Self-rated health and mortality after kidney transplantation

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Part IV

Discussion of the study findings

Chapter 8

Discussion

8.1 General discussion

This thesis dealt with self-rated health (SRH), morbidity and mortality in kidney transplant recipients. Our findings have improved the understanding of these domains, which are connected to health perceptions after kidney transplantation (KT). We showed that a) self-rated health in transplanted recipients is predicted by sociodemographic, psychological and medical determinants; b) post-transplant anemia is associated with mortality independently of kidney function; and c) self-rated health might be used as an independent predictor of graft loss and patient mortality. This chapter summarizes and discusses the main findings of our study, examines its strengths and limitations and finally indicates implications for practice as well as possibilities for further research.

8.2 Main findings

Research question 1

Chapter 3 focuses on the relationship between SRH in transplant recipients and their graft function. We compared the absolute level of glomerular function (GF) at baseline versus its change over time regarding its impact on SRH at follow-up, because we expected a more precise prediction of the change over time on SRH at follow-up during the observation period. We found that SRH at the 12th month after transplantation was influenced not by the success of the transplantation shortly after transplant surgery, but rather by the change in GF over time. The absolute level of kidney function did not contribute significantly to the explanation of the variance in SRH at follow-up. However, the change in graft function over time contributed significantly to the explanation of the variance in SRH at twelve months after transplantation.

Research question 2

Chapter 4 explored changes over time in the medical and non-medical factors associated with SRH and compared their associations with SRH at follow-up for early and late cohorts stratified by time since transplantation. Furthermore, this chapter also evaluated and discussed the differences between outcomes in varying periods since transplantation and their significant relationship to SRH.

During the follow-up observation period in the early and late cohorts, SRH and glomerular filtration rate (GFR) increased, and transplantation-associated psychological distress decreased. The change in GFR over time consistently predicted SRH at follow-up in both cohorts. Furthermore, better SRH at follow-up was predicted by fewer late acute rejection episodes during the observation period in the late cohort after KT. Age was a predictor of SRH at follow-up in the early cohort only.

Research question 3

Chapter 5 focused on the long-term impact of post-transplant anemia (PTA) on SRH at up to 8 years follow-up in kidney transplant recipients stratified according to chronic kidney disease (CKD) stages: CKD stages 1-2 versus CKD stages 3-5. Unexpectedly, SRH

at baseline was not found to be associated with SRH at follow-up in either CKD cohort, in those with well-functioning graft as well as in the advanced stages of CKD. As a result, male gender, a decrease in hemoglobin value and decreased graft function over time predicted poorer SRH at up to 8 years follow-up in patients after kidney transplantation with CKD stages 1-2, but not in patients with CKD stages 3-5; in the latter group, higher age, male gender and chronic renal allograft dysfunction predicted poorer SRH. Surprisingly, changes in the hemoglobin value in both CKD groups during the whole period after transplantation were minor and not statistically significant. This might be explained by an increase in the prevalence of antianemic therapy in those patients with a decreasing hemoglobin value. Furthermore, the prevalence of antianemic therapy significantly increased from baseline to follow-up in patients with CKD stages 3-5.

Research question 4

Chapter 6 explored whether PTA shortly after KT predicts mortality at up to 10 years follow-up. The study was based on stratification of the sample according to CKD stages: CKD stages 1-2 versus CKD stages 3-5. We found that PTA was a predictor of mortality independently of kidney function. Mild and severe PTA in the first year after transplantation increased the higher risk of mortality independently of kidney function at up to 10 years follow-up. Mild PTA predicted a 6-fold higher risk of mortality and severe PTA a 10-fold higher risk of mortality compared with no PTA in CKD stages 1-2. However, patients with more advanced stages of CKD showed no association of mild PTA with mortality, probably as this only reflects their worse kidney function; however, severe PTA predicted a 10-fold higher risk of mortality. The other factor associated with increased risk of mortality was advanced age, and with decreased mortality female gender.

Research question 5

Chapter 7 established SRH as a general predictor of mortality and graft loss at up to 10 years follow-up. We found that average SRH was associated with a 4-fold higher and poor SRH with an 11-fold higher risk of patient mortality. Additional factors associated with mortality were higher age and decreased graft function. Average SRH was associated with a 3-fold higher risk of graft loss, and poor SRH with a 6-fold higher risk of graft loss. Additional factors associated with graft loss were chronic renal allograft dysfunction and new-onset diabetes mellitus after transplantation.

