

Review

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Health-related quality of life outcomes after kidney transplantation

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Abstract

With the improvements in short and long term graft and patient survival after renal transplantation over the last two decades Health-Related Quality of Life (HRQL) is becoming an important additional outcome parameter. Global and disease specific instruments are available to evaluate objective and subjective QOL. Among the most popular global tools is the SF-36, examples of disease specific instruments are the Kidney Transplant Questionnaire (KTQ), the Kidney Disease Questionnaire (KDQ) and the Kidney Disease-Quality of Life (KDQOL). It is generally accepted that HRQL improves dramatically after successful renal transplantation compared to patients maintained on dialysis treatment but listed for a transplant. It is less clear however which immunosuppressive regimen confers the best QOL. Only few studies compared the different regimens in terms of QOL outcomes. Although limited in number, these studies seem to favour non-cyclosporine based protocols. The main differences that could be observed between patients on cyclosporine versus tacrolimus or sirolimus therapy concern the domains of appearance and fatigue. This may be explained by two common adverse effects occurring under cyclosporine therapy, gingival hyperplasia and hair growth. Another more frequently occurring side effect under calcineurin inhibitor therapy is tremor, which may favour CNI free protocols. This hypothesis, however, has not been formally evaluated in a randomised trial using HRQL measurements.

In summary HRQL is becoming more of an issue after renal transplantation. Whether a specific immunosuppressive protocol is superior to others in terms of HRQL remains to be determined.

Introduction

Health-related quality of life (HRQL) contains multiple aspects of health related issues from the patients' perspective including physical, psychological, and social functioning and overall well-being [1-3]. Numerous clinical trials have established the importance of HRQL in various diseases, and it is increasingly popular to evaluate disease-specific and generic HRQL in clinical trials as a measure of patients' subjective state of health.

HRQL is also increasingly recognised as an important measure of outcome following solid organ transplantation. Along with significant quantitative improvements in patient and graft survival, HRQL has been appreciated as another valid outcome measurement.

HRQL investigations take a broad view on subjective health issues and consider health as a puzzle of singular domains of well-being. The pieces of this puzzle are psychological and social aspects of well-being in addition to physical and mental health. Some of these pieces are eval-

uated on either a subjective or an objective basis, some domains by both dimensions [3].

Kidney transplantation is the treatment of choice for end stage renal disease (ESRD). Advances in renal transplant procedures and immunosuppressive therapies have increased dramatically over the last decades, one year allograft survival rates are currently over 90 % [4]. The major goal of transplantation is the achievement of maximal quality and quantity of life while minimising the effects of disease and in renal transplantation also the costs of care. The units in which these socio-biological terms are reported depend on the condition that is being evaluated. Examples of these measures are quality-adjusted life years gained, disease-free life years gained, or healthy-year equivalents per unit cost of care. In renal transplantation the costs of care are not only limited to the transplant procedure but also to the evolving costs to treat adverse events, some of them caused by the immunosuppressive therapy.

Since the first successful kidney transplantation in the early 1950s, immunosuppressive therapies improved considerably, the most revolutionary development being the introduction of cyclosporine in the early 1980s. The introduction of new immunosuppressive agents has further increased the therapeutic options for immunosuppressive combination therapies in transplanted patients.

In parallel to better patient care and new immunosuppressive regimens the median survival of renal allografts improved continuously [5]. Hand in hand with these achievements, greater attention has been given to long-term QOL. However, so far HRQL was evaluated only in a limited number of clinical trials as subjective state of health [6-15]. It is generally accepted however, that patients with a functioning renal allograft have an improved HRQL as compared to patients on dialysis [14,16].

Measurement tools for HRQL after kidney transplantation

To evaluate the impact of a specific disease on HRQL, specific evaluation tools have to be utilised. These tools are sensitive enough to determine longitudinal changes of a disease but they are not appropriate to compare different diseases.

Disease-specific tools in HRQL evaluation after renal transplantation include the Kidney Transplant Questionnaire (KTQ) [17], the Kidney Disease-Quality of Life (KDQOL) [18] and the End Stage Renal Disease Symptom Checklist Transplantation Module (ESRDSC-TM) [19]. The same authors that invented the KTQ previously devel-

oped a dialysis specific HRQL questionnaire which is known as the Kidney Disease Questionnaire (KDQ) [17].

