functions. Patients are independent from any elimination method after a successful kidney transplantation, though lifelong use of immunosuppressive medication is necessary to prevent immunological rejection of the transplanted graft.

Kidney transplantation is the method of choice among renal replacement therapies due to its superior results in mortality, morbidity, cost utilization and quality of life in comparison to dialysis [3,4]. The research into graft and patient survival after transplantation is quite impressive and a wide range of factors is already known to influence mortality and morbidity of transplanted patients [5,6]. Less information is available about quality of life and variables that have an impact on it.

1.2. Quality of life and perceived health status

The World Health Organization Quality of Life assessment group has defined quality of life as 'Individuals' perception of their position in life in the context of the culture and the value system in which they live and in relation to their goals, expectations, standards and concerns' [7]. Quality of life according to the WHO definition is a multidimensional construct comprising physical, mental, social and economic components [7-9]. Spilker's hierarchical model includes overall quality of life, separate domains of quality of life, as well as a third level covering more specific aspects of each domain [9-11].

Health is defined by WHO as being not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being [12]. It is evident that various medical parameters are important factors in some domains of quality of life. Instead of exploring quality of life, many researchers therefore study only the physical, mental and social domains of health and call it 'health-related quality of life' [13,14], while others decline this and prefer the term 'perceived health status' [15]. The term quality of life covers much broader aspects than perceived health status, as it includes also environmental and economic factors as well as psychological well-being, with their combined impact on patients' sense of well-being [16]. Despite the uncertainty in definitions, perceived health status is not a mere construct devoid of clinical relevance. Recent research has shown that it is a very important predictor of other outcomes, including survival, in patients with chronic diseases [17,18]. Therefore patients' self-assessment of their health has become accepted as an important measure for evaluation and comparison of treatments as well as for the management of individual patients [19].

1.3. Conceptual framework

1.3.1. The model of the disablement process

The International Classification of Functioning, Disability and Health (ICF) [20] is based on principles derived from the Disease-Handicap Model, which clarifies the consequences of diseases in terms of resulting impairments, disabilities and handicaps. The more elaborate version of this model was worked out by Verbrugge and Jette in 1994 and it was entitled 'the disablement process' [21]. The simplified model of the disablement process based on Verbrugge's and Jette's model as well as the ICF is described in Figure 1.1 and consists of two parts interacting with each other; the first including functioning and disability and the second comprising contextual factors.

The first part of the ICF is based on body functions and structures. Any intrinsic pathology or disorder which results in significant deviation or loss of body functions or structures is called 'impairment'. Activities and participation form the second component of the first part of the ICF. The term 'activity limitations' refers to difficulty to perform a certain activity in normal manner as a result of impairment. 'Participation restrictions' are problems an individual may experience in involvement in life situations as the result of disability or impairments.

The second part of the ICF has two components as well – environmental and personal factors. Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives. These factors are external to individuals and can have positive or negative influence on their performance as members of society, on their capacity to execute actions or tasks, or on their body functions or structure. Personal factors are the particular background of an individual's life and living, and comprises features of the individual that are not part of a health condition or health states [20,21].

The disablement process may be seen as the link between pathology, impairments and activity limitations, and it ultimately leads to restrictions in participation. An individual with restrictions in participation (physical or social) may temporarily report a deterioration of quality of life. Because participation restrictions may be consequences of disease, alterations in perceived health status are reported as well. Any significant pathology therefore modifies perceived health status and quality of life.

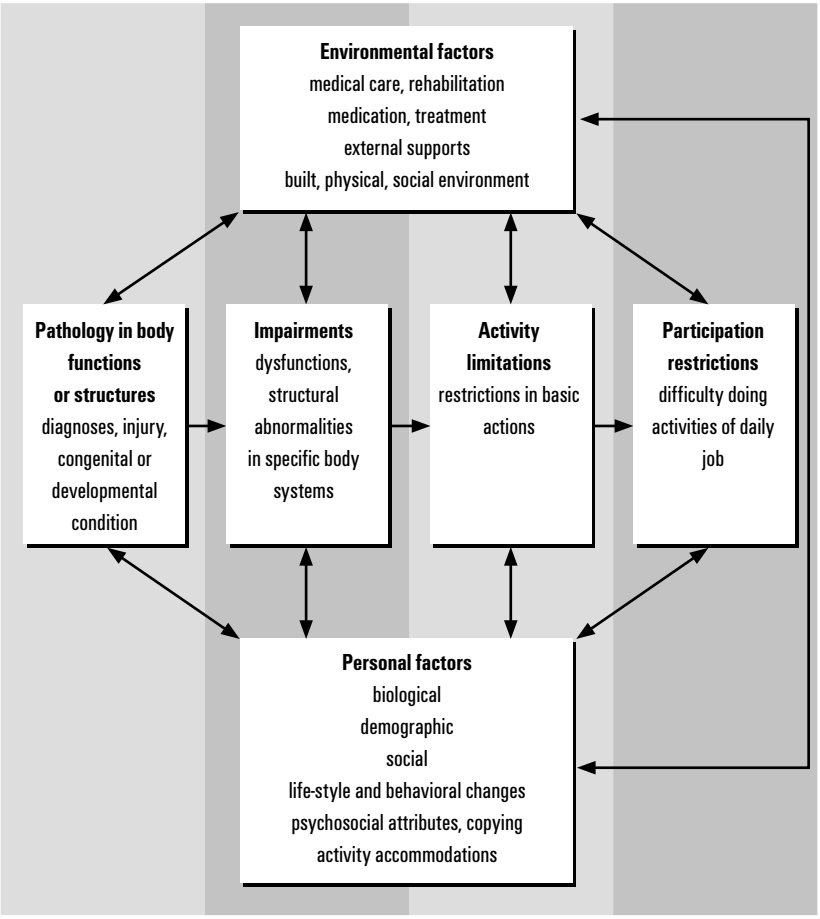
Contextual factors are important influences and mediators which aggravate or reduce the disablement process. These factors may interfere in any part of the disablement process, and vice versa, the disablement process may modify some contextual factors. In addition, environmental and personal factors may interact with each other. The individual's health status and quality of life are therefore the results of a wide range of interacting factors influencing various parts of the disablement process.

1.3.2. Perceived health status in patients with kidney diseases

The research into perceived health status after kidney transplantation mostly focuses on the description of its determinants using univariate and bivariate statistics. A variety of medical and non-medical factors have been identified as characteristics of perceived health status in previous studies. However, research with more proper analysis of predictive variables is scarce.

Despite many studies in this field there are still doubts about the importance of medical factors for perceived health status after kidney transplantation. However, medical variables are at the center of nephrologists' attention. In the majority of studies in the field of chronic

Figure 1.1. The model of the disablement process



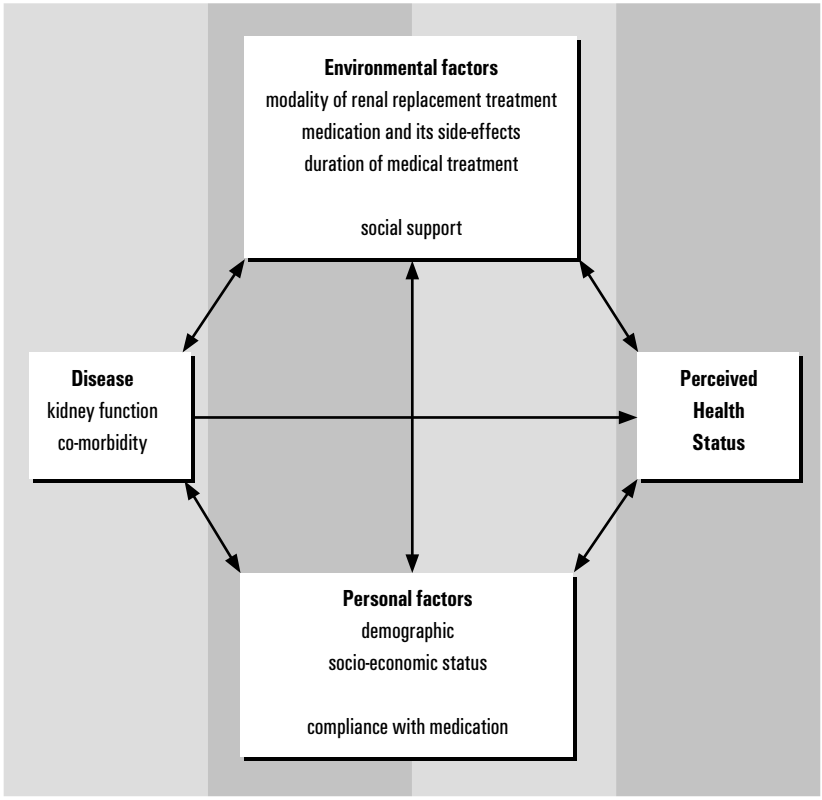
diseases, medical factors are believed to rank among the most important determinants of perceived health status in patients with chronic diseases, and thus also in kidney transplant recipients. On the other hand, research in this field also shows that patients can evaluate their health rather differently even when their medical variables are very similar of identical [8]. One possible explanation is that there are many possible confounders among non-medical variables, including age, gender, socio-economic status (education, occupational and employment status), social support or psychological characteristics. So, the interaction between environmental and personal factors, as well as their influence on various parts of the disablement process, may result in differing perceived health status [22]. Research aiming at comprehensive assessment of several predictors of perceived health status is lacking.

According to the model of the disablement process, a complex variety of environmental and personal factors exist with possible impact on perceived health status. The following model gives an overview of several medical and non-medical variables with possible influence on perceived health status in patients after kidney transplantation (Figure 1.2).

1.5. Research questions

The variables described in the model may be categorized into two groups – medical and non-medical. Variables directly related to kidney disease or connected to treatment are called 'medical'. Other 'non-medical' variables are not related to the underlying disease or to treatment. Searching the literature, we found studies identifying some predictors of perceived health status [4,22-30]. Based on preliminary knowledge, the present research wants to address medical variables, to show their relationship to perceived health status, and to explore the combined influences of medical factors

Figure 1.2. Predictors of perceived health status in patients with end-stage renal disease



on each other. As the current knowledge lacks a comprehensive view of variables with possible impact on perceived health status, the main aim of this research is to create a comprehensive model of medical and non-medical predictors of perceived health status and to discuss their clinical importance. Therefore the following questions in the population of kidney transplant recipients are discussed.

1 What health status do successfully transplanted patients with end-stage renal diseases perceive?
2 Which medical and social-demographic factors influence their perceived health status?

These general research questions are specified as follows.

1 Are the differences in perceived health status between transplant and dialysis populations based on modality of therapy or on selection bias?
2a Which medical variables (kidney function, adverse effects of immunosuppressive treatment, co-morbid diseases, duration of kidney disease, number of hospitalizations, period after transplantation) influence perceived health status?
2b What is the relation of adverse effects of treatment and noncompliance with the therapy to perceived health status? Is noncompliance related to adverse effects of treatment?
2c Are there non-medical confounders (age, gender, socio-economical status, social support) that are related to perceived health status in addition to medical variables?

1.6. Research context of the study

In May 2001, a proposal for co-operation in the project named Societal Reintegration After Kidney Transplantation was signed between the University Hospital Košice, P. J. Šafárik University Košice and the University of Groningen. The main goals of this research were to evaluate the possibilities and problems which people are confronted with after renal transplantation in the process of societal reintegration, and which factors increase or decrease the chance of societal reintegration after renal transplantation. Since 2001, research has been carried out by two independent teams, one in Košice and the other in Groningen. While the team in Košice has mostly focused on studying perceived health status and its determinants, the Groningen team has been interested in patient participation in society. After years of mutual international colaboration, data were collected and analyzed. Several presentations at international

and national conferences as well as articles in scientific journals have resulted from this study. This thesis is intended to give an overview of the research work done on this project during the period 2001-2006.

1.7. Study design and procedure

Between the start of the transplant program in 1972 and the end of the year 2005, 1352 kidney transplantations were performed in Slovakia. The annual transplantation rates varied between 73 and 133 in the last five years. Today four kidney transplant centres exist in Slovakia (Bratislava, Košice, Banská Bystrica and Martin). The sample for the present research was recruited from the Košice and Bratislava transplant centres, which manage more than half of the Slovak transplant population.

A protocol was designed to examine 200 kidney transplant recipients with a functioning graft between one and seven years after their transplant surgery, with the aim of studying the perceived health status of these patients some time after their transplant surgery. A second group was meant to include 50 incident kidney transplant recipients with a functioning graft 3 months after their transplant surgery, with the aim of studying the perceived health status of patients shortly after their transplant surgery. A further group of dialysed patients was meant to contain 100 dialysis patients, with 50 of them on waiting lists for cadaveric kidney transplantation.

The local Ethical Committee approved the study. Only patients who signed informed consent prior to interview were included.

1.8. Outline of the thesis

It is believed that perceived health status in patients after transplantation is higher than in those on dialysis [4]. But before a patient is transplanted, two processes of selection are applied. Any comparison of perceived health status of transplant recipients to patients on dialysis is therefore doubly biased, resulting in comparison of young and relatively healthy transplanted to older and more ill dialysis patients [31]. The differences in perceived health status between two renal replacement modalities are explored in Chapter 2. The differences in socio-demographic variables, social support and medical factors are presented as well.

In Chapter 3 medical predictors of perceived health status are evaluated in a sample of 128 kidney transplant recipients. Stepwise linear regression analysis of 17 demographic, dialysis-, transplantation- and co-morbidity-related factors was performed in order to explore medical predictors of worse perceived health status controlled for basic demographic variables.

Chapter 4 describes the adverse effects of immunosuppressive treatment as an important transplant-specific medical factor. Adverse effects can have little or no direct effect on morbidity or survival, but can be perceived by the patient as highly disturbing [8,32]. Factors which can modify stress from adverse effects are explored in this chapter as well.

Noncompliance with the therapy is the subject of Chapter 5. The consequences of noncompliant behaviour are very negative in terms of the final clinical outcome. The detection of noncompliers is a permanent concern of the transplant team, because noncompliance is associated with higher frequency of late graft dysfunction, which is directly related to graft loss [8]. In addition, noncompliance is associated with significantly decreased quality of life [32].

Chapter 6 makes a synthesis of medical and non-medical factors and analyses their impact on perceived health status. Out of 218 patients after kidney transplantation, 138 participated in the study. Linear regression analysis was performed to predict perceived health status, with the patients divided into three age categories (<40, 40-59, ≥60 years). Independent variables included socio-demographic variables (age, gender, education, employment status, house-keeping activities), social support, dialysis and transplantation related variables, co-morbidity, side-effects of treatment and compliance with immunosuppression.

In the last chapter we discuss the theoretical and clinical consequences of our research and we recommend possible interventions which can improve perceived health status in kidney transplant recipients. In addition, suggestions aimed at future research on this topic are given in this final chapter.

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CHAPTER 2

Are differences in perceived health status between kidney transplant recipients and dialysed patients based on a selection bias?

Are differences in perceived health status between kidney transplant recipients and dialysed patients based on a selection bias? Rosenberger J, Nagyova I, van Dijk JP, Madarasova Geckova A, Roland R, van den Heuvel WJA, Groothoff JW. submitted 2006

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Abstract

Background: Kidney transplantation offers longer survival, less morbidity and lower costs than dialysis. It is believed that it improves quality of life as well. The aim of present study was to compare perceived health status (PHS) of dialysed patients on waiting list with kidney transplant recipients 3 months after transplantation, matched for age, gender and co-morbidity.
Methods: Out of 103 dialysed patients 45 on waiting list for cadaveric kidney transplantation were matched for age, gender and co-morbidity to 42 incident transplant recipients. An interview was conducted to collect socio-demographic variables. PHS was measured by the SF-36, social support by Social Support List Discrepancies questionnaire. Medical data were retrieved from patients' medical records.
Results: Patients on dialysis had worse physical (37.7±23.3) and mental

(50.6±19.4) PHS than transplant recipients (54.2±20.5 and 60.7±20.0, $p \leq 0.001$ and $p \leq 0.01$, respectively). If transplanted patients were compared to their matched pairs on waiting list, no differences in PHS were found.
Conclusions: PHS after kidney transplantation is much better than on dialysis. However, this fact is significantly influenced by a selection bias as only some dialysed patients are put onto waiting list and some of them are actually transplanted. When the correction of this bias is done using matching criteria, differences in PHS disappear.

Introduction

Kidney transplantation offers longer survival, less morbidity than dialysis and the cost of transplantation is lower as well [1]. It is also reported that quality of life after kidney transplantation is improved [2,3].

While research into graft and patient survival after transplantation is quite impressive, studies focused at quality of life, functional status or perceived health status are less common. Comparisons of health status between patients after transplantation and those remaining on dialysis are even less frequent and mostly published more than ten years ago. In general, two different populations are usually evaluated. When considering a recipient of cadaveric kidney, one should be aware that patients who are being transplanted are coming from a waiting list. As the first step, a patient's status is evaluated and only if no contraindications are found, a patient is placed on waiting list. As the second step, when a suitable organ is available, a patient is checked again before transplant surgery. It is common that transplant surgeons carefully choose the very best candidates for transplantation. In some published studies, transplant recipients had half as much coronary and peripheral vascular disease than patients on dialysis [4]. In summary, two processes of selection are happening before a patient is transplanted. Therefore, any comparison of health status of transplant recipients to patients on dialysis is twicely biased, resulting in comparison of young and relatively healthy to older and more ill patients [5].

The majority of research papers that explore differences in quality of life between kidney transplant recipients and dialysed patients is outdated (from 1984 till 1996) and has a cross-sectional design. Another problem is the number of transplant patients recruited in these studies varying between 30 and 144 [6-12]. Research with larger samples is rare, the exceptions are the study by Muthny and Koch who included 761 transplanted, 290 hemodialysed and 68 peritoneal dialysis patients [13], the study by Gudex with 367 transplanted, 144 hemodialysed and 93 peritoneal dialysis patients [14], the study by Wight et al. with 228 transplanted, 183 hemodialysed and 109 peritoneal dialysis patients [3], and the study by Reimer et al. with 149 transplanted, the same number

of hemodialysed patients and healthy controls [15]. All cited studies found better quality of life in transplant recipients when compared to dialysed patients, but some of their authors pointed at heterogeneity within their samples. The differences in age between (younger) transplanted and (older) dialysed patients are the most common findings [3,6,9,13], but different time on treatment [3,6,13] and unequal gender proportions [13] are reported as well. Contrasting with earlier findings, Morris and Jones did not prove striking differences in quality of life between 69 transplanted and 24 home hemodialysis patients. Although the authors found reduced quality of life in 24 hospital hemodialysis patients compared to that of transplant recipients, but also to that of home hemodialysis patients [16]. Another study without significant differences in quality of life was published by Johnson et al. Twenty kidney transplant recipients were compared to 10 hemodialysed patients on the waiting list for kidney transplantation, 19 hemodialysed patients not on waiting list and 10 failed transplants. Only the last category displayed a diminished quality of life [17].

Very few studies with repeated evaluations of quality of life before and then after transplantation have been published on this topic. Three studies contain a low number of transplanted patients – 16 in the study by Park et al. [10], 23 in the study by Kutner et al. [18] and 27 in the study by Russell et al. [19]. Three larger studies were published – Jofre et al. followed 88 kidney transplant recipients [20], Laupacis et al. 168 [2] and Manninen et al. 226 [21]. All papers, except for Kutner et al., studied only transplant recipients without any control group.

It is evident that perceived health status is influenced by age, gender, education, employment status, social support, side-effects of treatment, co-morbidity, and not only by the success of transplantation [22]. Because dialysis and transplant patients differ in these variables, their perceived health status is different too [17].