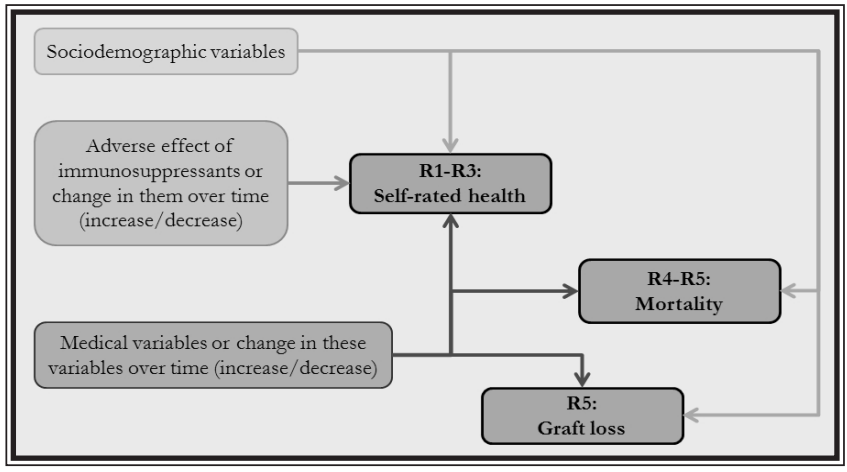
8.3 Discussion of the main findings

Figure 8.1 presents information based on the associations between independent factors (such as sociodemographic data, individual perceptions regarding side-effects of immunosuppressants and medical factors) and dependent outcomes (SRH, graft loss and mortality) according to the research questions (R1-R5). (Figure 8.1)

These research questions (R1-R5) might be combined when more variables are used to explain SRH or mortality. Therefore, the outcomes regarding SRH at follow-up as a dependent variable (R1-R3) are discussed in the first part of this chapter, namely "Self-rated health in transplanted recipients is predicted by sociodemographic, psychological and medical determinants". The second part, "Post-transplant anemia is associated with

mortality independently of kidney function", describes and analyzes the importance of PTA connected to mortality in transplanted recipients with well-functioning graft, because anemia is still an underestimated problem in KT patients (R4). The last part of this chapter, "Self-rated health might be used as independent predictor of graft loss and patient mortality", shows and discusses SRH as an independent predictor of patient's mortality as well as that of a graft (R5).

Figure 8.1 Diagram describing the relationships between independent factors and dependent outcomes (SRH, graft loss and mortality) according to the research questions (R1-R5)



Self-rated health in transplanted recipients is predicted by sociodemographic, psychological and medical determinants

Prediction of worse SRH among elderly, females and those of lower socioeconomic status has been well described in previous studies.[1-4] We partially found an association between age, gender and SRH at follow-up as mentioned above. In contrast, our results showed no associations between socioeconomic status and SRH; what might have played a role was that all patients were focused on their health perceptions during the regular interview. On the other hand, we incorporated socioeconomic status only as a confounder into the analyses of research question 1. Thus, we cannot exclude whether its impact on SRH might be possible in the stratified models and/or models based on mortality and graft loss. In this study, our main interest in the predictors of SRH was based on sociodemographic (age, gender), psychological and medical data.

Higher age was found to be an independent predictor of patients' SRH in our findings for studies without stratification. When the sample was stratified and became more specialized (stratification according to time since KT and CKD stages), we found no impact of age on SRH in the late cohort or in the cohort with well-functioning graft, most likely because other factors became more significant.

Female gender has been connected to poorer SRH generally;[3,5] surprisingly, our outcomes showed no comparable results. Gender was only associated with worse SRH at

up to 8 years follow-up in cohorts stratified according to CKD stages. Previously, no such association between men and worse SRH has been found. Benjamins et al. described related findings as a stronger relationship between SRH and mortality risk among men.[6]

Several psychological aspects regarding the association between SRH and kidney transplant recipients have been studied as well.[7-9] Our interest was to find the impact of individual adverse effects on SRH in accordance with a stratification related to time since transplantation. We found that a decrease in transplantation-associated psychological distress was linked to better SRH in the late cohort. Similar to our findings, Drent et al. (2008) divided their group of liver transplant patients into an early and a late cohort and showed differences between these groups in such a way that the late cohort reported more individual negative experiences than the early one.[10] A result based on increasing individual adverse effects by time since transplantation and its association with poor well-being was shown by "the Patient Outcomes Registry for Transplant Effects on Life (PORTEL)" study as well.[8] On the other hand, this study was based on the comparison between adverse effects of different immunosuppressive regimens (tacrolimus-based versus cyclosporine-based) and their impact on well-being.[8]