The KTQ as the first cited examples contains 26 questions in five domains (physical symptoms, depression, fatigue, relationship with others, frustration) each of which can be scored on a scale from 1 to 7, where the lowest score represents the lowest QOL. For the final analysis all points are summed up, thus the maximum score is 182 and the minimum 26 points. As others, these questionnaire need to be evaluated in the native language of the patient. A recent example of a KTQ evaluation study was performed by colleagues from Oviedo, Spain [20].

The KDQOL was initially developed for patients with chronic renal disease and dialysis patients. However, recent papers used this tool for the evaluation of transplant patients as well in order to compare them to patients on hemo- and peritonealdialysis [21]. The original KDQOL covers eleven dimensions with a different number of items. The dimension symptoms/problems include 34 items, effects of kidney disease on daily life 20 items, burden of kidney disease 4 items, cognitive function 6 items, work status 4 items, sexual functions 4 items, quality of social interaction 4 items, sleep 9 items, social support 4 items and patient satisfaction 2 items. In case of dialysis patients the domains dialysis staff encouragement with 6 items completes the list. The response options is a Likert scale whereas higher scores denote better QOL.

The ESRDSC-TM was specifically developed to evaluate the effects of immunosuppressant medication on QOL. The distributed questions are scored on a five-point Likert scale, again where higher scores represent better QOL.

The authors tested over 400 transplant patients and evaluated the test-retest correlation in a subset of 88 patients at an interval of one year and found adequate validity.

As in the above study, global indices are also used in renal transplant recipients. These tests summarize the global assessment of functioning and well-being into a single index value. In order to define this value the patient is asked to indicate her/his preference for a variety of specified health states.

Until now no single method has been shown to be ideal for measure HRQL under all circumstances. By comparing HRQL results from studies using different measuring tools, it is possible to get similar numerical results but a discrepancy in meaning. It has been shown that very different HRQL results can be obtained in the same population if different tools are used [22].

There are also generic tools used to determine the impact of any of a number of diseases in HRQL. Generic tools are useful for comparisons among groups and studies and for evaluating the impact of different diseases on QOL. These tools are used in HRQL research and include tests such as the Sickness Impact Profile (SIP), the 36-item short-form of Medical Outcomes Survey (SF-36), and the Nottingham Health Profile (NHP).

With more than 2000 publications, the SF-36 is one of the most widely used quality of life instruments worldwide [23,24]. The SF-36 questionnaire is a self administered survey and contains 36 items that take a few minutes to complete. It includes one multi-item scale that assesses eight health domains: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality; 8) general health perceptions.

Six dimensions are formed of Likert- or summative scales with three to six answer categories and verbal anchors for each answer category. Two tests are designed as Guttman- or cumulative scales with four dichotomous yes/no items for each category. Five of these dimensions are similar to the Nottingham health profile (NHP), but items in the SF-36 questionnaire are claimed to detect positive as well as negative states of health. For each dimension, item scores are coded, summed and transformed on a scale between 0 (worst) and 100 (best).

Studies evaluating HRQL after renal transplantation

The first to study the long-term quality of life after kidney and simultaneous kidney and pancreas transplantation were colleagues from Minnesota. In 1998 Matas and coworkers described the QOL assessed by using the SF-36 form [25]. The authors managed to have 446 patients evaluated once, 632 twice and 53 three times. The patients were between one and ten years after transplantation. The SF-36 scores did not change significantly over the years after transplantation and were consistently lower compared to the normal US population. Interestingly, diabetic and non-diabetic subjects scored similar on the mental health scales whereas non-diabetic patients scored better on physical functioning and on general health.

The same authors recently published a longitudinal relationship between adverse effects particular of immunosuppressive drugs in renal transplant recipients and QOL [9]. In this huge study 4247 self-selected patients were enrolled and assessed by a QOL questionnaire. The authors conducted a multivariate analysis which showed

that emotional problems, reduced sexual interest and headache were the main factors that negatively influenced QOL in these patients. Preliminary data from this self-reported health information program entitled the "Transplant Learning Center" were published by Hricik and colleagues [10]. The initial results obtained in 3676 patients were similar to those published in the final report one year later on 4247 patients.

A recent paper, also from the University of Minnesota but from different authors, evaluated the impact of transplantation on QOL in diabetic patients with ESRD [11]. Specifically, the authors addressed the interesting question whether simultaneous kidney/pancreas transplantation (KPT) confers a better QOL than kidney transplantation alone with subcutaneous insulin therapy. Most QOL readings improved after transplantation in both groups. After adjustment for co-morbidities, the authors found higher SF-36 scores in KPT in the domains of physical functioning, bodily pain, general health and the physical component. The better physical scores could be attributed to the perceived benefits of reduced secondary diabetes complications, the higher mental scores remained unexplained.