With aiming at these facts the present study was designed as the comparison of perceived health status between dialysed patients on waiting list for cadaveric transplantation and incident kidney transplant recipients 3 months after kidney transplantation, matched for age, gender and co-morbidity. To our knowledge, few papers with similar approach have been published, however without exploring differences between dialysed and transplanted patients [23] or without matching them for co-morbidity [15].

Methods

Sample and procedures

Two patient cohorts were examined – patients on dialysis and those after transplantation. The protocol was designed to examine 100 dialysis patients, 50 of them who are on waiting list for cadaveric kidney transplantation,

and to match those on waiting list for age (in decades), gender and co-morbidity category with 50 incident kidney transplant recipients from the same region. Co-morbidity was evaluated using the information about co-morbid diseases from medical records based on criteria for Wright co-morbidity index [24]. Thereafter patients were stratified into low-risk category (no comorbidity), intermediate-risk (one co-morbid condition) and high-risk (more than one co-morbid condition).

The local Ethical Committee approved the study. Only patients who signed informed consent prior to interview were included.

Dialysis patients

The group of 109 dialysed patients from four different dialysis centers in the Slovak Republic was invited to participate, 6 patients refused or provided incomplete data (response rate 94.5 %). Out of these, 45 patients (and 3 nonresponders) were on a waiting list for cadaveric transplantation. Nonresponders did not differ from participants whether in age or gender. All patients who agreed with their participation were included except for fifteen with severe dementia and two with mental retardation (dementia or mental retardation were listed in their medical records).

Transplanted patients

The group of 61 incident kidney transplant recipients three months after their transplant surgery from the same region of Slovak Republic was invited to participate, 19 patients refused or provided incomplete data. 42 patients remained (response rate 68.9 %). Nonresponders did not differ from participants whether in age or gender. All patients with a functional graft who agreed with their participation were included except for one with mental retardation (mental retardation was listed in the medical record).

After matching for age, gender and co-morbidity index, 31 dialysis (on waiting list) and 31 transplant patients remained for analysis.

Measures

All participants were interviewed by a trained individual. The interview was focused on basic demographic information (age, gender), education (categorized as elementary, secondary or university), employment status (categorized as employed for full-time or part-time and not employed – disabled, retired or unemployed), house-keeping activities (measured in hours per week spent for shopping, cooking, clearing, or caring for family members), family status (categorized as single, married, divorced or widowed).

Perceived health status was measured using the Short Form Health Survey (SF-36). The SF-36 is a 36-item questionnaire for assessment of perceived health status [25]. It consists of 8 sub-scales which can be combined

as the physical summary component and the mental summary component. All sub-scales as well as the summary components are presented as scores between 0 and 100, with higher scores indicating better health status. The validity and reliability of SF-36 have been tested in patients with renal disease, including those after kidney transplantation [3,23,26,27]. Skalska et al. validated the questionnaire in the Czech population [28]. The Cronbach's α in the present sample was 0.94.

Social support was measured using the Social Support List Discrepancies questionnaire (SSL-D). The items in this questionnaire are grouped into 6 scales and they can be computed into a summary score (higher score indicates better social support). The validity and reliability of this questionnaire have been previously tested in various patient populations [29,30]. The Cronbach's α of the questionnaire in the present research was 0.88.

Information about medical variables was taken from patients' medical records. Medical variables were as follows: dialysis modality, either current or in the past (categorized as hemodialysis, peritoneal dialysis or both methods), length of dialysis period (either current or before transplantation), primary nephrologic diagnosis, presence of co-morbidity. Information about current serum creatinine and current immunosuppression protocol were searched in the group of transplanted patients as well.

Statistics

Descriptive statistics were used for sample description. Differences in continuous variables between dialysis and transplant patients as well as between dialysis on waiting list patients and transplant patients were analysed by t-test. Differences in categorical variables between dialysis and transplant patients as well as between dialysis on waiting list patients and transplant patients were analysed by χ^2-test. SPSS 12.0.2 was used for statistical analyses.

Results

Out of 103 dialysed patients with mean age of 55.9 ± 14.1 years (63 males, 40 females) 45 were on waiting list for cadaveric kidney transplantation (mean age 48.6 ± 12.7 years, 27 males and 18 females). The mean age of the group of 42 transplanted patients was 45.5 ± 12.5 years (26 males, 16 females). After matching, 62 patients (31 dialysed patients on waiting list and 31 transplant recipients) remained for analysis.

Demographic, socio-economic variables and social support are described in Table 1. Patients on dialysis were significantly older than patients after transplantation ($p \leq 0.001$). There were significantly less single ($p \leq 0.05$)

and more widowed ($p \leq 0.05$) persons among dialysed patients. When matched pairs were compared, no significant differences in demographic, socio-economic variables and social support were found.

Medical variables are presented in Table 2. Majority of patients had hemodialysis as their elimination modality, but it was more frequent in the dialysed group than in the transplanted group ($p \leq 0.01$). There were more cases who switched the elimination therapy in the transplant group when compared to whole dialysis patients ($p \leq 0.01$) or dialysis patients on waiting list ($p \leq 0.01$). Patients on dialysis differed significantly from those after transplantation in their primary nephrologic diagnosis – there were less glomerulonephritis ($p \leq 0.01$) and more polycystic kidney diseases ($p \leq 0.05$) among dialysed patients. Marked differences were found in co-morbid conditions as dialysed patients more frequently suffered from heart diseases ($p \leq 0.001$) and severe anemia ($p \leq 0.01$). Dialysed patients on waiting list had more often severe anemia when compared to transplant recipients ($p \leq 0.05$). When co-morbidity index was calculated, two thirds of dialysed patients belonged to high-risk category and one quarter to intermediate-risk category. Among transplant recipients these ratios were nearly reversed ($p \leq 0.001$). Patients on waiting list did not differ significantly from those after transplantation in distribution of their co-morbidity index. When matched pairs were compared, no significant differences in medical variables were found except for more frequent anemia among dialysed patients ($p \leq 0.05$).

Patients on dialysis on waiting list and not on waiting list together reported worse physical (37.7 ± 23.3) and mental (50.6 ± 19.4) perceived health status than patients after kidney transplantation (54.2 ± 20.5 and 60.7 ± 20.0, $p \leq 0.001$ and $p \leq 0.01$, respectively). If patients after kidney transplantation were compared to their matched pairs on waiting list, no differences in perceived health status were found (Table 3).

Discussion

The present study confirmed the fact that patients after kidney transplantation feel better than those on dialysis [13]. Physical component of perceived health status is reduced in dialysis patients in particular. In contrast to previous research, we have shown that this is not true when comparing perceived health status of transplant recipients to their matched pairs (with the same age, gender and co-morbidity) on waiting list.

Majority of papers confirmed sharp differences in age between general dialysis population and kidney transplant recipients [2,6,8,9,13,16]. In the present study, the sample of all dialysed patients was older than transplant recipients in average of 10 years. There are other demographic,

social variables and social support, which are potential confounders. Our sample did not present significant differences in these variables, despite in dialysed patients was a different distribution of family status from those after transplantation.

It is common to control for medical variables in graft or patient survival analyses. Dialysed patients in the present research suffered more from cardiovascular diseases and anemia when compared to transplant recipients. But in the research focused on differences in quality of life among various end-stage renal disease treatment modalities this is often neglected. Primary diagnosis or co-morbidity is usually presented, but seldom included into analyses [3,8]. However, the best way how to avoid confounding is to stratify the sample or to conduct a matched pairs study.

The present study has some weaknesses to be mentioned. The number of participants was not high as we included 145 patients with end-stage renal disease treated by dialysis or transplantation. Majority of studies on this topic contained a similar number of patients, but there are exceptions, unfortunately with no matching [13] or matching for age and gender only [15]. The design of our research was cross-sectional, therefore it is not possible to evaluate the effect of time after transplant surgery. In contrast to our approach, Laupacis et al. evaluated 168 patients within the period of 19.5 months and found an improvement in health status 6 months after transplantation [2]. It seems to be of value to continue in our study and examine all participants after one year. But it is necessary to calculate with the fact that small fraction of dialysed patients on waiting list would move to transplant category, reducing the sample [18]. Another problem of the interpretation of present research is in the tool, which was used. The SF-36 is the questionnaire designed for evaluation of perceived health status. This mesure is definitely not equal to quality of life, as the later term covers much broader aspects. So, the differences in instruments might be the source of contrary conclusions.

Perceived health status after kidney transplantation is much better than on dialysis. However, this statement is significantly influenced by a selection bias as only some dialysed patients are put onto waiting list and some of them are actually transplanted. When the correction of this bias is done using matching criteria (age, gender and co-morbidity), differences in perceived health status disappear. The consequences for clinical practice are aimed at the group of patients on dialysis awaiting for transplantation. They expect improvement in their health status after successful transplantation, but are often encountered with new health complaints, including adverse effects of immunosuppressive drugs, fear from rejection and infection or anxiety about long-term kidney function [31-34]. Therefore intensive attention should be paid not only to transplant recipients, but to patients on waiting list as well.

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Table 1 Basic characteristics of all dialysed patients, dialysed patients on waiting list, all transplanted patients, and the matched pairs of patients on waiting list and after transplantation

		D N = 103	WL N = 45	Tx N = 42	matched WL N = 31	matched Tx N = 31
age (years)		55.9±14.1***	48.6±12.7	45.5±12.5	46.6±12.3	46.7±13.3
gender	male	61.2 %	60.0 %	61.9 %	67.7 %	67.7 %
	female	38.8 %	40.0 %	38.1 %	32.3 %	32.3 %
education	elementary	60.2 %	64.5 %	51.9 %	61.3 %	54.8 %
	secondary	32.0 %	28.9 %	33.3 %	29.0 %	38.7 %
	university	7.8 %	6.7 %	4.8 %	9.7 %	6.5 %
employment status	employed	10.5 %	17.8 %	17.1 %	22.6 %	19.4 %
	not employed	89.5 %	82.2 %	82.9 %	77.4 %	80.0 %
housekeeping (hours/week)		17.8±14.7	22.3±13.2	19.7±18.5	23.6±13.3	17.6±16.8
family status	single	12.6 % *	22.2 %	29.3 %	19.4 %	33.3 %
	married	71.8 %	73.3 %	65.9 %	80.6 %	60.0 %
	divorced	1.9 %	0.0 %	4.9 %	0.0 %	6.7 %
	widowed	13.6 % *	4.4 %	0.0 %	0.0 %	0.0 %
social support (SSL-D)		56.2±12.4	57.2±12.5	55.0±10.9	59.4±10.8	54.2±9.9

figures are percentages or means ± standard deviations

D – dialysis patients, WL – dialysis patients on waiting list, Tx – transplanted patients

* – significant difference when compared to all transplanted patients ($p \leq 0.05$)

*** – significant difference when compared to all transplanted patients ($p \leq 0.001$)

Table 2 Medical characteristics of all dialysed patients, dialysed patients on waiting list, all transplanted patients, and the matched pairs of patients on waiting list and after transplantation

		D N = 103	WL N = 45	Tx N = 42	matched WL N = 31	matched Tx N = 31
dialysis modality	hemodialysis	88.3 % **	84.4 %	69.0 %	83.9 %	74.2 %
	peritoneal dialysis	7.8 %	13.3 %	9.5 %	16.1 %	9.7 %
	both modalities	3.9 % **	2.2 % **	21.4 %	0.0 %	16.1 %
dialysis duration (years)		3.7±3.5	4.0±3.7	4.2±2.8	3.4±2.9	4.2±2.8
primary diagnosis	glomerulonephritis	23.3 % **	33.3 %	47.6 %	38.7 %	41.9 %
	tubulointerstitial nephritis	32.0 %	26.7 %	35.7 %	19.4 %	41.9 %
	diabetic nephropathy	20.4 %	8.9 %	7.1 %	9.7 %	9.7 %
	polycystic kidneys	10.7 % *	8.9 %	0.0 %	8.7 %	0.0 %
	other or unknown	13.6 %	22.2 %	9.6 %	23.5 %	6.5 %
co-morbidity	diabetes mellitus	35.0 %	20.0 %	26.2 %	25.8 %	35.5 %
	hypertension	94.2 %	97.8 %	100.0 %	96.8 %	100.0 %
	heart diseases	63.1 % ***	46.7 %	28.6 %	35.5 %	25.8 %
	stroke	15.5 %	13.3 %	11.9 %	12.9 %	12.9 %
	hepatitis	10.7 %	8.9 %	9.5 %	6.5 %	6.5 %
	anemia	32.0 % **	26.7 % *	7.1 %	29.0 % #	6.5 %
	cancer	8.7 %	8.9 %	0.0 %	9.7 %	0.0 %
	bone disease	28.2 %	24.4 %	21.4 %	22.6 %	22.6 %
co-morbidity index	low-risk	3.9 %	6.7 %	7.1 %	9.7 %	9.7 %
	intermediate-risk	26.2 % ***	37.8 %	54.8 %	38.7 %	38.7 %
	high-risk	69.9 % ***	55.6 %	38.1 %	51.6 %	51.6 %
serum creatinine (µmol/l)				144 ± 48		148 ± 52
immuno-suppression	CsA + MMF + P			83.3 %		80.6 %
	Tac + MMF + P			14.3 %		16.1 %
	Tac + MMF			2.4 %		3.2 %

figures are percentages or means ± standard deviations

D – dialysis patients, WL – dialysis patients on waiting list, Tx – transplanted patients

CsA – cyclosporin A, MMF – mycophenolate mofetil, P – prednison, Tac - tacrolimus

* – a significant difference when compared to all transplanted patients ($p \leq 0.05$)

** – a significant difference when compared to all transplanted patients ($p \leq 0.01$)

*** – a significant difference when compared to all transplanted patients ($p \leq 0.001$)

– a significant difference when compared to matched transplanted patients ($p \leq 0.05$)

Table 3 Physical and mental perceived health status of all dialysed patients, dialysed patients on waiting list, all transplanted patients, and the matched pairs of patients on waiting list and after transplantation

	D N = 103	WL N = 45	Tx N = 42	matched WL N = 31	matched Tx N = 31
physical perceived health status	37.7 ± 23.3 ***	47.7 ± 22.0	54.2 ± 20.5	47.9 ± 22.9	51.7 ± 20.6
mental perceived health status	50.6 ± 19.4 **	55.9 ± 17.1	60.7 ± 20.0	58.2 ± 18.4	60.5 ± 19.9

figures are means ± standard deviations

D – dialysis patients, WL – dialysis patients on waiting list, Tx – transplanted patients

** – a significant difference when compared to all transplanted patients ($p \leq 0.01$)

*** – a significant difference when compared to all transplanted patients ($p \leq 0.001$)

Do dialysis- and transplantation-related medical factors affect perceived health status?

Do dialysis- and transplantation-related medical factors affect perceived health status? Rosenberger J, van Dijk JP, Nagyova I, Roland R, Madarasova Geckova A, van den Heuvel WJA, Groothoff JW. Nephrol Dial Transplant 2005, 20, 2153-2158. doi: 10.1093/ndt/gfh965

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Abstract

Background: Quality of life and perceived health status (PHS) are important indicators of patient care together with morbidity, mortality and health-care resource utilization. The aim of this study is to explore how various medical conditions might influence perceived health status.

Methods: The study sample consisted of 128 kidney transplant recipients. PHS was measured using the self-administered SF-36 questionnaire. Stepwise linear regression analysis of 17 demographic, dialysis-, transplantation- and co-morbidity-related factors was performed in order to explore predictors of worse PHS.

Results: Older age, female gender, lower education, increased number of hospitalizations during the dialysis period and diabetes mellitus were identified as significant predictors of worse PHS. Age was the most important predictor of PHS, explaining 23.3 % of variance in the SF-36

physical component and 4.4 % in the SF-36 mental component. Between age groups, major differences were found in predictors of perceived health status – serum creatinine was the most important for patients younger than 45 years and the number of hospitalizations for patients of 45 years and over.
Conclusions: Biological and medical factors are significant predictors of the physical component of PHS, although they can explain only up to one third of its variance. Other dimensions of PHS are weakly influenced by these medical parameters. It seems important to evaluate perceived health status separately among the age groups because they differ in their predictors.

Introduction

Kidney transplantation is the method of choice among renal replacement therapies due to its superior results in morbidity, mortality, cost utilization and quality of life in comparison with dialysis [1,2]. A wide range of factors is already known to influence morbidity and mortality of transplanted patients. Less information is available about those variables that have an impact on quality of life.

The World Health Organization Quality of Life (WHOQoL) assessment group has defined quality of life as 'Individuals' perception of their position in life in the context of the culture and the value system in which they live and in relation to their goals, expectations, standards and concerns' [3]. Quality of life according to the WHO definition [3] is a multidimensional construct comprising physical, mental, social and economic components [3-5]. Spilker's hierarchical model includes overall quality of life, separate domains of quality of life, as well as a third level covering more specific aspects of each domain [5]. Due to the complexity of each domain there are many factors that can influence quality of life somehow, including demographic, psychosocial and medical parameters. It is for this reason that so many different methods are used for evaluation of quality of life [6]. Depending on the method chosen, various factors are identified as predictors of good or bad quality of life. The major problem in this field is the lack of clear definitions and measures for quality of life and the related terms. Quality of life is an umbrella term and is often interchanged with perceived health status, functional status, self-rated health or health-related quality of life [7]. It is evident that various disease-specific parameters that can affect health are important factors in quality of life. Many researchers therefore call it "health-related quality of life" [8], while others refuse such simplification and prefer term "perceived health status" [7]. In this research paper the authors have decided to use the term perceived health status because it seems the most appropriate. Despite the uncertainty in definitions health-related quality of life or perceived

health status is not a mere construct devoid of clinical relevance. Recent research has shown that it is a very important predictor of other outcomes in patients with chronic renal disease [8,9].

The research into quality of life after kidney transplantation is mostly focused on the description of its determinants using univariate statistics. With these methods, a variety of medical and non-medical factors have been identified as characteristics of perceived health status. Unfortunately, research with more proper analysis of predictive variables is scarce. Searching the literature, we identified six such studies [2,10-14]. Griva et al. found among 347 transplant recipients that worry about the transplant is a predictor of the mental component of SF-36, whereas age, income, co-morbidity and time on dialysis predict the results in the physical component of SF-36 [11]. The study by Siegal et al. analyzed 3676 kidney transplant recipients on cyclosporin-based immunosuppression. The authors found significant influence of co-morbid conditions on perceived health status, but they rated joint and eye diseases as the most important psychological problems, as well as the presence of side-effects of immunosuppression. In their study the presence of co-morbidity was assessed by patient self-referral, which could decrease the true frequency level of various diseases [14]. A longitudinal study of 68 patients by Hathaway et al. identified employment status, 6-months hospital admittance, age, education and social support to be predictors of perceived health status [12]. Wight et al. compared cohorts of 292 dialysis and 228 transplanted patients and they found higher age, female gender and lower hemoglobin to be predictors of worse physical functioning in kidney transplant recipients. As the most important predictor they reported age [2]. Julius et al. studied a cohort of 459 end-stage renal disease patients including transplanted patients. Race, age, diabetes mellitus as primary cause of renal failure, co-morbidity and modality of treatment were significantly related to physical dysfunction. However, Julius et al. did not describe separate analysis exclusively for transplanted patients [13]. Fujisawa et al. analyzed 117 transplanted patients and found serum creatinine to be the predictor of results in physical functioning, general health perceptions and vitality scales of the SF-36 questionnaire [10]. All but the last two above-mentioned studies identified mostly non-medical factors as predictors of perceived health status; of the biological and medical variables, age and co-morbidity are the most relevant.