SRH was shown as a possible measure in health care alongside traditional biomarkers.[11] In line with this, our findings regarding SRH showed a strong association between kidney function and SRH in transplanted recipients during varying times since KT as well as in varying CKD stages. Kidney function was associated with SRH in patients with worse stages of CKD, probably as their partial reconciliation with a worsening transplanted kidney. Moreover, it seemed as if the existing chronic renal allograft dysfunction (CRAD), as a fact of kidney failure, played a role in the SRH of these recipients. Late acute rejection episodes had a significant relationship with SRH in the late cohort at 2 years of follow-up and CRAD at up to 8 years follow-up in worse CKD stages. Both of these rejections were shown as markers of graft failure in association with worsening of individual well-being.[10,12] In this thesis, post-transplant anemia (PTA) was the last medical factor to be studied as a possible predictor of worsening SRH. A decrease in the hemoglobin value over time predicted a poorer SRH at up to 8 years follow-up in patients with a very well-functioning transplanted kidney, but not in those with CKD stages 3-5. This might be interpreted as meaning that patients in CKD stages 3-5 have a well-known comorbidity of chronic kidney failure and this is therefore usually diagnosed and corrected in these patients. According to our findings no similar study has yet been published.

Post-transplant anemia is associated with mortality independently of kidney function

Anemia is a known predictor of mortality independently of kidney function.[13-15] Conversely, management practices, including therapy of PTA overall, have remained largely unchanged over the last 5 to 7 years.[16] A study performed by Amaral et al. in a dialyzed population showed that patients with mild and severe anemia of renal origin had an increased risk for mortality independently of their CKD stage and discovered that a hemoglobin value of 11.0 g/dl and higher led to a 60-70% reduction risk of mortality.[14] In our sample 31.1% of respondents had various grades of anemia; moreover, 8.5% of them did not reach even a hemoglobin value of 10.0 g/dl.

In line with these outcomes, "The National Kidney Foundation Disease Outcomes Quality Initiative" (NKF/KDOQI), the "Kidney Disease Improving Global Outcomes"

(KDIGO) and the "European Best Practice Guidelines" (EBPG) for diagnosis and treatment of renal anemia recommend a global assessment of the patient, which should consist of an inventory of complications of the dialyzed, or the perioperative and post-transplantation period, including inflammatory diseases, rejections, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), immunosuppressants and comorbidities as well as an using an adequate combination and dose of anti-anemia drugs.[13,15,17-20] In 2009, Spiegel and Chertow showed the benefit of renal anemia treatment by Erythropoiesis Stimulating Agents (ESA) and iron therapy in CKD patients, mainly in a dialyzed population.[21] In our sample more than two-thirds of the patients were treated by a combination of two antianemic drugs. As a contrast, outcomes from the last three to five years on the relative adequate-serum hemoglobin value showed a higher risk of stroke, thrombosis and progression of cancer;[22,23] thus, recent recommendations favor targeting treatment on the lower hemoglobin level than was practiced in the previous period.[24] However, the optimal strategy in treating anemia in a kidney transplant recipient has not yet been prescribed by guidelines, as anemia management studies in this group of patients have not sufficiently described. Furthermore, anemia management separately for patients with well-functioning graft is still an underestimated problem. These assumptions bring up new questions about the initial hemoglobin value to treat: dosing algorithms aimed at achieving and maintaining optimal target hemoglobin levels always along with taking care of the survival the transplant patient.