Despite many studies in this field there are still doubts about the importance of medical factors for perceived health status after kidney transplantation [4]. The direct relationship between adverse medical conditions and mortality is well known in nephrology. Diabetes, cardio-vascular morbidity and anemia are the conditions most negatively associated with survival. An important question then arises – do medical factors play a similar role in perceived health status and its dimensions?

The aim of this study is to explore how various medical conditions controlled for basic demographic factors might influence perceived health status in patients after kidney transplantation.

Subjects and methods

Patients

Out of 208 adult kidney transplant recipients with a functioning graft, transplanted more than 3 months ago and less than 7 years ago, 128 responded and returned the completed questionnaire (response rate 61.5 %). Nonresponders did not differ either in age, gender, education or employment status significantly from the analysed group (p=0.125, 0.505, 0.062 and 0.093, respectively). Data collection took place from September 2002 to February 2004 in two transplant centers in Slovakia (Košice and Bratislava). Five patients with severe dementia or mental retardation were not invited to participate (the only exclusion criterium). All patients signed an informed consent before the interview. The local ethical committee approved the study.

Methods

Patient medical records were searched for information about their dialysis treatment before transplantation (hemodialysis, peritoneal dialysis or both methods), dialysis duration before transplantation, number of hospitalizations before and after transplantation, graft source (cadaveric, living), time since transplantation, number of acute rejection episodes, current immunosuppressive therapy, current serum creatinine and the presence or lack of co-morbid diseases (hypertension, heart disease, diabetes mellitus, stroke, peripheral artery disease, anemia, cancer, bone disease, other clinically relevant serious diseases).

Each patient completed the SF-36 questionnaire form. The Short-Form Health Survey (SF-36) is a 36-item questionnaire for assessment of perceived health status. The SF-36 consists of 8 sub-scales: bodily pain, physical functioning, physical role limitations, general health perceptions, vitality, emotional role limitations, mental health, and social functioning. The first four sub-scales can be combined as the physical summary component and the last four as the mental summary component. All sub-scales as well as the summary components are presented as scores between 0 and 100, with higher scores meaning better health. The validity and reliability of SF-36 have been tested in patients with renal disease, including those after kidney transplantation [2,9,10]. Skalská et al. validated the questionnaire in the Czech population [15]. The Cronbach α in the present sample was 0.83, while the Cronbach α for each sub-scale varied between 0.76 (for emotional role limitations) and 0.91 (for physical functioning).

Statistics

Stepwise linear regression was used for analysis of relation between gender, age, education, employment status, medical characteristics and the SF-36 sub-scales. The analyses were performed with the total patient sample as well as with the sample divided into patients younger than 45 years and those aged 45 years and more.

Gender, age, education and employment status were used for demographic description of the patient sample.

Dialysis-related factors were considered to be: type of dialysis treatment before transplantation, duration of dialysis treatment and number of hospitalizations during dialysis period (none, 1-3, 4-5, or more than 5).

Transplantation-related characteristics were as follows: time since transplantation, number of hospitalizations after transplantation (none, 1-3, 4-5, or more than 5), number of acute rejection episodes, current immunosuppressive protocol and current serum creatinine.

Co-morbidity was evaluated as the presence or lack of the following diseases: hypertension, heart disease, diabetes mellitus, stroke, and other serious co-morbidity. The model did not separately explore some co-morbid diseases of possible importance, such as heart failure, anemia, peripheral vascular disease, bone disease or cancer. There is evidence that these co-morbid conditions can have an impact on perceived health status after kidney transplantation [16], but they were not included in our analysis as individual variables due to their low occurrence among the patients in our sample. We decided to create the variable "all other serious co-morbid conditions" for this purpose. For separate assessment of these potential medical factors a larger study is needed, which should definitely contain more patients with severe co-morbidity. For the same reason neither graft source nor the number of secondary transplantations were added into the model, despite the existence of studies identifying some differences in quality of life depending on these variables [11].

SPSS for Windows 11.0.1 was used for statistical analysis. The level of significance was set to $p<0.05$. The tests were two-tailed.

Results

The analyzed sample consisted of kidney transplant recipients with mean age 48.6 years; at average 28 months since their transplantation; and a median serum creatinine of 137.8 μmol/l (1.56 mg/dl). Approximately two thirds of the sample were males, and the patients were on hemodialysis treatment before transplantation for median 2.6 years. All but three patients had a kidney from a cadaveric donor. Hypertension and heart disease were the most common co-morbid diseases among the patients

(96.1 % and 31.2 %, respectively). The predominant immunosuppressive protocol was based on cyclosporin and mycophenolate mofetil (45.7 % with prednison and 10.1 % without prednison), and fewer patients were treated with the older protocol based on combination of cyclosporin and azathioprin (12.2 % cyclosporin + azathioprin + prednison, 3.2 % prednison + azathioprin, 12.8 % cyclosporin + prednison and 6.4 % cyclosporin alone). A more detailed description of the sample is given in Table 1 and Table 2.

Means and standard deviations for the eight SF-36 sub-scales for the whole sample were as follows: bodily pain 61.0 ± 26.5, physical functioning 63.6 ± 25.6, physical role limitations 46.9 ± 40.7, general health perceptions 45.1 ± 21.6, vitality 53.4 ± 19.6, emotional role limitations 61.7 ± 42.0, mental health 64.2 ± 18.6, social functioning 63.1 ± 26.8. The summary physical component score was 55.2 ± 20.9, and the summary mental component score was 60.2 ± 18.5.

Table 3 shows the results of stepwise linear regression analysis of the relationships between the selected model of parameters and the dimensions of the SF-36 questionnaire. The physical component of SF-36 was negatively associated with older age, lower education and higher number of hospitalizations during the dialysis period, while the mental component was negatively affected only by lower education and older age. The following variables played a significant role in prediction of worse results in the eight SF-36 sub-scales: older age, lower education, female gender, higher number of hospitalizations during dialysis period and presence of diabetes mellitus.

When the patient sample was split into two age groups, major differences were found (Table 4). In the group of younger patients (younger than 45 years), the most important predictor of the physical dimension of SF-36 was serum creatinine (SCr). Increased SCr was associated with worse results in the physical component of SF-36 including its physical functioning and general health perceptions sub-scales. On the other hand, the mental component of SF-36 was only influenced by education. Among older patients (45 years and more) presence of diabetes mellitus, more hospitalizations during the dialysis period and after transplantation predicted worse perceived health status.

Discussion

In general, perceived health status in the sample of transplanted patients measured by SF-36 sub-scales is lower than HRQoL in the healthy population. The results indicate that some degree of physical restriction still persists among our patients despite successful transplantation. In addition, high standard deviations (especially in the emotional and physical role limitations sub-scales) indicate major differences within the

patient sample. Similar findings of floor and ceiling effect in these two dimensions are described by other authors [2,10].

The preliminary univariate analysis of the effect of various medical factors on perceived health status found that many variables have significant association with some of the SF-36 sub-scales (the results are not shown here). These findings are in accordance with other studies [16,17]. The heterogeneity of our sample could have produce these results. Some studies have already pointed out that case mix may strongly influence the interpretation of findings, giving importance to variables which are not in fact significant [2,18]. For this reason, more complicated models and statistical methods should be considered to eliminate such misleading interpretations. This is also the reason why we chose to construct a model consisting of 17 possible bio-medical factors that can predict outcomes on SF-36, and why we analyzed it using stepwise linear regression.

Knowing the results from univariate analyses it was surprising that only a few variables proved to be significant predictors of perceived health status in regression analysis. Age is the strongest factor, explaining 23.3 % of variance in the physical and 4.4 % in the mental component of SF-36. More advanced age predicts worse results independently from other factors. When considering the eight sub-scales of SF-36, age is very important for the physical functioning, pain and general health perceptions sub-scales (explaining from 9.4 to 26.2 % of variance); in other sub-scales it plays a significant, but less important role. These results are in accordance with previous research [11,12,17].

Number of hospitalizations during the dialysis period is a significant predictor of worse results in the physical component of SF-36 and in two sub-scales, but its contribution is less than 5 %. In contrast to previous research [12], our study did not find the number of hospitalizations after transplantation to be a significant predictor of perceived health status. A possible reason for this is in the cross-sectional approach we followed, resulting in the situation that each patient was questioned in a different time period after transplantation. The type of immunosuppressive treatment is not a significant predictor of perceived health status. One possible explanation for this surprising fact is that combination therapy is usually used. The protocols consist of several drugs and their doses vary in different time periods with quick tapering after first weeks after transplant surgery. Therefore differences in adverse effects are visible even within each protocol group. Rosenberger et al. have pointed out this issue in their research [19]. Our study found that presence of diabetes mellitus weakly predicts worse scores in the physical and emotional role limitations sub-scales, and other co-morbid conditions are not significant factors at all. Heart disease predicted worse results in the physical role limitations, mental health and pain sub-scales. Its influence was borderline and non-significant. These results are in contrast to other studies [11,13,14,16,17]. However, from these papers only the studies by Griva et al., Siegal et al.

and Julius et al. used a similar approach to the one we followed, and the other authors performed univariate statistical procedures [11,13,14].

Another model including the Wright co-morbidity index was evaluated in addition to the described model of medical factors. Co-morbidity indices are commonly used for analysis of the effect of various diseases on clinical outcomes [16,17]. The Wright co-morbidity index consists of combined information about age and co-morbidity, making it potentially more sensitive. When we used it in our model instead of separate age and specific co-morbid conditions, we found it to be a significant predictor of perceived health status, although the explanation of variance was lower than in the previously presented model.

With regard to physical functioning it was found that serum creatinine is a borderline, non-significant predictive factor for perceived health status. Serum creatinine is the crucial parameter for assessment of graft function, so one can assume that it should also play an important role in perceived health status [10]. In general our results do not support this theory. On the other hand, when we separately analyzed the sub-group of patients younger than 45 years, serum creatinine became the only important factor for the physical component of SF-36, including its physical functioning and general health perceptions sub-scales (creatinine explained from 13.3 to 16.5 % of variance). In the group of older patients creatinine plays no role; the number of hospitalizations before transplantation predict physical functioning and mental health instead. In addition, fewer hospitalizations after transplantation is a predictor of better general health perceptions and vitality, and presence of diabetes mellitus predicts worse results in the physical and emotional role limitations sub-scales. These results indicate that significant differences exist between age groups. In older patients serious co-morbid conditions that require medical attention (represented by number of hospitalizations) and presence of diabetes mellitus decrease perceived health status, in contrast to younger patients, in whom kidney function is the main predictor of results in SF-36. Similar results for the relationship between SCr and perceived health status are presented by Fujisawa et al. Comparing our patient sample with the patients from that study, differences in age are visible. Patients after transplantation in that sample were younger than our patients (43.9 ± 9.1 vs. 48.6 ± 12.0 years). The patients studied by Fujisawa et al. are therefore similar to those from our "young" sub-sample, and so their results are also similar [10].

Perceived health status does not share the same predictors with quantity of life, represented by graft and patient survival. Medical variables, which are highly evaluated by physicians and form their center of attention, do not seem to play a crucial role from the patients' perspective. Other factors are rather more important, including age, gender, adverse effects of treatment [19,20] and compliance. Another category includes socio-demographic and economic factors [12].

Biological and medical factors are significant predictors of the physical component of SF-36, although they can explain only up to one third of its variance. Other dimensions of perceived health status are weakly influenced by these medical parameters. Patients should be assessed with regard to their age, because the main differences exist between the younger and the older patients. In the group of younger patients kidney function is the best predictor of SF-36 in contrast to the older patients, who are more affected by co-morbidity.

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Table 1 Description of the patient sample (N=128)

variable		N	% or mean with SD (range)
gender	male	79	61.7 %
	female	49	38.3 %
age			48.6 ± 12.3 years (18-74)
dialysis treatment before transplantation	hemodialysis	93	72.7 %
	peritoneal	20	15.6 %
	both	15	11.7 %
duration of dialysis			2.6 years (0.1-35)
number of hospitalizations during dialysis period	0	7	5.7 %
	1-3	72	58.5 %
	4-5	20	16.3 %
	> 5	24	19.5 %
graft source	cadaver donor	125	97.7 %
	living donor	3	2.3 %
secondary transplantation		4	3.1 %
time since transplantation			28 months (3-84)
number of hospitalizations after transplantation	0	52	40.9 %
	1-3	60	47.2 %
	4-5	11	8.7 %
	> 5	4	3.1 %
number of acute rejection episodes			0.53± 0.66 (0-3)
current serum creatinine			137.8 µmol/l (75-444.4) 1.56 mg/dl (0.85-5.05)

Table 2 Description of co-morbid diseases in the patient sample (N=128)

variable		N	%
hypertension	yes	123	96.1 %
	no	5	3.9 %
coronary artery disease	yes	40	31.2 %
	no	88	68.8 %
heart failure	yes	8	6.2 %
	no	120	93.8%
diabetes mellitus	yes	27	21.1 %
	no	101	78.9 %
stroke	yes	12	9.4 %
	no	116	90.6 %
peripheral vascular disease	yes	4	3.1 %
	no	124	96.9 %
anemia (hemoglobin less than 100 g/l)	yes	7	5.5 %
	no	121	94.5 %
lymphoma	yes	1	0.8 %
	no	127	99.2 %
bone disease with fractures	yes	4	3.1 %
	no	124	96.9 %
other serious co-morbidity	yes	96	75.0 %
	no	32	25.0 %

Table 3 Linear regression analysis of significant relations between selected variables and SF-36 in total sample

SF-36 sub-scale	variables	R^2 change	ß	95 % CI	p
physical component summary	age	23.3 %	-0.509	-1.089; -0.574	0.000
	education	4.5 %	0.214	1.568; 9.680	0.007
	dialysis hospitalization	2.4 %	-0.172	-7.814; -0.429	0.029
mental component summary	education	7.7 %	0.261	2.042; 9.967	0.003
	age	4.4 %	-0.229	-0.575; -0.081	0.010
bodily pain	age	13.0 %	-0.389	-1.116; -0.047	0.000
	dialysis hospitalization	4.1 %	-0.220	-1.161;-0.165	0.010
physical functioning	age	26.2 %	-0.505	-0.267; -0.146	0.000
	education	5.5 %	0.227	0.517; 2.450	0.003
	dialysis hospitalization	3.4 %	-0.199	-2.032;-0.307	0.008
physical role limitations	education	6.5 %	0.233	0.126; 0.825	0.008
	age	4.6 %	-0.194	-0.047; -0.002	0.030
	diabetes mellitus	2.8 %	-0.191	-1.404;-0.067	0.031
general health vitality	age	9.4 %	-0.318	-0.166; -0.049	0.000
	age	7.8 %	-0.264	-0.134; -0.028	0.003
	education	4.0 %	0.219	0.234; 1.927	0.013
emotional role limitations	education	5.8 %	0.242	0.110; 0.665	0.007
	diabetes mellitus	4.3 %	-0.225	-1.206;-0.158	0.011
mental health	education	4.5 %	0.230	0.303; 2.354	0.012
social functioning	education	7.6 %	0.289	0.311; 1.261	0.001

dialysis hospitalization – number of hospitalizations during dialysis period, tx hospitalization – number of hospitalization after transplantation, SCr – serum creatinine, R^2 change – % of explained variance (adjusted), ß – standardized ß coefficient, CI – confidence interval, p – p-value of significance

Table 4 Linear regression analysis of significant relations between selected variables and SF-36 in the group of patients younger than 45 years[Y] and in the group of patients aged 45 and more years[O]

SF-36 sub-scale	variables	R^2 change	ß	95 % CI	p
physical component summary	[Y]SCr	9.6 %	-0.344	-0.141; -0.010	0.026
	[O]gender	6.0 %	-0.266	-20.403;-2.047	0.017
	[O]education	4.8 %	0.243	0.620; 11.289	0.029
mental component summary	[Y]education	11.8 %	0.374	1.941; 16.773	0.015
	[O]employment status	6.8 %	0.301	6.836; 40.934	0.007
	[O]tx hospitalization	5.0 %	-0.248	-11.410;-0.811	0.024
bodily pain	[Y]dialysis hospitalization	7.4 %	-0.311	-1.750;-0.022	0.045
	[O]SCr	7.0 %	0.287	0.004; 0.026	0.010
physical functioning	[Y]SCr	16.5 %	-0.380	-0.031; -0.006	0.006
	[Y]education	8.1 %	0.405	0.712; 3.639	0.005
	[Y]gender	8.0 %	-0.317	-4.393; -0.349	0.023
	[O]dialysis hospitalization	7.4 %	-0.283	-2.858;-0.423	0.009
	[O]education	5.8 %	0.262	0.325; 2.975	0.015
physical role limitations	[Y]education	10.1 %	0.351	0.112; 1.422	0.023
	[O]diabetes mellitus	4.9 %	-0.250	-1.649;-0.109	0.026
	[O]gender	3.7 %	-0.219	-1.479;-0.003	0.049
general health	[Y]SCr	13.3 %	-0.393	-0.037; -0.005	0.010
	[O]tx hospitalization	4.1 %	-0.231	-2.635;-0.032	0.045
emotional role limitations	[Y]education	12.3 %	0.380	0.151; 1.209	0.013
	[O]diabetes mellitus	5.6 %	-0.262	-1.331;-0.111	0.021
mental health	[Y]education	10.7 %	0.359	0.384; 4.132	0.019
	[O]employment status	6.3 %	0.262	0.929; 9.497	0.018
	[O]dialysis hospitalization	3.9 %	-0.223	-2.203; -0.037	0.043
vitality	[O]employment status	5.1 %	0.268	4.428; 41.964	0.016
	[O]tx hospitalization	4.0 %	-0.228	-11.951;-0.286	0.040
social functioning	[Y]education	9.5 %	0.308	0.164; 22.382	0.047
	[O]education	6.9 %	0.263	1.366; 15.645	0.020

dialysis hospitalization – number of hospitalizations during dialysis period, tx hospitalization – number of hospitalization after transplantation, SCr – serum creatinine, R^2 change – % of explained variance (adjusted), ß – standardized ß coefficient, CI – confidence interval, p – p-value of significance

Conflict of interests: none declared

Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients

Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients. Rosenberger J, Geckova AM, van Dijk JP, Roland R, van den Heuvel WJA, Groothoff JW. Clin Transplant 2005; 19: 70-76

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Abstract

Introduction: The adverse effects of immunosuppression appear in the majority of patients with a negative impact on morbidity, mortality and quality of life. The group of adverse symptoms manifested as changes in appearance, mood and energy are often more stressful than serious metabolic changes because of their direct negative influence on patients' well-being. The aim of this study is to explore the adverse symptoms of immunosuppressive medication which are the most stressful for transplanted patients, and which are the modifying factors.

Patients and methods: 157 adult kidney transplant recipients from two transplant centres in Slovakia with a functioning graft transplanted less than 7 years ago were examined. Patients participated in an interview focusing on stress from adverse effects, and their education and social support. Medical records were searched for information about immunosuppression protocols, dialysis treatment before transplantation,

type of received organ and period after transplantation. The effect of the selected variables on the total score for stress from adverse effects was tested using ANOVA. The effect of the selected factors on stress from each single adverse effect was explored using t-test and ANOVA.
Results: The most stressful symptoms were pain, weakness, weight gain, facial changes, depression and anxiety. The mean value of the total score for stress from adverse effects was 8.03 ± 6.53 (minimum 0, maximum 30, range 0-64), indicating low stress. Women and patients with lower education significantly more often felt the adverse effects of immunosuppression as stressful ($p<0.001$ and $p<0.05$, respectively). Age, social support, dialysis modality before transplantation, time from transplantation and type of immunosuppressive treatment did not affect the total score for stress from adverse effects. However, variables that were not significant in the overall score reached significance in some symptoms.
Conclusions: Women and patients with lower education significantly more often felt the adverse effects of immunosuppression as stressful; in a more detailed analysis the use of new drugs was connected with less stress in some symptoms. The use of these drugs can improve life quality for transplant recipients, decrease non-compliance, and thus prevent graft loss.