Self-rated health might be used as independent predictor of graft loss and patient mortality

Poor SRH is well known as a valid risk of mortality in the general population.[6,11,25,26] Surprisingly, studies separately based on the association between mortality, graft loss and SRH in kidney transplant recipients were lacking prior to our study.[27] Tanikella et al. (2010) studied the impact of SRH on mortality in liver transplanted patients and showed poor SRH to be an increased mortality predictor at up to 3 years follow-up.[28]

On the other hand, an excellent SRH as a survival and/or poor SRH as a mortality predictor were found in CKD populations, including dialyzed patients.[29-31] Previously, the impact of pre-transplant SRH on higher risk of mortality after KT had only supposed.[32] These findings, together with ours, establish SRH as a valid and a reliable indicator which can be used for a first impression of risk and might provide additional information on a patient's risk, independently of demographic, socioeconomic and clinical risk factors for mortality and graft loss.[27]

8.4 Strengths and limitations of the study

The strength of this thesis is its longitudinal design, varying from one to 10 years of follow-up, which enabled us to explore the impact of change over time in medical as well as psychological factors on SRH at follow-up and the impact of the mentioned factors together with SRH on mortality and graft loss. Thus far, the impact of our findings has a greater informative value in Chapter 4, because of the sample stratification by time since transplantation (early versus late cohort), and in Chapter 5 and 6 because of the sample stratification according to CKD stages (CKD stages 1-2 versus CKD stages 3-5). These stratifications of the sample in the mentioned chapters were performed to compare the possible influence of the impact of

independent factors on SRH by time since transplantation (Chapter 4) and to prevent bias due to the known impact of the kidney function on hemoglobin value (Chapter 5 and 6). Last but not least, all patients originating from one major transplant center in Slovakia over a number of years were asked to participate in the study to prevent selection bias as well as a biased approach specific to SRH.

The total number of the patients (n=76) who dropped out are a limitation of this study; on the other hand, there were no differences in age and gender between participants and non-participants or between those who provided complete or incomplete data at baseline (Chapter 3-7) or at follow-up examination (Chapter 3-5). Regarding the follow-up examinations, the varying time since transplantation, such as from 1 through 8 years in Chapter 5 and from 1 through 10 years in Chapter 6 and Chapter 7, might have a potential impact on the study findings. However, when compared with other studies[10,33] which were oriented on the transplant population the possibilities for this interpretation was shown. Therefore, more relevant studies, such as randomized control trials, are necessary to further explore this aspect. The SRH question and testing of clinical data were not conducted immediately after transplantation to prevent false findings due to perioperative stress, complications and subjective anticipation or suspense. Therefore, patients who died or lost their transplanted kidney before the first 3 months after KT were not incorporated into the study.

An additional limitation of our study is the fact that these findings such as post-transplant anemia, rejection episodes, chronic renal allograft dysfunction as well as other comorbidities, might be partially due to their potential lack of generalizability, as we used data from a single center sample; however we used consecutive patients without selection.

8.5 Practice implications

First of all, to increase patients' SRH and the probability of their survival, we suggest diagnosing and treating post-transplant anemia, a decrease in graft functions together with rejections episodes and chronic renal allograft dysfunction. Patients with a well-functioning transplanted kidney but with a post-transplant anemia might benefit from clinical evaluation as well as treatment (e.g. ESA, iron therapy, etc.) to reduce their otherwise higher risk of mortality and increase their SRH.

Second, SRH might be used as an inexpensive and swift predictor of risky kidney transplant recipients. Patients with poor SRH could undergo relevant clinical as well as laboratory assessment and/or treatment to reduce their high risk of mortality and graft loss. Furthermore, the pathways between other medical determinants associated with poor SRH, decreased quality of life and survival, such as comorbidities, impact of drugs and so on, should be unraveled as well.

Third, findings from comparing the prevalence of the dialysis modality as well as the overall score of performed transplantations and patients still on the waiting list between 2010 and 2011 in Slovakia are alarming. The prevalence of dialysis increased, while the prevalence of patients on waiting list decreased. In addition, transplantations performed from 2010 to 2011 decreased as well. At these points, there might be other factors, such as the aging population (the mean age was more than 60 years[34]), an increase in the number of comorbidities, and so on. On the other hand, the cooperation between the coordinating centers has increased, along with slight increase in the number of living donors, while the

number of deceased donors has stabilized, and the number of pre-empty transplantations has drawn attention to the complex problem of the necessary health care resources. This must be solved in order to increase the possibilities for dialyzed patients to have a chance for "a new transplanted kidney", which improve their SRH and extends their survival.