Introduction

Successful kidney transplantation requires effective immunosuppression. However, immunosuppressive drugs are well-known for their wide range of adverse effects, which puts them in one of the top positions in the ranking of various stressors [1-3].

Among the most significant adverse effects are infections, because of their graft and life threatening potential [4]. New immunosuppressive drugs in particular are very effective in preventing acute and chronic kidney damage, but they also increase the potential for various infections [5]. Oncological adverse effects are very menacing, and the risk of acquiring cancer is 3 to 5-fold higher in transplanted patients when compared with the standard population [6,7]. The most common adverse effects are hypertension and metabolic changes (e.g. diabetes, hyperuricemia, hypercholesterolemia), and their importance lies in their negative influence on long-term cardiovascular morbidity and mortality [8,9].

Besides these well-known effects another group of adverse symptoms causes distress to transplanted patients. These emerge as the results of the complex mechanism of immunosuppressive treatment and they become manifest as changes of appearance, mood and energy [10-12]. For patients, these symptoms are often more stressful than serious metabolic changes because of the direct negative influence on their well-being [11,13]. Deterioration of well-being may even cause non-compliant behaviour [14,15], which is one of the leading causes of late acute rejection and graft loss [16-18].

Traditionally, a lot of side effects are linked to steroids. They are responsible for weight gain, weakness, negative psychological symptoms, edemas and skin changes [19,20]. Increased growth of gum and hair is usually connected with calcineurin inhibitors.

The adverse effects of immunosuppression appear in the majority of patients and they have a negative impact on morbidity and mortality as well as on quality of life. This makes their follow-up necessary [21].

The aim of this study was to explore which non-infectious, non-oncological adverse symptoms of immunosuppressive medication are the most stressful for a transplanted patient. It also focuses on the contribution of various socio-demographic, medical factors and social support to the developement of stress from these adverse effects. Finally, the study explores the role of these factors affecting stress from each separate adverse effect.

Patients and methods

Patients

Data collection took place from September 2002 till September 2003 in two transplant centres in Slovakia (Košice and Bratislava). Adult kidney transplant recipients with a functioning graft transplanted less than 7 years ago were informed about the study by their nephrologist. Out of 167 informed patients, 157 agreed to participate. The only exclusion criterion was the inability to answer questions during the interview due to severe dementia or mental retardation. All patients signed an informed consent before the interview. The study was approved by the local ethical committee.

Interview

Each patient participated in an interview with a trained interviewer focusing on the stress from adverse effects of immunosuppression. Based on literature search [19,20,22,23] and the results of a small pilot study, 16 various adverse symptoms of immunosuppression were identified. Stress from each of these adverse effects of immunosuppression was measured with a 5 point scale (0 – no stress, 1 – low stress, 2 – moderate stress, 3 – high stress, 4 – very high stress). For each patient, a total score of all adverse effects was calculated as the sum of scores in all items (possible range 0-64).

Education was categorized as elementary, secondary or university. Satisfaction with social support was also measured using a 5-point scale (1 – excellent, 2 – good, 3 – fair, 4 – poor, 5 – bad). However, after preliminary results this variable was trichotomised by merging three last categories (1 – excellent, 2 – good, 3 – bad).

Medical records
Patient medical records were searched for information about their immunosuppressive regimen, dialysis treatment before transplantation (hemodialysis, peritoneal dialysis or both methods), type of received organ (cadaveric, living) and the moment of transplantation.

Statistics
Statistical analysis was performed using SPSS 10.1.0. The effect of selected socio-demographic variables (age, gender, education), social support, dialysis modality before transplantation, time from transplantation, and immunosuppressive regimen on the total score for stress from adverse effects was tested using ANOVA. Two models were explored: one model including the main effects and all two-way interactions and one without interactions. The effect of selected factors on stress from each single adverse effect was explored using a t-test for dichotomous (age, gender, immunosuppression treatment) and one-way ANOVA for trichotomous (education, social support, time from transplantation) variables. Post-hoc tests were performed for variables that were found to be significant in ANOVA.

Results

The sample consisted mainly of middle-aged cadaveric kidney recipients with secondary education and hemodialysis treatment before transplantation. The majority of patients declared their social support as excellent or good, and the mean score for social support was 1.66 ± 0.8 (range 1-3), indicating a supportive environment. Nearly all patients had their immunosuppressive protocol based on cyclosporin, and the predominant regimen consisted of prednison, cyclosporin and mycofenolate mofetil. According to their immunosuppressive regimens patients were considered to be steroid-treated (75.8 %), cyclosporin-treated (95.4 %), mycofenolate-treated (59.5 %), azathioprin-treated (17.6 %) and tacrolimus-treated (4.6 %). A more detailed description of the patient sample is shown in Table 1.

Results of stress from each single adverse effect are presented in Table 2 in descending order according to stressfullness. The most stressful symptoms were pain, malaise, muscle weakness and major physical cosmetic changes like weight gain and facial changes, followed by psychological symptoms (depression and anxiety). The total score for stress from all items varied between 0 and 30 (possible range 0-64), and the mean value for the whole sample was 8.03 ± 6.53, indicating low mean stress.

The effects of gender, age, education, social support, modality of dialysis before transplantation, immunosuppression protocol and time from transplantation on stress from adverse effects of immunosuppression was analysed (Table 3). None of the explored two-way interactions was

significant, so only the model including main effect without interactions is described. Women compared with men ($p<0.001$), and patients with lower education compared with those with university education ($p<0.05$), more often felt the adverse effects of immunosuppression as stressful. Age, social support, dialysis modality before transplantation, time from transplantation and modality of immunosuppressive treatment did not affect the total score for stress from adverse effects.

On the other hand, the main effect of the selected variables on the score for stress is not visible in each symptom. In addition, variables that were not significant in the overall score (age, social support, modality of dialysis, time from transplantation) reached significance in some symptoms. These results are presented in Table 4. Women felt pain, malaise, weakness and physical cosmetic symptoms (weight gain, facial changes, edemas, hair loss) to be more stressful than men. Younger patients were more stressed by physical changes (hair loss, facial changes and gingival hyperplasia) and they reported less trouble with sleep. Less-educated patients more often reported depression, anxiety and stress from leg edemas and fragile skin. Patients with poor social support were more troubled by diarrhea. Patients who were on peritoneal dialysis before transplantation reported more trouble with gingival hyperplasia. Stress from facial changes and edemas was more likely present in the first months after transplantation; pain was reported more frequently in later periods.

One of the important medical factors is the immunosuppressive medication because it causes adverse effects that are sources of stress for a patient. However, immunosuppressive protocols involve several drugs, so it was impossible to include them in the analysis we performed. For this reason the analysis of the effect of separate immunosuppressive drugs (steroids, cyclosporin A, mycofenolate mofetil, azathioprin, tacrolimus) on each symptom was performed. Surprisingly, the effects were significant only in a few symptoms. When steroid (P) treatment was present, patients reported more stress from facial changes. Patients treated with azathioprin (Aza) were more stressed by diarrhea. Adversely, usage of mycofenolate mofetil (MMF) was connected with less stress from pain, malaise, skin lesions and diarrhea. There was no relationship between stress and treatment with cyclosporin (CsA) or tacrolimus (Tac).

Discussion

This study focuses on non-infectious, non-oncological adverse effects of immunosuppression which patients themselves are able to identify and rate. In contrast to Lough et al., De Geest et al. and Moons et al. [17,19,20,22,23], we only measured distress and not frequency of adverse symptoms. We found that the most stressful symptoms are pain, weakness, physical changes and psychological symptoms. In general, these results are similar

to those from earlier studies [12,20,23], but there are some differences from other studies [13,19], which are possibly caused by predominance of different immunosuppression protocols.

Pain comes at the top of the list of stressors [12,20,23]. Our patients mostly report backache related to osteoporosis, and headache. Stress from pain is gender specific with females reporting more stress than males [20,23]. As osteoporosis progressively deteriorates with time, pain is reported with increasing frequency as well. Use of mycofenolate mofetil enables steroid dose reduction and these patients report less trouble with back pain.

Malaise and muscle weakness are also rated as strong stressors by our patients. A study by Lough et al. with immunosuppression after heart transplantation found a high occurrence of fatigue distress – rated as the third item after impotence and overeating [19]. Weakness is differently perceived by the two genders. Females are more stressed by these symptoms than males. These results accord with the findings of De Geest et al. and Moons et al. Their female patients ranked stress from muscular weakness in first place in comparison with the males, who ranked it in the fourth place [20,22,23]. We found a significant reduction of stress from malaise in patients with mycofenolate mofetil treatment, probably as a result of lower steroid doses in these patients.

Major cosmetic defects – weight gain and facial changes – are also rated as strong stressors and they disturb significantly more women than men. In addition, distress from facial changes is more often reported in young patients in comparison with the older ones, and in patients in the early post-transplant period compared with those in the late post-transplant period. These differences are connected with steroid use, which is more intensive in early post-transplant period and young patients [20]. Steroid-sparing immunosuppressive regimens, as well as protocols with early withdrawal of steroids, produce fewer side effects and they improve the patient's well-being [24,25].

Patients requiring any renal replacement therapies are well-known for their considerable emotional difficulties [11-13]. It is not surprising therefore that we found psychological symptoms (depression, fear, anxiety) strongly represented in our sample. Most papers report that fear of rejection, fear of infection, uncertainty about the future and the possibility of repeated hospitalization are strong sources of anxiety and depression [1-3,10,21,26]. Sutton et al. found a significant correlation between stressor scores and coping scores [26]. Our results suggest that there is some association between education level and psychological symptoms. Higher-educated persons seem to develop more coping strategies and so they are less worried and depressed.

The rest of the assessed symptoms show lesser importance. Sleep disorders are more common in older patients, but this pattern is the same in any population. Hair loss and edemas are uncommon symptoms, and

they are felt the same way as major cosmetic defects – they stress more women and younger people. In addition, edemas are found mostly in the early post-transplant period.

Previous research rated impotence and decreased interest in sex as very stressful for males [11,13,19,20,22,23]. We were surprised by the low stressfulness of sexual dysfunction among our patients, and we failed to find any gender and age differences. In contrast to our findings, Breza et al. reported a very high prevalence of erectile dysfunction (72 %) among transplanted Slovak men in his study [27]. We may speculate that sexual troubles are still a taboo amongst the Slovak population, and our study did not intensively focus on this topic, in contrast to the study by Breza et al.

Surprisingly, our study did not identify the type of immunosupressive regimen as a significant factor affecting stress from all adverse effects. Previous research mostly studied protocols based on steroids, cyclosporin and azathioprin [9,13,16,19,20,22,23]. In contrast, the majority of patients in our sample were treated with a combination of cyclosporin, steroids and mycofenolate mofetil. Azathioprin was used only in 17.6 % of patients. Our findings showed a negative influence of steroids leading to stress from facial changes (e.g. moon face, increased hair growth). This symptom is stressful for patients in the early post-transplant period who are on higher steroid and cyclosporin doses, but after some time, when drugs are tapered down, the importance of this symptom decreases. Today, quick steroid tapering as well as lower cyclosporin levels are allowed due to the use of mycofenolate mofetil and antibodies induction therapy [28]. This leads to lower occurrence of stress from various symptoms in mycofenolat-treated patients. As a result, a well-balanced combination of immunosuppressive drugs causes fewer adverse effects and is superior to regimens used in the past. Tacrolimus was recently used only for rescue therapy in Slovakia, so very few patients were recruited into our study. Unfortunately, our tacrolimus sub-sample is too small (4.6 %) to show any significant differences. But in the light of some studies we believe that tacrolimus-based protocols produce better quality of life and fewer adverse effects when compared with cyclosporin [28-31]. There is only a limited amount of information about the impact of other new immunosuppressives on patients' life quality. However, it is believed that their use diminishes the side-effects [28].

Our aim was to explore which factors contribute to the severity of stress from adverse effects. The mean total score for stress is relatively low (8.03 out of 64) and only gender and education have a significant influence on it. Gender differences unfavorable for females are expected and the female population in general reports more stress and a lower quality of life [17,19-21,23]. Some previous findings indicate that quality of life after transplantation is negatively related to total stress but positively related to

coping [3,26]. We expect people with higher education to use more efficient coping strategies which decrease their stress. However, this statement needs further evaluation.

From the patient's perspective the most stressful non-infectious non-oncological adverse effects of immunosuppression are pain, weakness, cosmetic changes and psychological symptoms. The stress from adverse effects is higher in women and less educated patients. The type of immunosuppressive regimen does not seem to influence the overall score of stress, but the use of new drugs exhibits less stress in some symptoms. More research should be performed in this field to identify the best-balanced protocols with minimum of adverse effects. Such efforts can identify patients at risk of severe adverse effects. This could help to decrease their stress and thus improve quality of life for kidney transplant recipients. Diminished stress from adverse effects can contribute to reduction of their non-compliance and thus can help to prevent graft damage due to late acute rejection episodes, which will lead to prolonged graft and patient survival.

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Table 1 Basic description of patient sample and treatment characteristics (N=157)

variable		N	% or mean and SD (range)
gender	male	94	59.9 %
	female	63	40.1 %
age			47.7 ± 11.7 years (18.3-74)
	≤ 50 years	90	58.1 %
	> 50 years	65	41.9 %
education	elementary	28	18.7 %
	secondary	107	71.3 %
	university	15	10.0 %
social support			1.66 ± 0,8 (1-3)
	excellent	74	50.7 %
	good	53	36.3 %
	bad	19	13.0 %
organ donor	living donor	4	2.6 %
	cadaveric donor	151	97.4 %
dialysis before transplantation	hemodialysis	119	79.9 %
	peritoneal dialysis	19	12.8 %
	both	11	7.3 %
time from transplantation			37.7 ± 27.3 months (3-144)
	≤ 3 months	24	15.5 %
	4-36 months	56	36.1 %
	> 36 months	75	48.4 %
immunosuppressive regimen	CsA	11	7.1 %
	P+ CsA	24	15.6 %
	CsA + Aza	6	3.9 %
	CsA + MMF	20	13.0 %
	P + CsA + Aza	21	13.6 %
	P + CsA + MMF	65	42.2 %
	P + Tac + MMF	7	4.5 %

P – prednison, CsA – cyclosporin A, Aza – azathioprin, MMF – mycofenolate mofetil, Tac – tacrolimus

Table 2 Scores for stress from adverse effects of immunosuppression

symptom	mean and standard deviation, (range)
pain	0.90 ± 1.05
malaise	0.87 ± 1.01
muscle weakness	0.79 ± 0.96
weight gain	0.77 ± 1.00
facial changes	0.66 ± 0.94
depression	0.58 ± 0.94
fear, anxiety	0.58 ± 0.95
sleep disorders	0.49 ± 0.84
gingival hyperplasia	0.43 ± 0.89
skin leasions	0.38 ± 0.83
leg edemas	0.38 ± 0.80
hair loss	0.34 ± 0.82
sexual dysfunction	0.33 ± 0.81
facial edemas	0.22 ± 0.52
diarrhea	0.18 ± 0.56
fragile skin	0.12 ± 0.47
mean total score for stress from all items	8.03 ± 6.53 (0-30)

Table 3 Effects of selected factors on total score for stress from adverse effects of immunosuppression

factor		mean and SD	p-value
gender	male	6.28 ± 5.51	0.000 ***
	female	10.46 ± 7.00	
age	≤ 50 years	8.06 ± 6.62	0.540
	> 50 years	7.62 ± 6.22	
education	elementary	9.96 ± 8.16	0.027 *
	secondary	7.89 ± 5.90	
	university	3.57 ± 3.92	
social support	excellent	7.51 ± 6.15	0.559
	good	8.31 ± 6.42	
	bad	8.06 ± 7.77	
dialysis before transplantation	hemodialysis	8.00 ± 6.47	0.671
	peritoneal dialysis	7.61 ± 6.48	
	both modalities	7.00 ± 6.48	
time from transplantation	≤ 3 months	7.38 ± 5.27	0.555
	4 to 36 months	6.92 ± 5.87	
	> 36 months	8.71 ± 7.06	
immunosuppression protocol	CsA	7.60 ± 6.59	0.612
	P, CsA	9.61 ± 8.05	
	CsA, Aza	5.33 ± 4.41	
	CsA, MMF	6.88 ± 5.35	
	P, CsA, Aza	9.90 ± 7.03	
	P, CsA, MMF	7.07 ± 5.99	
	P, Tac, MMF	8.14 ± 5.58	

P – prednison, CsA – cyclosporin A, Aza – azathioprin, MMF – mycofenolate mofetil, Tac – tacrolimus

Table 4 Efects of selected factors on stress from each separate adverse effect of immunosuppression

symptom	gender (female)	age (young)	education (low)	SoS (low)	dialysis (peritoneal)	time (≤3mn)	type of immunosuppression				
							P	CsA	MMF	Aza	Tac
pain	↑***	ns	ns	ns	ns	↓*	ns	ns	↓**	ns	ns
malaise	↑**	ns	ns	ns	ns	ns	ns	ns	↓*	ns	ns
muscle weakness	↑**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
weight gain	↑**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
facial changes	↑**	↑*	ns	ns	ns	↑**	↑**	ns	ns	ns	ns
depression	ns	ns	↑*	ns	ns	ns	ns	ns	ns	ns	ns
fear, anxiety	ns	ns	↑*	ns	ns	ns	ns	ns	ns	ns	ns
sleep disorders	ns	↓***	ns	ns	ns	ns	ns	ns	ns	ns	ns
gingival hyperplasia	ns	↑*	ns	ns	↑*	ns	ns	ns	ns	ns	ns
skin lesions	ns	ns	ns	ns	ns	ns	ns	ns	↓*	ns	ns
leg edemas	↑**	ns	↑*	ns	ns	↑*	ns	ns	ns	ns	ns
hair loss	↑*	↑*	ns	ns	ns	ns	ns	ns	ns	ns	ns
sexual dysfunction	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
facial edemas	↑**	ns	ns	ns	ns	↑*	ns	ns	ns	ns	ns
diarrhea	ns	ns	ns	↑***	ns	ns	ns	ns	↓*	↑**	ns
fragile skin	ns	ns	↑**	ns	ns	ns	ns	ns	ns	ns	ns

SoS – satisfaction with social support, dialysis – dialysis modality before transplantation, time – time from transplantation
P – prednison, CsA – cyclosporin A, Aza – azathioprin, MMF – mycofenolate mofetil, Tac – tacrolimus
ns – not significant, * – p≤0,05, ** – p≤0,01, *** – p≤0,001
↑(↓) – variable shows increased (decreased) stress in displayed reference category (in parenthesis below main category)

Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients

Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. Rosenberger J, Madarasova Geckova A, van Dijk JP, Nagyova I, Roland R, van den Heuvel WJA, Groothoff JW. Transplant Int 2005, 18, 1072-1078. doi: 10.1111/j.1432-2277.2005.00183.x

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Abstract

Noncompliance with the therapy is one possible explanation for the observation that long-term graft survival is not sufficiently improved by the development in immunosuppression.
The aim of the study was to explore the prevalence, characteristics and risk factors of noncompliance with immunosuppression. 161 adult kidney transplant recipients were interviewed about their self-rated health, social support, education, stress from adverse effects and compliance with the immunosuppression.
Prevalence of subclinical noncompliance was 54%. Noncompliant patients declared significantly worse self-rated health, less satisfaction with social support and higher stress from adverse effects. Male gender (OR 7.5, CI

2.4-23.39), high stress from adverse effects (OR 12.27, CI 2.44-61.88), fair self-rated health (OR 4.45, CI 1.04-19.55) and fair satisfaction with social support (OR 4.55, CI 1.08-19.24) were predictors of noncompliance.
Standardized detection methods should be developed with the aim of identifying patients who are at risk of noncompliance in order to prevent graft loss.

Introduction

The important prerequisite and necessary condition for sucessful organ transplantation is effective immunosuppressive therapy. New potent immunosuppressive drugs are available for clinical use today and they dramatically decrease the number and severity of acute rejection episodes in the early post-transplant period. Unfortunately, long-term graft survival is not improved in the same manner. One possible factor is patient noncompliance, which emerges as a major problem in modern transplantology, because all regimens have one thing in common – their effect depends on patients' willingness to accept the use of medication and properly follow the treatment.

A variety of explanations has been suggested to describe the causes and the determinants of noncompliance. It seems that at least five complex factors play a significant role in increased noncompliance: higher prevalence of side-effects of medication, reduced social support, pre-transplant noncompliance, low socio-economic status, and certain psychological and personality characteristics of the patient (e. g. presence of anxiety, depression, cognitive disorder, the use of avoidant coping strategies). However, none of these factors seems to lead to absolute predisposition to noncompliance [1-5].

There is no doubt that major noncompliance is an important cause of acute rejection episodes and severe graft damage. Major noncompliance is the situation when a patient dramatically violates the immunosuppressive regime with following rejection episode and graft loss as a consequence. Fortunately major noncompliance is a rather rare situation, occurring only in about 5 % of patients [6]. Less accurate data are known about subclinical noncompliance, which involves violation of treatment assessed in the absence of any apparent rejection episode or graft loss. This is due to difficulties with the measurement of subclinical noncompliance, because this phenomenon is hidden and it requires specific instruments for its detection [3,5,7]. Depending on the detection method, its prevalence varies between 15 and 53 % [2,7]. Such a wide interval demonstrates that more precise detection methods are needed for getting a realistic insight into noncompliance and its clinical consequences. Subclinical noncompliance is mostly represented by patients taking lower doses of medication, prolonging intervals between doses or forgetting to

take immunosuppressive medication [8-10]. The assessment of subclinical noncompliance encounters a methodological problem – there is no golden standard which can be used for its evaluation. This leads to heterogeneity of results in different studies [2,7,8,11]. It seems that electronic monitoring produces the most accurate results, but its use in daily practice is impossible. So self-reporting in an interview with an independent researcher is often taken as the measure of choice for use in routine clinical practice [12,13]. However, even the best interview system always omits some patients who refuse to declare their noncompliance. This is the reason why in our study we decided to combine the self-reporting method with the assessment of noncompliance by a transplant physician who also has some reliable methods of detection of noncompliance (e. g. information about CsA levels, knowledge about the amount of prescribed immunosuppressive medication).

Despite the ˝minority˝ of subclinical noncompliance in comparison to major noncompliance, the consequences are very negative in terms of the final clinical outcome. The detection of noncompliers is a permanent concern of the transplant team, because noncompliance is associated with higher frequency of late graft dysfunction, which is directly related to graft loss [1,2,14,15]. In addition, noncompliance is associated with significantly decreased quality of life [9,16].

The aim of this study is to examine the prevalence of subclinical noncompliance in kidney transplant recipients and to explore its characteristics. In addition, the study focuses on the identification of risk factors for noncompliant behaviour.

Materials and Methods

Patients

Data collection took place between September 2002 and September 2003 in two transplant centres in the Slovak Republic (Košice and Bratislava). All adult kidney transplant recipients with functioning graft, transplanted more than 3 months and less than 7 years previously, were informed about the study by their nephrologist. Patients were not interviewed during any acute disease requiring hospitalization. Five patients with severe dementia or mental retardation were excluded. 161 out of 171 patients agreed with their participation in this study (response rate 94.1 %). Due to incomplete data 22 patients were omitted from the analysis, so the remaining number of patients was 139 (effective response rate 81.3 %). All patients signed an informed consent statement before interview. The study was approved by the local ethical committee.

Procedures and measures

After literature search [2,7,17] a small pilot study was performed (N=11,

January 2002). The main aim was to assess the comprehensibility of selected instruments for patients. The interview was constructed based on the results from this pilot study, which included the list of 16 various adverse effects of immunosuppression that can contribute to noncompliance (Table 1). Stress from each of these adverse effects of immunosuppresion was measured on a 5 point scale (0 – no stress, 1 – low stress, 2 – moderate stress, 3 – high stress, 4 – very high stress). For each patient a total score of all adverse effects was calculated as the sum of scores in all items.
Each patient participated in a structured interview with trained interviewers focused on self-rated health, social support, education, stress from adverse effects of immunosuppression and compliance with the immunosuppressive therapy.

Self-rated health was assessed on a 5 point scale (1 – excellent, 2 – good, 3 – average, 4 – fair, 5 – bad) using the first item from the standardized SF-36 questionnaire. Satisfaction with social support was measured on a 5 point scale (1 – excellent, 2 – good, 3 – average, 4 – fair, 5 – bad). Both scales were recoded after preliminary analysis into 3 point scales due to the low number of patients in categories 4 and 5, merging the last three categories together. The scales were changed as follows: 1 – excellent, 2 – good, 3 – fair. Patients defined their highest level of education as elementary, secondary or university.

Compliance with the immunosuppression therapy was measured on a 5 point scale: 1 – excellent, hardly ever modify the treatment (no more than once per last month); 2 – good, rarely modify the treatment (2-3x per last month); 3 – average, sometimes modify the treatment (once a week); 4 – fair, often modify the treatment (more than once a week), 5 – bad, always modify the treatment. Modification of treatment was explained as missing a dose, prolonging the intervals between doses by more than two hours or changing the dose of immunosuppressants. The nephrologist was interviewed about each patient's compliance with the immunosuppression therapy using the same scale as well. No specific single method was imposed on the nephrologist to identify noncompliance. Nephrologists mostly based their opinion on cyclosporin level variations or knowledge about prescribed and used immunosuppressants. Patients were considered to be compliant only if they declared their compliance by themselves as excellent, in accord with their physician's opinion.

Patient medical records were searched for information about their immunosuppressive regimens, dialysis treatment before transplantation (hemodialysis, peritoneal dialysis or both methods), graft source (cadaveric, living) and time from transplantation.

Statistical analyses

Differences between noncompliant and compliant patients were analysed by t-test or Mann-Whittney U test for continuous variables (age, summary

score of stress from immunosuppression, time from transplantation) and χ^2-test or Fisher exact test for categorical variables (gender, self-rated health, social support, education, immunosuppressive regimen, dialysis modality before transplantation). Logistic regression was used to predict the risk factors of noncompliance. Noncompliance was the dependent variable; independent variables were the following: gender; age (dichotomized into patients younger than 50 years and older); period of transplantation (trichotomized into a group less than 4 months after transplantation, patients between 4 and 36 months after transplantation and those more than 36 months after transplantation); immunosuppressive protocol; self-rated health; the summary score of stress from adverse effects, trichotomized into patients with high stress (score higher than 12; the fourth quartile), medium stress (score 6-12; the third quartile) and low stress (score less than 6; the first and second quartiles); social support; education; and modality of dialysis before transplantation. Cutoffs for dichotomization and trichotomization were based on data distribution.
Statistical analyses were performed using SPSS 10.1.0.

Results

A basic description of the patient sample is given in Table 2 (N=139). In general the sample consisted of more men than women (58.1% vs. 41.9%), patients were of middle age (mean age 47.7 years), they had secondary education (71.3 %) and they were on hemodialysis before transplantation (79.9 %). The majority of organs were from cadaveric donors (97.5 %). The predominant immunosuppression protocol consisted of cyclosporin, mycophenolate mofetil and prednison. The mean serum creatinine was 154.3 ± 63.2 μmol/l.
On average the patients reported good health (self-rated health mean score 2.01±0.8), a supportive environment (social support mean score 1.66 ± 0.8), and relatively low stress from adverse effects (mean summary score 8.03 ± 6.5; range 0-64). The highest stressors were malaise, pain, muscle weakness, weight gain, facial changes, depression and anxiety [18]. Adverse symptoms are presented in Table 1. Noncompliant patients declared more stress from all adverse symptoms; the differences are significant for gingival hyperplasia ($p \leq 0.001$), weight gain ($p \leq 0.05$) and depression ($p \leq 0.05$).
We asked the patients and their physicians about compliance with the immunosuppressive treatment (Table 3). During the interview 95 patients out of 139 (68.3 %) rated themselves as excellent compliers with their immunosuppressive treatment. On the other hand, their nephrologist categorized 82 out of 139 (59.0 %) as excellent compliers. When a combination was used for compliance assessment, 64 patients (46.0 %) were considered to be compliant and the rest (54.0 %) as noncompliant. In

one patient noncompliance was considered to be major, resulting in graft loss.

Table 4 shows the characteristics of compliant and noncompliant patients. Noncompliant kidney graft recipients suffered more from adverse effects of immunosuppression (p=0.003), they experienced worse health (p=0.011) and less satisfaction with social support (p=0.027). Patients on combination cyclosporin with MMF were less compliant with the therapy in comparison with the other protocols (p=0.049). Compliers did not differ from noncompliers in other variables.

Risk factors for noncompliant behaviour were examined using logistic regression (Table 5). Male gender was associated with 7.5-times greater chance of being noncompliant when compared with female gender (p=0.001). High stress from adverse effects of immunosuppression was a significant risk factor of noncompliance (p=0.002). Patients with high stress had 12.3-times higher probability of being noncompliant in contrast to those with low stress. However, medium stress was not a risk factor of noncompliance. Patients with fair self-reported health had 4.5-times greater chance of being noncompliant in comparison with those with better self-reported health (p=0.045). Patients with fair satisfaction with their social support had 4.5-times increased chance of noncompliance in comparison with those with better social support (p=0.039). None of the other analysed variables (age, period from transplantation, immunosuppressive protocol, education, and modality of dialysis before transplantation) was identified as a significant risk factor of noncompliance. The best regression model presented in Table 5 explained 39.4 % variance.

Discussion

Using self-reports, 31.7 % of patients rated themselves as noncompliers; adding the physician's opinion this number increased to 54 %, which is a more realistic figure than the wide interval of 15-53 % presented in previous studies [2,7,19-23]. This level of subclinical noncompliance is quite high compared with previous studies [11], but it is due to the very strict definition we chose to use. Patients and their physicians shared the same opinion in 64.7 % of cases (in 64 cases both sides declared full compliance and in 26 cases noncompliance), while in 35.3 % they had different opinions. Combining these two measures together definitely increased the rate of detection of false noncompliers, although it decreased the number of false compliers, which is of high clinical importance. Their detection is a prerequisite for possible actions aiming at improving of compliance and therefore reducing the threat of rejection.

The logistic regression analysis of risk factors identified four significant variables leading to noncompliance in our sample – male gender (7.5-times higher risk), high stress from adverse effects of immunosuppression

(12.3-times higher risk), worse self-rated health (4.5-times higher risk) and fair satisfaction with social support (4.5-times higher risk). There exists some diversity in findings of risk factors of noncompliance among various studies depending on the method of compliance assessment, statistical analysis and the composition of studied samples. The majority of studies found younger age as a significant risk factor [19-22,24]. However, pediatric patients were included in these studies in contrast to our research, where only 10 % of included patients were of age younger than 30 years.

Frazier et al. demonstrated on self-reports from 241 kidney transplant recipients that female gender and marital status is connected with noncompliant behaviour. In their analysis transplant-related stress was revealed as the strongest predictor of noncompliance, explaining 12 % variance, and gender and marital status together accounted for only 8 % of explained variance [24]. In contrast, Kiley et al. found among 105 renal allograft recipients that male gender was associated with noncompliance with the medication [25]. These results are in concordance with our findings, although their definition of noncompliance was based on cyclosporine levels and the statistical approach was quite different from ours. Other studies did not show gender to be a risk factor of noncompliance; their definitions of noncompliance were based on self-reports from mailed questionnaires [19,20]. These results are in accordance with previous research regarding gender differences in health – females usually report worse health indicators despite their mortality and morbidity being lower than in the male population. According to Gijsbers van Wijk and Kolk, females perceive health problems more precisely and accurately than males, who are inclined to deny them [26].

Patients with low socio-economic status were found to be at risk of becoming noncompliant in six studies [19-21,24,25,27]. This variable was partially assessed in our study, and we used education as an indicator, although we still did not find it to be a risk factor for noncompliance. One possible explanation for this fact can be that all immunosuppressive medication as well as erythropoetin is fully covered by the compulsory health insurance in Slovakia and every patient receives it free of charge. Other drugs (antihypertensives, diuretics, vitamin supplements, etc.) are partially covered by the health insurance and patients have to pay approximately 2-13 € per month for this additional medication. Secondly, our sample contained only 15 patients with elementary education and such a low number of people at possible risk could affect the results as well. We found high stress from adverse effects to be a very important risk factor of noncompliance, similarly to studies by DeGeest et al. [2], Frazier et al. [24] and Raiz et al. [20]. Some studies found psychological factors, including depression, anxiety, patient's beliefs and coping strategies, to be predictors of noncompliance [1,28,29]. These variables were not assessed in our study and one might expect them to be behind the unexplained

variance of noncompliance. These factors require a study with use of valid and reliable instruments to assess their possible influence on patients' compliance. However, adding more psychological questionnaires could decrease the cooperation of patients and lower their response rate, so we deceided not to evaluate them. Another possible predictor which was not evaluated in our study was pretransplant noncompliance, which can be (validly) measured only before transplantation. The design of our study was cross-sectional and the recruited patients were questioned at various times after transplantation (3 months – 7 years). Measurement of pretransplant noncompliance retrospectively in such a study might produce questionable results.

The results of the present study also demonstrate that self-rated health affects compliance. Previously this parameter was known to be a predictor of morbidity and mortality [4,30], but it seems that it plays a crucial role in patients' adherence to the therapy as well. This means that self-rated health can be used as a cheap and easily-measurable predictor of noncompliance in routine clinical practice.

In accord with previous research, social support was found to be an important predictor of noncompliance [2]. While some researchers use marital status as a proxy of social support, others prefer complex validated questionnaires. In our study we decided to ask about satisfaction with patients' social support, which seems to be more appropriate.

Despite nonsignificant differences in serum creatinine between compliers and noncompliers, we do not think that noncompliance is without influence on graft function [1,2,6,11,14,23]. Our research had cross-sectional design and therefore selection bias is present. We only evaluated patients with functional graft, and those with graft failure (e. g. due to noncompliance) were not invited. For assessment of the influence of noncompliance on graft survival or graft function longitudinal research is needed.

Our findings show that subclinical noncompliance is a quite common situation, appearing in more than half of our patients. The detection of this feature is of important clinical interest and the investigation techniques require constant updates [13]. It seems reasonable to increase the rate of detection of noncompliers by adding the physician's opinion to the patient's self-referral.

The presented regression model predicted noncompliance in 70 patients, 20 of them were observed as compliers (71.4% were correctly classified). We may expect these 20 patients to become noncompliers. From the practical point of view, identification of patients at risk of becoming noncompliant is necessary. With the help of prediction models we might be able to detect subclinical noncompliers (approximately 15 % of all patients). Based on these results we suggest the policy of assessing compliance and its predictors at the third and twelfth months after transplantation and each year thereafter.

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Table 1 Frequency of adverse symptoms of immunosuppressive treatment identified by patients

symptom	all patients	compliers	noncompliers	p-value
malaise	52.3 %	46.9 %	56.4 %	
pain (headaches, backaches)	51.7 %	46.9 %	57.7 %	
muscle weakness	47.7 %	37.5 %	56.4 %	
weight gain	43.6 %	36.9 %	53.6 %	*
facial changes (moon face, hirsutism)	40.3 %	40.6 %	42.3 %	
depression	34.2 %	26.6 %	42.3 %	*
fear, anxiety	33.6 %	29.7 %	37.2 %	
sleep disorders	30.9 %	25.0 %	35.9 %	
gingival hyperplasia	23.5 %	12.5 %	32.1 %	***
leg edemas	22.8 %	17.2 %	29.5 %	
skin lesions (eczema, skin tumors, warts)	20.8 %	12.5 %	26.9 %	
hair loss	17.4 %	17.2 %	19.2 %	
facial edemas	17.4 %	15.6 %	19.2 %	
sexual dysfunction	16.8 %	12.5 %	19.2 %	
diarrhea	11.4 %	9.4 %	14.1 %	
fragile skin (easy bruises)	10.1 %	10.9 %	10.3 %	

* - $p \leq 0.05$, *** - $p \leq 0.001$

Table 2 Basic description of the patient sample (N=139)

variable		% or mean, SD (range)
gender	male	59.9 %
	female	40.1 %
age		47.7 ± 11.7 years (18.3-74)
	50 years and less	58.1 %
	more than 50 years	41.9 %
education	elementary	18.7 %
	secondary	71.3 %
	university	10.0 %
organ donor	living donor	2.5 %
	cadaveric donor	97.5 %
dialysis before transplantation	hemodialysis	79.9 %
	peritoneal dialysis	12.8 %
	both	7.3 %
time from transplantation		37.7 ± 27.3 months (3-144)
	≤ 3 months	15.5 %
	4-36 months	36.1 %
	> 36 months	48.4 %
immunosuppressive protocol	CsA + Aza + P	13.7 %
	CsA + P	15.7 %
	CsA + MMF + P	41.8 %
	Tac + MMF + P	4.6 %
	CsA + MMF	13.1 %
	Aza + CsA	3.9 %
	CsA	7.2 %

CsA – cyclosporin A, Aza – azathioprin, MMF – mycophenolate mofetil, Tac – tacrolimus, P – prednison

Table 3 Compliance declared by patients and the opinion of their nephrologists

	patient's opinion				
physician's opinion	excellent	good	average	fair	bad
excellent	64	18	0	0	0
good	29	16	0	0	0
average	2	4	1	0	0
fair	0	4	1	0	0
bad	0	0	0	0	0

Table 4 Differences between compliant and noncompliant patients

variables in χ^2-test or Fisher exact test[F]	frequency		p-value
	compliant	noncompliant	
gender			0.071
male	34	53	
female	30	25	
current immunosuppressive regimen			
CsA, Azathioprin, Prednison	12	8	0.111
CsA, Prednison	9	15	0.283
CsA, MMF, Prednison	26	29	0.734
Tacrolimus, MMF, Prednison	4	3	0.388[F]
CsA, MMF	3	13	0.049*[F]
Azathioprin, CsA	3	3	0.751[F]
CsA	4	5	0.627[F]
self-rated health			0.011*
excellent	24	13	
good	30	41	
fair	10	23	
satisfaction with social support			0.027*
excellent	38	31	
good	22	29	
fair	4	15	
education			0.682
elementary	6	9	
secondary	47	52	
university	11	17	
dialysis modality before transplantation			0.570
hemodialysis	53	59	
peritoneal dialysis	8	10	
both methods	3	7	
variables in t-test or Mann-Whittney U test [M]	means and standard deviations		p-value
	compliant	noncompliant	
age	46.5±11.4	49.4±11.9	0.149
serum creatinine	158.7±72.1	153.1±60.9	0.675
time from transplantation	41.2±27.7	37.2±26.5	0.384[M]
total score of stress from adverse effects	6.4±4.9	9.7±7.5	0.003**[M]

* $p<0.05$, ** $p<0.01$

Table 5 Logistic regression analysis of risk factors of noncompliance

variable[s]	p-value	Odds ratio	95 % CI	
male gender	0.001 **	7.49	2.40	23.39
immunosuppressive protocol				
CsA, Azathioprin, Prednison	0.066	3.22	0.93	11.17
CsA, MMF	0.057	0.24	0.057	1.05
self-rated health				
fair	0.045 *	4.50	1.04	19.55
good	0.067	2.96	0.93	9.44
summary score of stress from adverse effects				
high stress (summary score > 12)	0.002 **	12.23	2.4^{4}	61.8^{8}
medium stress (summary score 6-12)	0.649	1.27	0.46	3.53
satisfaction with social support				
fair	0.039 *	4.55	1.0^{8}	19.2^{4}
good	0.745	0.85	0.32	2.25
education				
elementary	0.214	3.01	0.53	17.09
secondary	0.191	0.46	0.14	1.48
peritoneal dialysis before transplantation	0.066	3.69	0.9^{2}	14.8^{3}

* $p<0.05$, ** $p<0.01$

Predictors of perceived health status in patients after kidney transplantation

Predictors of perceived health status in patients after kidney transplantation. Rosenberger J, van Dijk JP, Nagyova I, Zezula I, Madarasova Geckova A, Roland R, van den Heuvel WJA, Groothoff JW. Transplantation 2006; 81: 1306-1310

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Abstract

Background: Patients after kidney transplantation have decreased mortality, morbidity and better quality of life compared to people on dialysis. Major efforts are being directed towards research into graft and patient survival. Research into quality of life is less intensive. The aim of this study was to explore the predictors of perceived health status (PHS) in kidney transplant recipients.
Methods: Out of 218 patients after kidney transplantation 138 participated in the study. Linear regression analysis was performed to predict PHS, measured with the SF-36 questionnaire, in three age categories (<40, 40-59, ≥60 years). Independent variables included social support (measured with the Social Support List Discrepancies questionnaire), socio-demographic and medical variables, side-effects and compliance.