8.6 Possibilities for further research

In kidney transplant recipients

Firstly, according to our findings based on SRH in a prospective observation design from a single centre cohort study, we suggest continuing in this research in transplanted recipients covering national data from all four transplant centers in the Slovak Republic. Moreover, there would be the possibility to keep moving forward through international cooperation, such as the previous thesis managed by Rosenberger[35] in a cross-section study design. Our project as a first step studied SRH after KT and the causal pathway between SRH and mortality and graft loss and parts of the determinants of SRH. Thus, as a next step, other medical and non-medical factors in the transplant population regarding SRH should be studied. Furthermore, an additional study based on the association between sufficient antianemic therapy and SRH from a longitudinal perspective is necessary, because the current findings show that when a patient with anemia is treated and the Hb-value is kept in the normal range, no association between the change in the Hb-value over time and SRH at follow-up is evident.

Secondly, a further study into a sufficient hemoglobin value in transplant recipients has to be performed. This specific group of CKD does not yet have a confirmed definitive target hemoglobin level. The early initiation of treatment and maintaining of an adequate hemoglobin value might be enough to prolong the survival of patients after KT and their SRH. Therefore, a randomized controlled trial in ESA treatment of post-transplant anemia with a target hemoglobin value above 10.0 g/dl would be appropriate. It could then be verified whether treatment of anemia after KT decreases mortality as well as improves SRH in kidney transplant recipients and thus fills a gap in the guidelines for ESA in post-transplant anemia regarding hemoglobin value.

In pre-dialyzed and dialyzed patients

A previous cross-sectional research project carried out by Rosenberger[35] showed relationships between immunosuppressants, their adverse effects, compliance, kidney function and perceived health status in transplanted patients and compared quality of life after transplantation in KT recipients with that of dialyzed patients. In this longitudinal project we used SRH as an important indicator of health in transplanted recipients. Therefore, these findings enable us to elaborate a similar longitudinal prospective observational (non-intervention) study in the Slovak dialyzed population, because SRH is related to mortality and morbidity and finally also to resource utilization in the general population and in patients with chronic kidney disease as well. Such a project should study the associations between sociodemographic, psychological and medical factors as well as mortality in patients with chronic kidney disease.

The fact that SRH is easy to administer could enable the proposing of an additional international study. Currently dialysis clinics which are members of NephroCare use the

European Clinical Database (EuClid5)[36] for data management of their dialysis and pre-dialysis patients. A dialysis record also contains patients' self-evaluations of their problems between dialyses, if any occurred. Therefore, we would propose to NephroCare Coordination to add this very short, easy and significant question to the pre-dialysis nurse assessment in EuClid5[36] with a possible choice of answers: "In general, would you say your health is: a) excellent, b) very good, c) good, d) fair and e) poor." Patients all over the world would provide answers three times per week and therefore validation of the SRH concept would be multicenter and would include not only a large number of patients but also multiple measurements.

8.7 Conclusion

We found that the absolute level of kidney function shortly after successful transplantation was a very difficult measure to estimate a patient's SRH at follow-up because of the lack of a significant association with SRH one year after successful KT. On the other hand, a change in graft function over time showed a significant impact on SRH at follow-up; this means at one, two and up to 8 years follow-up after successful KT. At different times since transplantation, depending on CKD stages, different medical factors, such as late acute rejection episodes, chronic renal allograft dysfunction and post-transplant anemia, were found to be independent predictors of worsening SRH. Transplantation-associated psychological distress was the lone factor associated with SRH at a longer period after KT. Thus far, mild and severe anemia during the first year after KT have been found to be a patient's mortality predictor independently of kidney function in patients with CKD stages 1-2; on the other hand, severe anemia only increased the mortality risk in transplanted patients with CKD stages 3-5. Moreover, SRH at an early time since transplantation was approved as an independent predictor of a patient's and a graft's mortality. We confirmed that average SRH was associated with a 4-fold higher and poor SRH with an 11-fold higher risk of patient mortality at up to 10 years follow-up. Previously, average SRH had been associated with a 3-fold higher risk of graft loss, and poor SRH with a 6-fold higher risk of graft loss at up to 10 years follow-up.

Improving long-term post-transplantation medical and non-medical outcomes should be a priority in the management of transplant recipients to reduce the risk of morbidity and mortality. According to our findings from a single centre, further research based on SRH after KT, which as suggested will cover national and international data, would be essential to approve SRH as an independent predictor of the mortality risk. Similar research in a dialyzed population would also be interesting to study. These investigations might start with a very short, easy and significant question: "In general, would you say your health is: a) excellent, b) very good, c) good, d) fair, e) poor." The answer the patient provides to this question at the beginning of a consultation would provide a rather precise idea of the risk the patient is running.

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