Results: Predictors of better PHS in patients <40 years were better social support ($p \leq 0.001$), lower creatinine ($p \leq 0.001$) and lower stress from adverse effects ($p \leq 0.001$). In the group of patients aged 40-59 years higher education ($p \leq 0.05$), increased housekeeping activities ($p \leq 0.01$) and lower stress from adverse effects ($p \leq 0.001$) predicted better PHS. In the last age group predictors of better PHS were lower rate of dialysis ($p \leq 0.05$) and post-transplant hospitalizations ($p \leq 0.01$), absence of diabetes mellitus ($p \leq 0.01$) and lower stress from adverse effects ($p \leq 0.05$).
Conclusions: Major differences exist in PHS among kidney transplant recipients depending on their age. Side-effects of therapy are the most important predictor of PHS for all age groups. PHS of young patients mostly depends on their renal function and their social support. Education and working activities are most important for middle-aged people whereas in older patients PHS is mostly affected by co-morbidity.

Introduction

At the present time increasing attention is being paid to quality of life evaluation. Together with mortality, morbidity and cost utilization it has become one of the major indicators of medical care [1]. Many factors are known to be predictors of morbidity and mortality in dialysed and transplanted patients. Less information is available about those variables that have an impact on quality of life.

Quality of life according to the WHO definition is a multidimensional construct comprising physical, mental, social and economic components [2]. Due to the complexity of each domain and depending on the method of evaluation there are many variables identified as predictors of good or bad quality of life, including demographic, psychosocial and medical parameters [3]. Quality of life is an umbrella term and is often interchanged with perceived health status, functional status, self-rated health or health-related quality of life. This is the source of frequent problems in this field as definitions and measures for quality of life and the related terms are not clear. Many researchers therefore focus their research involving evaluation of the impact of disease and health on quality of life, and they use the term "health-related quality of life", while others refuse such simplification and prefer the term "perceived health status" [4]. Both terms are interchanged frequently, meaning the same – they evaluate mainly the functional (physical) and mental status of patients as the reflection of their disease. Despite the uncertainty in definitions, health-related quality of life or perceived health status is not a mere construct devoid of clinical relevance. Recent research has shown that it is a very important predictor of other outcomes in patients with chronic renal disease [5,6].

Research into perceived health status in patients after kidney transplantation is broad, but mostly limited to the description or analysis

of its determinants using univariate statistics. Studies with more proper analysis of predictive variables are unfortunately scarce. Searching the literature, we identified ten such studies [7-16]. Their results are heterogenous, depending on study design, composition of the target population and explored variables. Age is the best explored variable, and the majority of studies found higher age to be the most important negative predictor of perceived health status [8,11,13,14,16]. The results are less clear for gender, because only the study made by Wight et al., who compared cohorts of 292 dialysis and 228 transplanted patients, found female gender to be connected with worse physical functioning in kidney transplant recipients [16]. Race is not a frequently reported variable, as only a few multiethnic studies have been performed in this field, all showing white race associated with better results [7,9,14]. Similarly, only a few studies have explored socio-economic variables. Hathaway et al. confirmed that higher education and employment status predict better results in the Sickness Impact Profile, Ferran's and Power's QoL Index and Adult Self-Image Scales questionnaires [13]. Crom et al. found higher education to be associated with better psychological score [9]. Griva et al. used the SF-36 questionnaire and found higher income to be a predictor of a better mental component [11]. Two studies explored the impact of social support on perceived health status and found it to be an important predictor of psychological health status [9,13]. Medical variables are at the center of attention and most research papers include them. Surprisingly, only two studies explored the impact of side effects of treatment and reported them to be predictors of poor health status [12,15]. Fujisawa et al. found serum creatinine to be the only predictor of results in physical functioning, general health perceptions and vitality scales of the SF-36 questionnaire [10]. Many researchers have found co-morbid conditions, including anemia, diabetes mellitus, hypertension, joint and eye diseases, to be associated with poor health status [9,11,14-16]. In addition, length of hospital stay, number of hospitalizations and time on dialysis, which reflect morbidity, have also been found to have impact on perceived health status [9,11,13].

The aim of this study is to explore predictors of perceived health status depending on age in patients after kidney transplantation. A wide range of variables is analyzed with the aim of merging the importance of medical and non-medical factors, including demographic, socio-economic variables, social support, dialysis and transplantation factors, side-effects of immunosuppression and compliance with the treatment. In addition, the authors discuss the clinical importance of medical and non-medical predictors of perceived health status and the consequences for possible interventions.

Materials and methods

Patients

Out of 218 patients with a functioning graft after kidney transplantation from two transplant centers in Slovakia, 208 agreed to participate in the study and 138 sufficiently completed the given questionnaires (effective response rate 63.3 %). Nonresponders did not differ significantly from the analysed group whether in age, gender, education or employment status. All patients after the third month and before 7 years post-transplantation were asked to participate, with the exception of those with severe dementia or mental retardation. The lower limit of three months was chosen as it is a common period for short-term evaluations [8,11,13,15]. Two, five or ten years are usually used for long-term evaluations. As the aim of this study was to study approximately 200 patients, the upper limit was set at 7 years after transplantation after considering the number of patients in our transplant centres. All patients signed an informed consent before the interview. The local ethical committee approved the study.

Procedures and measures

Patients were interviewed by an independent observer in a structured interview, which focused on basic demographic information, education, employment status, house-keeping activities, family life, social activities, dialysis history, compliance with immunosuppressive treatment and adverse effects of immunosuppression.

Age, gender, education (elementary, secondary and university), employment status (employed full-time or part-time, not employed – disabled, retired or unemployed) and house-keeping activities (measured in hours per week spent shopping, cooking, cleaning, or caring for family members) were socio-demographic variables.

Patients completed the Short Form Health Survey (SF-36) and Social Support List Discrepancies questionnaire (SSL-D). The SF-36 is a 36-item questionnaire for assessment of perceived health status [17]. It consists of 8 sub-scales which can be combined as the physical summary component and the mental summary component. All sub-scales as well as the summary components are presented as scores between 0 and 100, with higher scores indicating better health status. The validity and reliability of SF-36 have been tested in patients with renal disease, including those after kidney transplantation [6,10,16,18]. Skalska et al. validated the questionnaire in the Czech population [19]. The Cronbach α in the present sample was 0.95, while the Cronbach α for each sub-scale varied between 0.77 (for social functioning) and 0.91 (for physical functioning). For the purposes of this study only summary component scores were used.

SSL-D is an instrument designed for assessment of social support [20]. The items in this questionnaire are grouped into 6 scales and they can

be computed into a summary score (higher score indicates better social support). The validity and reliability of this questionnaire have been previously tested in various patient populations [21-23]. The Cronbach α of the questionnaire in the research we performed was 0.89. For the purposes of this study only the SSL-D sumscore was used.

Information about medical variables was mostly taken from patients' medical records. Dialysis variables were as follows: duration of dialysis period (in years), number of hospitalizations during dialysis period and number of operations during dialysis period. Transplantation variables were as follows: serum creatinine (SCr), time since transplantation (in months), number of hospitalizations after transplantation, number of operations after transplantation and type of immunosuppression protocol. Presence of diabetes mellitus was used as a measure of co-morbidity.

Patients were asked to select from the list of 16 various adverse effects of immunosuppression during the interview (malaise, pain, muscle weakness, weight gain, facial changes, depression, anxiety, sleep disorders, gingival hyperplasia, leg edemas, skin lesions, hair loss, facial edemas, sexual dysfunction, diarrhea, fragile skin). Stress from each of these adverse effects of immunosuppression was measured on a 5-point scale (0 – no stress, 1 – low stress, 2 – moderate stress, 3 – high stress, 4 – very high stress). For each patient a total score of all adverse effects was calculated as the sum of scores in all items.

Compliance with the immunosuppression therapy was measured on a 5-point scale: 1 – excellent, hardly ever modify the treatment (no more than once per last month); 2 – good, rarely modify the treatment (2-3x per last month); 3 – average, sometimes modify the treatment (once a week); 4 – fair, often modify the treatment (more than once a week), 5 – bad, always modify the treatment. Modification of treatment was explained as missing a dose, prolonging the intervals between doses by more than two hours or changing the dose of immunosuppressants. The nephrologist was interviewed about each patient's compliance with the immunosuppression therapy using the same scale as well. No specific single method was imposed on the nephrologist to identify noncompliance. Nephrologists mostly based their opinion on cyclosporin level variations or knowledge about prescribed and used immunosuppressants. Patients were considered to be compliant only if they declared their compliance by themselves as excellent, in accord with their physician's opinion.

Statistics

Stepwise multiple linear regression analysis was performed in order to find predictors of perceived health status. Physical and mental component summary scores of the SF-36 were entered as the dependent variables. The model of independent variables consisted of socio-demographic variables, social support (SSL-D sumscore), dialysis variables, transplantation

variables, co-morbidity, sum score of stress from side-effects of immunosuppression and compliance with the immunosuppressive medication. The analysis was performed with the sample divided into three age categories – patients aged less than 40 years, patients between 40 and 59 years and patients over 60 years. The cutoff values were selected based on data distribution and information from the literature.
SPSS 10.0 was used for statistical analyses.

Results

Mean age was 48.4 ± 11.9 years and male/female ratio was 1.55. The majority of patients had a good graft function with median of serum creatinine 133 μmol/l (1.5 mg/dl). The predominant immunosuppressive protocol consisted of cyclosporin, mycophenolate mofetil and prednison. More detailed description of the patient sample is given in Tables 1 and 2.

The results of multiple linear regression analyses of predictors of perceived health status are presented in Tables 3-5. Only the models with the best explanation of variance in the mental and physical components of perceived health status are presented.

Better social support and fewer side-effects of immunosuppression predicted a better mental component of perceived health status in patients younger than 40 years. Better social support and lower SCr predicted a better physical component of perceived health status in this age group (Table 3).

Completely different results were found in the group of middle-aged patients (between 40 and 59 years). Higher education, increased housekeeping activities and lower stress from adverse effects of immunosuppression predicted better perceived health status (Table 4).

In the last age group (patients aged 60 years and older) the mental component of perceived health status was positively associated with lower post-transplant morbidity represented by lower post-transplant hospitalization rate, absence of diabetes mellitus and fewer side effects of immunosuppression. Similarly, the physical component was positively associated with lower dialysis hospitalization rate and fewer side effects of immunosuppression (Table 5).

Discussion

The aim of this study was to detect the most relevant bio-psycho-social predictors of perceived health status in kidney transplant recipients. Based on literature search and our previous experience [24], the presented models were created.

Age is the most important variable when considering perceived health status in kidney transplant recipients [8,11,13,24-26]. We decided therefore

to analyse patients separately in three different age groups (less than 40, 40-59 and more than 60 years). In all groups both medical and non-medical variables play an important role.

Perceived health status in young patients is mostly influenced by their social support, renal function and side-effects of immunosuppression. The models give an excellent explanation of variance in perceived health status (60.7 % for the mental and 78.3 % for the physical component). The study by Hathaway et al. with 91 patients with mean age 39.2 years found social support to be the most important predictor of all measures in the Sickness Impact Profile questionnaire [13]. Fujisawa et al. published their study based on 117 kidney transplant recipients with ages similar to our "young patients group". They found SCr to be a significant predictor of better results in SF-36 subscales [10]. Both of these papers support our results in this age category. It seems that for young people success of transplantation is one of the most important determinants of their health status. With good kidney function their reintegration into society is successful and they report excellent perceived health status.

The explanation of variance in perceived health status is less clear in middle-aged patients compared to the younger ones (47.4 % in the mental and 48.1 % in the physical component). Both groups also present major differences in predictors of perceived health status, as predicted by education, house-keeping activities and side effects of immunosuppression in middle-aged kidney transplant recipients. Surprisingly, lower education is a negative predictor of health status only in this age category. One possible explanation is that the sample contained only 10 university-educated persons, all middle-aged. Kidney function is not a predictor of health status in this age category, in contrast to younger patients. Adverse effects of immunosuppressive medication are the only significant medical variable. A possible explanation is that younger patients evaluate good kidney function as the most important prerequisite for long life without dialysis. Their major worries are connected with the fate of their graft [11]. On the other hand, older patients accept even lower kidney function as long as they feel the same benefit in terms of their health status. So they rate unpleasant effects of treatment [15] and barriers in their everyday life [12] as more important.

The models of predictors of perceived health status among the oldest patients explained 48.2 % of variance in the mental component and 34.6 % in the physical component. Major variations in health status appear to exist in this age group and no variable is predominant. Despite the lower percentage of explained variance, perceived health status has a quite clear determinant: co-morbidity (number of pre-transplant and post-transplant hospitalizations, presence of diabetes, side-effects of immunosuppression). These data are similar to the results of the study by Siegal et al. [15].

Participants in this study were recruited from two major transplant centers in Slovakia. The sample is representative and therefore the results may be extrapolated to the whole Slovak transplant population. However, perceived health status might be influenced by many cultural, ethnic and national variables, so additional larger multicenter studies are required to verify the results and allow their extrapolation to other populations. Another limitation of the study is that it had a cross-sectional design, so the results must also be verified longitudinally.

The most important medical variable for all age groups is the presence of unpleasant side-effects of immunosuppressive treatment. The consequence of this for clinical practice is that the adverse symptoms should be constantly evaluated by the transplant team, and major efforts should aim at decreasing their severity. Another important medical variable is kidney function, but only in the group of younger patients. Worry about viability of the graft and duration of its function is the major stressor for these patients [11,27]. The major concern in this age category lies therefore in optimizing the kidney function, but with careful balance in the treatment to minimize side-effects. On the other hand, kidney function is not the predictor of perceived health status in older patients at all, as they benefit even with „less successuful transplantation" with lower graft function. Instead, co-morbidity is more important for this age group, so the major implications for practice are connected with optimizing treatment and following up co-morbid diseases (mostly diabetes and cardiovascular morbidity). Of the non-medical variables, social support has a predominant effect on health status in younger patients, while ability to participate in everyday activities is the most important variable for older patients. These non-medical factors must be taken into account by the transplant team. Co-operation of medical staff with a psychologist, a social worker and the patient's family is necessary therefore in order to assure better quality of life as well as the patient's active rehabilitation and reintegration into society.

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Table 1 Demographic, social and social support characteristics of the patient sample (N=138)

variable		% or mean, SD (range)
gender	male	60.9 %
	female	39.1 %
age		48.4 ± 11.9 years (18-74)
	< 40 years	20.9 %
	40-59 years	60.4 %
	≥ 60 years	18.7 %
education	elementary	15.3 %
	secondary	77.4 %
	university	7.3 %
house-keeping activities		24.3 ± 18.5 hours/week
occupational status	full-time job	8.7 %
	part-time job	1.5 %
	disabled, retired or unemployed	89.8 %
family status	single	21.5 %
	married	67.4 %
	divorced	5.9 %
	widowed	5.2 %
social support (SSL-D questionnaire)	everyday emotional support	9.3 ± 2.1 (4-16)
	emotional support with problems	17.7 ± 3.8 (8-32)
	esteem support	13.0 ± 2.8 (6-24)
	social companionship	10.5 ± 2.7 (5-20)
	social support sumscore	50.4 ± 9.0 (23-92)

Table 2 Medical characteristics of the patient sample (N=138)

variable		% or mean, SD (range)
organ donor	cadaveric	96.3 %
	living	3.7 %
dialysis before transplantation	hemodialysis	74.3 %
	peritoneal dialysis	14.0 %
	both	11.7 %
time since transplantation		34.11 ± 24.6 months
primary kidney disease	glomerulonephritis	43.5 %
	tubulointerstitial nephritis	23.2 %
	polycystic kidneys	5.1 %
	diabetes mellitus	3.6 %
	congenital diseases	2.9 %
	systemic diseases, vasculitis	2.2 %
	other or unknown causes	19.6 %
immunosuppression protocol	Pred + CsA + Aza	12.8 %
	Pred + CsA	13.5 %
	Pred + CsA + MMF	40.6 %
	Pred + Tac + MMF	9.0 %
	CsA + Aza	3.8 %
	CsA + MMF	10.5 %
	Tac + MMF	0.8 %
	CsA	8.3 %
	Tac	0.8 %

Pred – prednisone, CsA – cyclosporin A, Aza – azathioprin, MMF – mycophenolate mofetil, Tac - tacrolimus

Table 3 Multiple linear regression analysis of predictors of perceived health status in age group < 40 years

predictors	R^2	mental component β, p	R^2	physical component β, p
	60.7 %		78.3 %	
employment status				-0.123
social support		0.570***		0.412***
SCr				-0.876***
side effects of IS		-0.550***		

SCr – serum creatinine, IS – immunosuppression
R^2 – explained variance (adjusted), β – β coeficient, *** p≤0.001

Table 4 Multiple linear regression analysis of predictors of perceived health status in age group 40-59 years

predictors	R^2	mental component β, p	R^2	physical component β, p
	47.4 %		48.1 %	
primary education		-0.274*		-0.300***
house keeping activities		0.238**		0.194*
side effects of IS		-0.584***		-0.605***

IS – immunosuppression
R^2 – explained variance (adjusted), β – β coeficient, * p≤0.05, ** p≤0.01, *** p≤0.001

Table 5 Multiple linear regression analysis of predictors of perceived health status in age group ≥ 60 years

predictors	mental component R^2	mental component β, p	physical component R^2	physical component β, p
	48.2 %		34.6 %	
male gender		-0.194		
elementary education		-0.369		-.0296
house keeping activities				0.170
social support		-0.24		
D hospitalizations		-0.282		-0.453*
D operations		0.465		
SCr		-0.233		
Tx hospitalizations		-0.906**		
diabetes mellitus		-0.797**		
side effects of IS		-0.679*		-0.395*
compliance		0.485**		

SCr – serum creatinine, IS – immunosuppression, D hospitalizations – number of hospitalizations during dialysis period, D operations – number of operations during dialysis period, Tx hospitalization – number of hospitalizations after transplantation, R^2 – explained variance (adjusted), β – β coeficient, * p≤0.05, ** p≤0.01

Chapter 7

Discussion, clinical implications and possiblities for future research

7.1. General discussion

Perceived health status, together with mortality, morbidity and cost utilization, is an important outcome measure necessary for evaluating the quality of medical care [1,2]. The main aim of this thesis was to explore predictors of perceived health status in kidney transplant recipients. The theoretical framework of this thesis included a model of the disablement process based on the Disease-Handicap Model by Verbrugge and Jette [3] as well as the International Classification of Functioning, Disability and Health [4]. The proposed model contained several medical and non-medical variables which may have an influence on perceived health status in patients after kidney transplantation. In this final chapter we discuss whether the model fits. In addition to theoretical consequences, the clinical importance and implications for practice are addressed here, as well as possibilities for future research.

7.1.1. Research question 1

The second chapter of the thesis discussed the following research question.

1 Are the differences in perceived health status between transplant and dialysis populations based on modality of therapy or on selection bias?

When considering recipients of a cadaveric kidney, one should be aware that two processes of selection happen before a patient is transplanted. Any comparison of health status of transplant recipients to patients on dialysis is therefore doubly biased, involving in comparison of young and relatively healthy transplant recipients to older and more ill dialysed patients [5]. Focusing on these facts, our study was designed as the comparison of perceived health status between dialysed patients on a waiting list for cadaveric transplantation and incident kidney transplant recipients 3 months after kidney transplantation, matched for age, gender and co-morbidity.

The present study confirmed that patients after kidney transplantation feel better than those on dialysis [6]. The physical component of perceived

health status is reduced in dialysis patients in particular. However, a significant selection bias is present as only some dialysed patients are put onto a waiting list and only some of them are actually transplanted. When patients after kidney transplantation were compared to their matched pairs on a waiting list, no differences in perceived health status were found.

7.1.2 Research question 2a

Chapters 3 and 4 provided answers to the following research question.

2a Which medical variables (kidney function, adverse effects of immunosuppressive treatment, co-morbid diseases, duration of kidney disease, number of hospitalizations, period after transplantation) influence perceived health status?

Age is the most important predictor of perceived health status in patients after kidney transplantation, as it explains 23.3% of variance in physical and 4.4% in mental perceived health status. With increasing age perceived health status worsens [7]. When patients are not stratified by age, the analysis of other predictors of perceived health status has very limited results. Additional analyses are therefore performed with the sample stratified by age.

Perceived health status in young patients is mostly influenced by their renal function and side-effects of immunosuppression. Fujisawa et al. published a study based on 117 kidney transplant recipients with ages similar to the patients younger than 40 years in our research, and found lower serum creatinine to be a significant predictor of better results in SF-36 subscales [8]. It seems that for young people success of transplantation is one of the most important determinants of their perceived health status. With good kidney function their reintegration into society is successful, and they report excellent perceived health status. The major concern in this age category lies therefore in optimizing the kidney function, but with careful balance in the treatment to minimize side-effects. On the other hand, kidney function is not a predictor of perceived health status in older patients (≥ 40 years old). Adverse effects of immunosuppressive medication are the most important medical variable in this age category. A possible explanation is that while the main worries of younger patients are connected with the long-term fate of their graft [9], older patients accept even lower kidney function as long as they feel the same benefit in terms of relieving their dependency on dialysis. Major variations in perceived health status are detected among elderly kidney transplant recipients, and no predictor is predominant. Despite the lower percentage of explained variance, perceived health status has quite clear medical determinants: co-morbidity (presence of diabetes mellitus, the number of pre-transplant and post-transplant hospitalizations). These results are similar to those in the study by Siegal et al.[10].

When considering perceived health status in elderly kidney transplant recipients, they appear to benefit even with 'less successful transplantation' with worse kidney function and higher serum creatinine. Instead of graft function, serious co-morbid conditions that require medical attention (represented by the number of hospitalizations) are more important for this age group [9], so the major implications for practice are connected with optimizing treatment and following up co-morbid diseases. Diabetes mellitus and cardiovascular morbidity are particulary important, as their prevalence among elderly transplant recipients is high [11].

The most important medical variable for all age groups is the presence of unpleasant side-effects of immunosuppressive treatment. From the patient's perspective the most stressful non-infectious non-oncological adverse effects of immunosuppression are pain, weakness, cosmetic changes and psychological symptoms (depression and anxiety). Other researchers found adverse symptoms to be connected to lower quality of life as well [12]. The stress from adverse effects is higher in women and less-educated patients. The type of immunosuppressive regimen does not seem to influence the overall score of stress, but the use of new drugs exhibits less stress in some symptoms.

7.1.3 Research question 2b

Chapter 5 switches the attention to personal factors which may play a role in perceived health status, and deals with the following research question.

2b What is the relation of adverse effects of treatment and noncompliance with the therapy to perceived health status? Is noncompliance related to adverse effects of treatment?

Our findings show that subclinical noncompliance is a quite common situation, appearing in more than half of the patients. The consequence of the findings presented in Chapter 5 for clinical practice is that the adverse symptoms should be constantly evaluated by the transplant team, and major efforts should aim at decreasing their severity [13-16], because they are strong predictors of noncompliance with the therapy (12.3-times higher risk). Other risk factors leading to noncompliance identified in our sample by the logistic regression analysis were male gender (7.5-times higher risk), worse perceived health status (4.5-times higher risk) and fair satisfaction with social support (4.5-times higher risk). The detection of this feature is of important clinical interest and the investigation techniques require constant updates [17], because noncompliance is associated with higher frequency of late graft dysfunction, which is directly related to graft loss [13,18-20]. It seems reasonable to increase the rate of detection of noncompliers by adding the physician's opinion to the patient's self-referral. From our

results we can conclude that the relationship between perceived health status and compliance is bi-directional, and adverse effects are very important predictors for both perceived health status and compliance as well.

7.1.4. Research question 2c

The main objective of the sixth chapter is to merge the impact of environmental and personal factors on perceived health status after kidney transplantation.

2c Are there non-medical confounders (age, gender, socio-economical status, social support) that are related to perceived health status in addition to medical variables?

Apart from medical predictors, a wide range of other variables may influence perceived health status. The impact of age has already been discussed above. Of the other non-medical variables, social support has a predominant effect on health status in younger patients, while the ability to participate in everyday activities and higher education are important for older patients.

Socio-economic status is frequently reported to be related to perceived health status [7,9,10,21]. Surprisingly, in our study lower education is a negative predictor of health status only in patients 40-59 years old. One possible explanation is that the sample contained only 10 university-educated persons, all middle-aged. We tried to explore the relationship between employment status and perceived health status, but our sample contained nearly 90% disabled, retired or unemployed patients, whereas many other studies have reported improvement of employment capabilities after transplantation [22]. On the other hand, we realized that transplanted patients usually work at home more than other people, so we questioned them about their time spent on house-keeping. We found that middle-aged patients with more house-keeping activities declared better perceived health status.

It seems that sufficient social support is another prerequisite for good perceived health status. Our results in the group of patients younger than 40 years are similar to those in the study by Hathaway et al. with 91 patients with mean age 39.2 years, who found social support to be the most important predictor of all measures in the Sickness Impact Profile questionnaire [7]. Other studies have proved the importance of social support as well [10,21].

Transplant nephrologists usually focus in their everyday practice on medical factors alone and the non-medical factors are not taken into account by the transplant teams. Our results provide the evidence that individual patients can evaluate their health rather differently even when

their medical variables are very similar or even identical [1].

7.1.5 Conclusions

We may conclude that not only medical factors (kidney function, side effects of immunosuppression, noncompliance with the treatment, comorbidity) but also social-demographic factors (age, education, social support) significantly influence the perceived health status after kidney transplantation. The explained variance is satisfactory. These findings are not only useful for enlarging the understanding of the disability and rehabilitation process of transplanted patients, but they also have direct consequences for clinical practice.

7.2. The disablement process in patients with end-stage renal disease

End-stage renal disease imposes a heavy burden on an individual's life due to several impairments and activity limitations. Diminished perceived health status is reported as a result of this disablement process. Our data from Chapter 2 indicate that the physical component of perceived health status is affected in particular.

The theoretical model of the disablement process in patients with end-stage renal disease proposed in Chapter 1 (Figure 1.2) was presented and explored in previous chapters of this thesis. The results of our research indicate that relations between disease factors, personal factors, environmental factors and perceived health status may in practice resemble those in the proposed model. Apart from the direct line leading from kidney disease (kidney function) [8] and other co-morbid diseases [9,10] to activity restrictions and perceived health status, we identified several environmental and personal factors with significant impact on perceived health status.

Of the environmental factors, social support seems to be the non-medical predictor of perceived health status with the strongest impact [7]. Research into immunosuppression is quite broad and new drugs are successfully used, resulting in decreased rate of rejection episodes and improved short-term graft survival. We expected that the type of treatment might be an important environmental factor. Surprisingly, we did not confirm this relationship. Instead, adverse effects of treatment and kidney function (creatinine) are predictors of perceived health status. We may therefore expect the relationships between these medical variables to be more complex.

The most important personal factors are age [7,9,23] and adverse effects of immunosuppressive treatment [10]. In addition, we found relationships between some of these factors, namely adverse effects of treatment, compliance with treatment and perceived health status [13,15,16].

Unfortunately, the design of this study does not allow us to address the causal pathway, so it is not possible to show whether noncompliance with immunosuppressive treatment is the cause or the effect of deteriorated perceived health status.

It seems that the proposed model may be generalized to any chronic disease. Disease-specific factors are unique to each chronic pathology, injury or disease, so their impact must be evaluated specifically to that disease; kidney function is such a factor in kidney transplant recipients. Other co-morbid diseases are important as well. Our experience indicates that restrictions resulting from co-morbidity (namely need for hospitalization) are more important for perceived health status than the type of co-morbidity itself. In addition, environmental and personal factors, as well as their interactions, are common to all chronic diseases [24-27].

7.3. Clinical consequences and recommendations for clinical practice

The results of our comparative study of perceived health status between dialysed patients on a waiting list for transplantation and their matches among incident kidney transplant recipients do not show significant differences between these two groups. The recommendations for clinical practice are aimed at the group of patients on dialysis waiting for transplantation. They expect successful transplantation to diminish their health complaints and improve their perceived health status. However, they often encounter new problems after transplantation, including adverse effects of immunosuppressive drugs, fear of rejection and infection or anxiety about long-term kidney function [28]. Intensive attention should therefore be paid not only to transplant recipients, but to patients on waiting lists as well. These potential candidates for transplantation need constant education and information aimed at improving their compliance even before transplantation.

The development and use of predicting schemes might help clinicians in uncovering noncompliance. The detection of patients with low adherence to the therapeutical regimen is a prerequisite for possible actions aimed at improving compliance and thereby reducing the threat of rejection and late graft loss [13,17]. Poor perceived health status is linked with worse compliance and therefore can be used as a cheap and easily measurable predictor of noncompliance in routine clinical practice. As adverse effects of immunosuppressive treatment are the main stressor for transplanted patients, their constant evaluation is crucial [12,14]. Another important strategy involves influencing non-medical predictors of noncompliance, mainly social support, so positive co-operation of medical staff with the patient's family members is also necessary.

Our data indicate that non-medical variables (age, education,

occupational status, social support) are as important predictors of perceived health status as the medical ones. This fact is often neglected by transplant physicians and nurses, who usually pay attention to medical factors only. Age predicts perceived health status independently from other factors [7,9,23], so it is necessary to stratify patients by age when evaluating perceived health status. In all age groups both medical and non-medical variables play an important role, but their significance is age dependent as well.

The importance of the causal pathway from kidney pathology to restrictions in everyday life activities and perceived health status is well established. Disease-related factors therefore receive a lot of attention from medical staf, but environmental and personal factors playing an equally important role are usually not addressed. Unfortunately, the current social system in the Slovak Republic is not very supportive for active rehabilitation of kidney transplant recipients. Patients on dialysis and up to one year after transplantations are usually registered as disabled, but then their ability to work is evaluated solely on the value of serum creatinine. Other factors are not taken into account. After months or years of disability these patients are rarely able to reintegrate into the work process without any help. Although Slovakian legislation supports the employment of handicapped people, financial compensation for employing a handicapped person is not sufficient for the majority of employers. In addition, no dialysis or transplant centre in the Slovak Republic has a social worker among the staff members, so social disability and rehabilitation are simply left to the patients' own devices. In summary, the vicious circle of 'restrictions – disability – social and working deprivation' is closed and still awaits resolution. Creation of multidisciplinary transplant teams comprising a transplant nephrologist, a transplant nurse, a psychologist and a social worker maintaining intensive collaboration with patients' families is necessary, therefore, in order to assure better perceived health status as well as the patients' active rehabilitation and reintegration into society [7].

7.4. Possibilities for future research

The present research focuses on perceived health status of patients after kidney transplantation and dialysed patients on waiting lists. However, all the findings are based on a cross-sectional study design. Previous research provided some clues that time after transplantation may play an important role. Laupacis et al. evaluated 168 patients within a period of 19.5 months and found that perceived health status 6 months after transplantation improved compared to pre-transplantation, and stayed improved at the next follow-up [29].

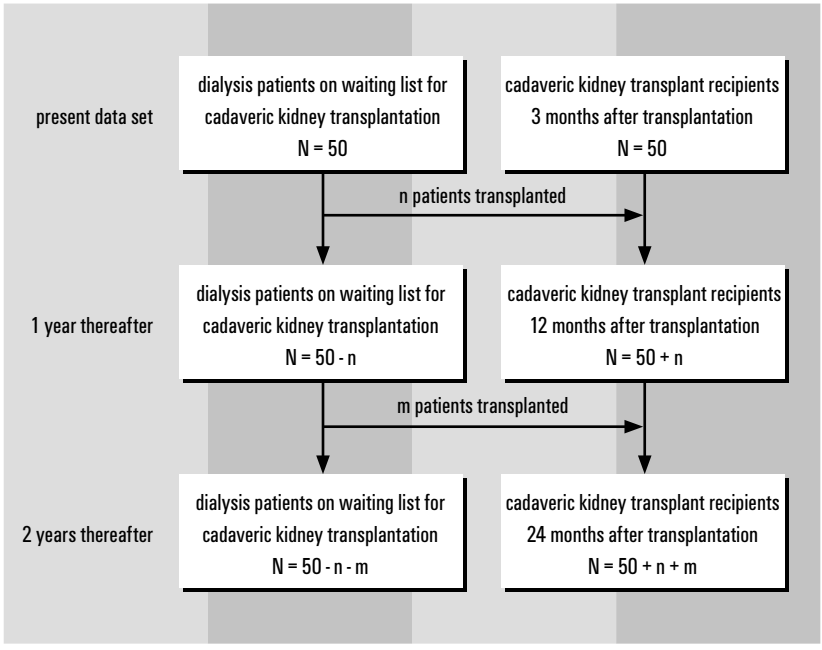
7.4.1. Medical and psychological variables in future research

It is important to continue our research and examine all participants (transplant recipients and dialysed patients as well) after one year and the next year thereafter. It is necessary to reckon with the fact that a small number of the dialysed patients on waiting lists will move into the transplant category, thus changing the numbers in both samples (Figure 7.1). Changes in perceived health status and its relationship to changes in medical determinants may form the topic of future research. Furthermore, a wide range of already-collected psychological data, combined with medical data, will enable us to clarify parts of the interaction between psychosocial and medical factors. The relationship of compliance to the treatment and personal characteristics, like mastery or type D personality profile, could be of particular interest.

7.4.2. Longitudinal research on compliance

Longitudinal research on compliance with immunosuppressive treatment is necessary as well [30]. It is possible to create a clinically-relevant

Figure 7.1. Design of future research



Dialysed patients on a waiting list for cadaveric kidney transplantation as well as patients already after transplantation will be assessed on an annual basis. Some fraction of dialysed patients will move into the transplant category.

prognostic model based on our cross-sectional data, which would help to predict noncompliers with the therapy. So long as the variables used in such a model are easily obtained and accessed by a transplant team, many rejections and subsequent graft losses could be prevented. The validity of this model must be evaluated in a longitudinal study. In addition, it is possible to design an intervention program for patients whose predicted compliance with the therapy is low. The intervention should aim at changing those factors with low scores within the model. The effectiveness of such a program should be evaluated.

Our data indicate that relationships between type of immunosuppresion, adverse effects of treatment, compliance, kidney function and perceived health status are very complex and multidirectional. Longitudinal research on our transplant sample could explore the causal pathways.

7.4.3. Multicenter study

Finally, a multicenter analysis of the data we collected during the present research would greatly support our results, as similar information is available in Groningen from a cohort of Dutch patients. As the medical treatment is very similar in both countries, the differences in perceived health status, if they exist, would have to be the result of cross-cultural dissimilarities in non-medical factors between the cohorts.

In addition, differences in participation and reintegration into the working process between Slovak and Dutch kidney transplant recipients may be analysed, as both countries have a different social security system.

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Summary

A substantial number of patients with end-stage renal disease require lifelong renal replacement therapy. Dialysis (hemodialysis and peritoneal dialysis) and kidney transplantation are common treatment modalities of kidney failure. Kidney transplantation is the method of choice among renal replacement therapies due to its superior results in mortality, morbidity, cost utilization and quality of life in comparison to dialysis. While the research into graft and patient survival after transplantation is quite impressive, less information is available about quality of life and perceived health status. For this reason, this study focuses on this aspect.

The disablement process is represented by the direct pathway starting from pathology and leading to impairments, activity limitations and ending with the restrictions in participation. Because participation restrictions may be consequences of disease, alterations in perceived health status are reported as well. Any significant pathology therefore modifies perceived health status and quality of life.

The research into perceived health status after kidney transplantation is mostly focused on the description of its determinants, resulting in a variety of medical and non-medical factors with possible impacts. However, studies aiming at a comprehensive assessment of several predictors of perceived health status are lacking. As both medical and non-medical variables are linked to perceived health status, the following questions in the population of kidney transplant recipients are discussed in this thesis.

1 *Are the differences in perceived health status between transplant and dialysis populations based on modality of therapy or on selection bias?*

2a *Which medical variables (kidney function, adverse effects of immunosuppressive treatment, co-morbid diseases, duration of kidney disease, number of hospitalizations, period after transplantation) influence perceived health status?*

2b *What is the relation of adverse effects of treatment and noncompliance with the therapy to perceived health status? Is noncompliance related to adverse effects of treatment?*

2c *Are there non-medical confounders (age, gender, socio-economical status, social support) that are related to perceived health status in addition to medical variables?*

Chapter 2 presents a comparison of perceived health status between dialysed and transplanted patients as well as dialysed patients on waiting lists for cadaveric transplantation and incident kidney transplant recipients 3 months after kidney transplantation, matched for age, gender and co-morbidity was performed. The results prove that perceived health status after kidney transplantation is much better than on dialysis. But when patients after kidney transplantation were compared to their matched pairs of dialysed patients on waiting lists, no differences in perceived health status were found. Differences in perceived health status between transplant and dialysis patients seem therefore to be influenced by a significant selection bias.

Medical predictors of perceived health status in kidney transplant recipients are explored in Chapter 3. Medical variables have a relationship to physical perceived health status in particular, as they can explain up to one third of its variance. Age was found to be the most important predictor of perceived health status in patients after kidney transplantation. When patients were not stratified by age, the analysis of other predictors of perceived health status had very limited results. After stratification by age, significant differences in predictors of perceived health status were found between the age categories – better kidney function predicted good perceived health status in patients younger than 45 years, while fewer hospitalizations had more positive effect on older patients.

In Chapter 4 side-effects of immunosuppressive treatment and noncompliance with the therapy are discussed, as they are important transplant-specific variables. The most stressful non-infectious non-oncological adverse effects of immunosuppression are pain, weakness, cosmetic changes and psychological symptoms. The stress from adverse effects is higher in women and less educated patients, and the use of new drugs exhibits less stress in some symptoms.

Of the personal factors modifying the disablement process, noncompliance with the therapy has very important clinical consequences, and we explore its predictors in Chapter 5. Higher stress from adverse effects is a strong predictor of noncompliance with the therapy (12.3-times higher risk) together with male gender (7.5-times higher risk), worse perceived health status (4.5-times higher risk) and fair satisfaction with social support (4.5-times higher risk).

The analysis of several medical and non-medical predictors of perceived health status is presented in Chapter 6. Side-effects of therapy are the most important predictor of perceived health status for all age groups. Perceived health status of patients younger than 40 years mostly depends on their renal function and the level of their social support. Education and working activities are most important for middle-aged people, whereas in patients older than 60 years perceived health status is mostly affected by co-morbidity.

In the last chapter, general discussion and conclusions are proposed. Based on the conclusion and the given results, clinical consequences and recommendations for practice are formulated and the possibilities for future research are suggested as well.

1. Intensive attention should be paid not only to transplant recipients, but to patients on waiting lists as well. Their education and information about future transplantation requires constant updates to improve their co-operation thereafter.
2. It is necessary to stratify the patient sample by age when evaluating perceived health status.
3. As adverse effects of immunosuppressive treatment are the main stressor for transplanted patients, their continuous assessment is crucial. The detection of patients with low adherence to the therapeutic regimen is a prerequisite for possible actions aimed at improving their compliance and therefore reducing the threat of rejection and late graft loss.
4. Non-medical variables are as important predictors of perceived health status as the medical ones. Creation of multidisciplinary transplant teams and intensive collaboration with patients' families are necessary to assure better perceived health status as well as the patients' active rehabilitation and reintegration into society.
5. Longitudinal research with the aim of addressing the effect of time on perceived health status is necessary as well as long-term evaluation of compliance with the immunosuppressive treatment.

Samenvatting

Een aanmerkelijk aantal patiënten in de eindfase van hun nierlijden heeft een levenslange nier-vervangende behandeling nodig. Dialyse (haemodialyse en peritoneaaldialyse) en niertransplantatie zijn de twee gebruikelijke behandelingsmodaliteiten bij nierfalen. Niertransplantatie heeft de voorkeur bij de niervervangende behandelingsmethoden vanwege de betere resultaten waar het gaat om sterfte, ziekte, kosten en levenskwaliteit in vergelijking tot dialyse. De hoeveelheid onderzoek naar de overleving van het transplantaat en de patiënt na transplantatie is imponerend, maar veel minder is bekend over levenskwaliteit en ervaren gezondheidstoestand. Om deze reden richt deze studie zich op dit aspect.

Het invalideringsproces kan worden voorgesteld door het directe pad dat begint bij de pathologie, dat leidt tot functiestoornissen, alsmede tot beperkingen van activiteiten en tenslotte uitmondend in belemmeringen in participatie. Omdat belemmeringen in participatie een gevolg kunnen zijn van het ziekteproces, worden veranderingen in ervaren gezondheidstoestand ook beschreven. Elke belangrijke pathologie heeft om die reden effect op de ervaren gezondheidstoestand en de levenskwaliteit.

Het onderzoek naar ervaren gezondheidstoestand na niertransplantatie richt zich meestal op de beschrijving van de determinanten ervan, wat resulteert in een verscheidenheid van medische en niet-medische factoren met een mogelijke invloed. Echter, onderzoek dat zich richt op een complexe evaluatie van verscheidene voorspellers van ervaren gezondheidstoestand, ontbreekt. Omdat beide, medische en niet-medische variabelen een verband hebben met ervaren gezondheidstoestand, is in dit onderzoek op de volgende vragen met betrekking tot de ontvangers van een niertransplantaat ingegaan.

1 *Zijn de verschillen in ervaren gezondheidstoestand tussen getransplanteerden en gedialyseerden gebaseerd op de verschillen in behandeling of op selectie?*

2a *Welke medische variabelen (nierfunctie, bijwerkingen van de immuunsuppresieve behandeling, comorbiditeit, duur van de nierziekte, het aantal ziekenhuisopnamen, de periode na transplantatie) beïnvloeden ervaren gezondheidstoestand?*

2a *Wat is het verband tussen de bijwerkingen van de behandeling en therapie-ontrouw en de ervaren gezondheidstoestand? Bestaat er een verband tussen therapie-ontrouw en de bijwerkingen van de behandeling?*

2c Zijn er niet-medische variabelen (leeftijd, geslacht, sociaal-economische status, sociale steun) die verband houden met ervaren gezondheidstoestand naast de medische variabelen?

In Hoofdstuk 2 wordt de ervaren gezondheidstoestand tussen gedialyseerde en getransplanteerde patiënten gematcht naar leeftijd, geslacht en comorbiditeit vergeleken, als ook tussen gedialyseerde patiënten op de wachtlijst voor een transplantatie en ontvangers van een niertransplantaat 3 maanden na de transplantatie, eveneens gematcht naar leeftijd, geslacht en comorbiditeit. De resultaten lieten zien dat de ervaren gezondheidstoestand na niertransplantatie veel beter is dan bij dialyse. Maar als patiënten na niertransplantatie werden vergeleken met hun gematchte paren gedialyseerde patiënten op de wachtlijst, werden geen verschillen in ervaren gezondheidstoestand meer aangetroffen. Verschillen in ervaren gezondheidstoestand tussen getransplanteerde en gedialyseerde patiënten lijken derhalve aangetroffen te worden als gevolg van een selectie bias.

Medische voorspellers van ervaren gezondheidstoestand bij ontvangers van een niertransplantaat werden onderzocht in Hoofdstuk 3. Medische variabelen hebben in het bijzonder een verband met de fysieke ervaren gezondheidstoestand, omdat ze een derde van de variantie daarvan kunnen verklaren. De leeftijd bleek de meest belangrijke voorspeller van ervaren gezondheidstoestand bij patiënten na niertransplantatie. Patiënten werden in eerste instantie niet naar leeftijd gestratificeerd; de analyse van de andere voorspellers van ervaren gezondheidstoestand had zeer beperkte resultaten. Maar na stratificatie naar leeftijd werden significante verschillen in de voorspellende waarde van ervaren gezondheidstoestand gevonden per leeftijdscategorie – een betere nierfunctie voorspelde een goede ervaren gezondheidstoestand bij patiënten jonger dan 45 jaar, en minder ziekenhuisopnames een goede ervaren gezondheidstoestand bij oudere patiënten.

In Hoofdstuk 4 is ingegaan op de immunosuppressieve behandeling en de therapie-ontrouw; beide zijn belangrijke transplantatie-specifieke variabelen. De meest hinderlijke niet-infectieuze en niet-oncologische bijwerkingen van immunosuppressiva zijn pijn, gevoel van zwakte, cosmetische veranderingen en psychische veranderingen. De hinder van bijwerkingen is groter bij vrouwen en lager opgeleide patiënten; het gebruik van nieuwere geneesmiddelen geeft met betrekking tot sommige symptomen minder overlast.

Van de individuele factoren die het invalideringsproces beïnvloeden heeft therapie-ontrouw ernstige klinische consequenties, waarvan de voorspellers werden onderzocht in Hoofdstuk 5. Meer hinder van bijwerkingen is een sterke voorspeller van therapie-ontrouw (12.3 maal hoger risico) evenals het behoren tot het mannelijk geslacht (7.5 maal

hoger risico), een slechte ervaren gezondheidstoestand (4.5 maal hoger risico) en matige tevredenheid met sociale steun (4.5 maal hoger risico).

De analyse van verscheidene medische en niet-medische voorspellers van ervaren gezondheidstoestand is beschreven in Hoofdstuk 6. Bijwerkingen van de behandeling zijn de meest belangrijke voorspeller van ervaren gezondheidstoestand voor alle leeftijdsgroepen. De ervaren gezondheidstoestand van patiënten jonger dan 40 jaar is afhankelijk van hun nierfunctie en het niveau van sociale steun. Opleidingsniveau en beroepsactiviteiten zijn het belangrijkst voor mensen van middelbare leeftijd, terwijl ervaren gezondheidstoestand bij patiënten ouder dan 60 jaar het meest beďnvloed wordt door comorbiditeit.

In het laatste hoofdstuk is een algemene discussie gevoerd en zijn conclusies getrokken. Gebaseerd op de conclusie en de resultaten zijn klinische consequenties en aanbevelingen voor de praktijk geformuleerd, alsmede de mogelijkheden voor toekomstig onderzoek gesuggereerd.

1. Intensieve belangstelling zou niet alleen moeten worden geschonken aan ontvangers van transplantaten, maar ook aan patiënten op de wachtlijst. Hun opleiding en voorlichting met betrekking tot de toekomstige transplantatie vereist een constant bij de tijd brengen met het oog op een betere samenwerking na de transplantatie.
2. Het is noodzakelijk om steekproeven met patiënten naar leeftijd te stratificeren bij het onderzoeken van de ervaren gezondheidstoestand.
3. Omdat bijwerkingen van immunosuppressieve behandeling de belangrijkste bron van overlast zijn voor getransplanteerde patiënten, is de constante bepaling ervan cruciaal. Het ontdekken van therapie-ontrouw is een voorwaarde voor mogelijke acties die ten doel hebben de therapietrouw te vergroten, en zodoende het gevaar van afstoting en laat verlies van het transplantaat te verkleinen.
4. Niet-medische variabelen zijn net zulke belangrijke voorspellers van de ervaren gezondheidstoestand als de medische. Het instellen van een multidisciplinair transplantatie team en intensieve samenwerking met de familie van de patiënt is noodzakelijk om een betere ervaren gezondheidstoestand te waarborgen, en bij te dragen aan de actieve revalidatie en reďntegratie in de samenleving.
5. Longitudinaal onderzoek met het doel het effect van de tijd op ervaren gezondheidstoestand te achterhalen is noodzakelijk, evenals een lange termijn onderzoek van therapietrouw aan immunosuppressiva.

Zhrnutie

Veľký počet pacientov s chronickým obličkovým zlyhaním vyžaduje doživotnú liečbu nahrádzajúcu funkcie obličiek. Medzi bežne dostupné modality liečby obličkového zlyhania patrí dialýza (hemodialýza a peritoneálna dialýza) a transplantácia obličky. Transplantácia je metódou voľby medzi jednotlivými liečebnými stratégiami, keďže v porovnaní s dialýzou ponúka lepšie výsledky čo sa týka mortality, morbidity, ceny a kvality života. Kým výskum zaoberajúci sa prežívaním pacientov po transplantácii je impozantný, informácií o kvalite života alebo seba posudzovanom zdraví je oveľa menej. Táto práca sa zaoberá práve týmito aspektmi života po transplantácii.

Proces vzniku funkčnej neschopnosti je reprezentovaný líniou začínajúcou patologickým stavom a končiacim obmedzeniami v dennodenných aktivitách. Keďže sú tieto obmedzenia následkom chorobného procesu, často sú badateľné aj zmeny v seba posudzovanom zdravotnom stave. Možno teda predpokladať, že každá závažná patologická odchýlka spôsobí aj zmenu seba posudzovaného zdravotného stavu a kvality života.

Doterajší výskum seba posudzovaného zdravotného stavu po obličkovej transplantácii je zameraný zväčša na popis jeho determinantov a zahŕňa veľké množstvo medicínskych ako aj nemedicínskych faktorov. Cielenejšie štúdie hodnotiace komplexné vzťahy medzi viacerými predpovednými faktormi sú však vzácnosťou. Pritom mnohé medicínske aj nemedicínske faktory sú priamo prepojené na seba posudzovaný zdravotný stav. Práve preto budú v tejto práci pojednávané nasledujúce výskumné otázky.

1 *Sú rozdiely v seba posudzovanom zdravotnom stave medzi pacientmi po transplantácii a na dialýze spôsobené liečebnou modalitou alebo sú iba dôsledkom selekčnej chyby?*

2a *Ktoré medicínske premenné (funkcia obličky, nežiadúce účinky imunosupresívnej liečby, trvanie choroby, hospitalizácie, čas po transplantácii) ovplyvňujú seba posudzovaný zdravotný stav?*

2b *Aký je vzťah medzi nežiadúcimi účinkami liečby, nedostatočnou spoluprácou pacienta s liečbou a seba posudzovaným zdravotným stavom? Je nedostatočná spolupráca viazaná na výskyt nežiadúcich účinkov?*

2c *Existujú aj nemedicínske premenné (vek, pohlavie, socio-ekonomický stav, sociálna opora), ktoré ovplyvňujú seba posudzovaný zdravotný stav?*

Porovnanie seba posudzovaného zdravotného stavu medzi dialyzovanými a transplantovanými pacientmi ako aj medzi vekovo, pohlavím a komorbiditami párovanými dialyzovanými pacientmi v čakacej listine na transplantáciu kadaveróznej obličky a novo transplantovanými pacientmi (3 mesiace po transplantácii) je uvedené v kapitole 2. Bol potvrdený fakt, že populácia transplantovaných udáva lepší zdravotný stav ako pacienti na dialýze. Na druhej strane, ak porovnáme pacientov po transplantácii s ich pármi na čakacej listine, rozdiely v seba posudzovanom zdraví zmiznú. Je teda zjavné, že je za nich vo veľkej mierne zodpovedná selekčná chyba.

V tretej kapitole sú skúmané medicínske predpovedné faktory seba posudzovaného zdravotného stavu v populácii transplantovaných pacientov. Medicínske premenné majú jasný vzťah najmä k fyzickému zdravotnému stavu a dokážu vysvetliť až jednu tretinu jeho variability. Ako najdôležitejší predpovedný faktor sa javí vek. Pokiaľ pacienti nie sú stratifikovaní podľa veku, výsledky analýz predpovedajúcich seba posudzovaný zdravotný stav sú veľmi obmedzené. Avšak po vekovej stratifikácii je možné nájsť výrazné rozdiely medzi predpovednými faktormi v jednotlivých vekových kategóriách. Kým seba posudzovaný zdravotný stav mladších pacientov (do 45 rokov) je jednoznačne predpovedaný mierou ich obličkovej funkcie, v skupine starších pacientov hrá úlohu množstvo hospitalizácií.

Kapitola 4 pojednáva o nežiadúcich účinkoch imunosupresívnej terapie a nedostatočnej spolupráci pacientov s touto liečbou. Pacientmi sú ako najstresujúcejšie vnímané bolesti, slabosť, kozmetické zmeny a psychologické symptómy. Stres z nežiadúcich účinkov liekov je výraznejšie prítomný v prípade žien a menej vzdelaných pacientov. Užívanie modernejších imunosupresív je spojené s menším pociťovaním niektorých symptómov.

V rámci osobnostných premenných modifikujúcich proces vzniku funkčnej neschopnosti hrá významnú úlohu nedostatočná spolupráca pacienta s liečbou. V prípade transplantovaných pacientov má tento faktor osobitne negatívne klinické dôsledky. V kapitole 5 sú popísané predpovedné faktory vzniku nedostatočnej spolupráce pacienta s imunosupresívnou liečbou. Silným prediktorom nedostatočnej spolupráce pacienta je vyšší stres z nežiadúcich účinkov liekov (12,3-násobne zvýšené riziko), mužské pohlavie (7,5-násobne vyššie riziko), horší seba posudzovaný zdravotný stav (4,5-násobne vyššie riziko) a nedostatočná spokojnosť so sociálnou oporou (4,5-násobne vyššie riziko).

V kapitole 6 sú analyzované viaceré medicínske a nemedicínske faktory predpovedajúce seba posudzovaný zdravotný stav. Vo všetkých vekových skupinách pacientov sa ako najdôležitejšia javí prítomnosť nežiadúcich účinkov liekov. V skupine pacientov mladších ako 40 rokov má na seba posudzovaný zdravotný stav vplyv funkcia štepu a úroveň sociálnej

opory. V skupine pacientov stredného veku sú dôležité vzdelanie a pracovné aktivity, kým seba posudzovaný zdravotný stav pacientov starších ako 60 rokov je ovplyvnený komorbiditami.

Záverečná kapitola obsahuje všeobecnú diskusiu a formuluje závery, na základe ktorých je rozoberaná klinická závažnosť uvedených zistení a odporúčania pre prax. V tejto kapitole sú tiež navrhované ďalšie potenciálne výskumné úlohy vyplývajúce so záverov tejto práce.

1. Okrem pacientov po transplantácii obličky je potrebné venovať intenzívnu pozornosť aj pacientom v čakacej listine na transplantáciu. Ich vzdelávanie a informovanosť o budúcej transplantácii vyžaduje trvalú aktualizáciu, aby bola po následnej transplantácii zaistená čo najlepšia spolupráca s liečbou.
2. Pre potreby hodnotenia seba posudzovaného zdravotného stavu je nutné pacientov stratifikovať podľa veku.
3. Nežiadúce účinky imunosupresívnej liečby sú hlavným zdrojom stresu pre pacientov po transplantácii obličky. Preto je rozhodujúce ich pravidelné sledovanie a vyhodnocovanie. Následná detekcia pacientov, ktorých spolupráca s liečbou je nedostatočná, je nevyhnutná na realizáciu opatrení zvyšujúcich spoluprácu pacienta. Len tak je možné znížiť hrozbu rejekcie a následnej straty štepu.
4. Nemedicínske prediktory seba posudzovaného zdravia sú rovnako významné ako medicínske. Preto by mal byť transplantačný tím multidisciplinárny a mal by sa snažiť čo najtesnejšie spolupracovať s rodinami pacientov. Tak bude nielen zlepšovaný seba posudzovaný zdravotný stav pacientov, ale aj zabezpečená ich aktívna rehabilitácia a reintegrácia do spoločnosti.
5. Je dôležité sledovať seba posudzovaný zdravotný stav dlhodobo, keďže postupom času po transplantácii môže dochádzať k jeho zmenám. Rovnako dôležitý je longitudinálny výskum zmien spolupráce s imunosupresívnou liečbou.

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Jaroslav Rosenberger was born on March 17th, 1975 in Košice, Slovak Republic. After completing the secondary grammar school in Košice he started to study general medicine at the Medical Faculty of University of P. J. Šafarik in Košice. In July 1999 he graduated as a medical doctor (MD).

Since September 1999 he worked in University Hospital Košice. Till April 2002 he worked at I. internal clinic of University Hospital, after finishing a specialization study in internal medicine he moved to Dialysis Department. Since May 2005 he works at Nephrology and Dialysis Center Fresenius Košice and Transplantation Department of University Hospital. He finished his specialization study in nephrology in December 2005.

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