Johnson and colleagues published the first study that evaluated changes in QOL in the first year after renal transplantation split by gender and race [13]. The authors used three questionnaires to assess HRQL, the Sickness Impact Profile, Ferrans and Powers' Quality of life index, and the adult self image scales. African-American patients observed less QOL improvement compared to Caucasian patients, and women scored consistently lower than men. This study demonstrates nicely the although all participants improved their QOL, considerable racial and gender differences exist and these differences may affect care requirements.

Very recently, Franke et al. evaluated the HRQL in patients with end stage renal failure [26]. The trial explored the differences in HRQL among patients on the waiting list for kidney transplantation while maintained on hemodialysis and recipients of renal transplants. The outcome was measured with generic (SF-36) and disease specific tools (End Stage Renal Disease Symptom Checklist-Transplantation Module). In that trial the group of 80 dialysis patients on the transplant waiting list experienced a decreased satisfaction with social support, while the 222 patients after successful renal transplantation exhibited an increase of social support. Similarly, psychological distress was higher among patients on maintenance haemodialysis compared to the transplanted subjects.

A similar study in design by Jofre and coworkers found similar improvements in 88 out of 93 patients after successful renal transplantation [14]. The authors used the

Karnovsky Scale and the Sickness Impact Profile as evaluation tools. It is of note that although each transplant patient served as her/his own control and exhibited improved scores after transplantation, mainly the male patients reported a marked improvement in global scores, similar to what has been demonstrated by Johnson in the same year. As anticipated older patients and subjects with more comorbidities revealed less improvement compared to younger and fitter subjects.

In a randomised open-label trial in Europe, Australia and Canada Oberbauer and coworkers investigated the HRQL outcomes in patients after kidney transplantation [6]. In that trial 430 kidney transplant patients were randomly assigned three months after transplantation to continue cyclosporine and sirolimus therapy or to have cyclosporine withdrawn over a period of four weeks. The HRQL was measured at randomisation, and at one and two years after transplantation using the disease-specific KTQ tool and the generic SF-36 tool. Randomisation worked fine and no differences in baseline HRQL could be observed. In the two years follow-up investigation, the authors found a statistically significant improvement in two domains of the KTQ, fatigue and appearance in the cyclosporine free group. Furthermore, vitality scores in the SF-36 questionnaire were higher in the cyclosporine free – sirolimus group at two years compared to baseline values, but decreased in the combination group. It is of interest that the SF-36 vitality score of 64 in the sirolimus-steroid group at two years is higher than the mean SF-36 vitality score in the general US population which is reported to average 61. The other SF-36 scores were not different among groups at two years and generally lower than those reported for the general US population. These findings are consistent with those reported elsewhere for renal transplant recipients [8]. Shield reported that one year after transplantation, the study population score in vitality was in the 50th percentile of an age matched general US population.

Reimer et al compared the HRQL among 63 cyclosporine and an equal number of tacrolimus treated renal transplant recipients between 1997 and 1999 [7]. HRQL was assessed using the SF-36 and a disease-specific QOL-instrument, the End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESDR-SCL). The measurements were performed at transplantation and one year thereafter, time after transplantation and the type of immunosuppression were included into the regression model as independent variables. Patients with tacrolimus-based immunosuppression reported significantly better global and disease specific HRQL than those receiving cyclosporine microemulsion.

Discussion

HRQL is becoming more of an issue in terms of outcome measurements after renal transplantation. Advances in immunosuppressive therapy improved graft and patient survival, but it remains unknown whether this objective success projected also in subjective patients appreciation and well-feeling. Kidney transplant recipients live with varying degrees of disease specific physical and psychological impairments, some of them attributed to immunosuppressant adverse effects. In few clinical trials of renal transplantation medium-term HRQL outcomes of patients on different immunosuppressive regimen were investigated [6-8].

Among the first authors that evaluated HRQL in renal transplant patients and compared different immunosuppressive regimens on that outcome were Shield and colleagues. Similar to subsequent studies by Oberbauer et al. and Reimer et al. the authors found an improvement of HRQL after transplantation. Rejection episodes were associated with less improvement of HRQL. Furthermore, HRQL was statistically significant different by treatment. Tacrolimus treatment was associated with better appearance in the Bergner Physical Appearance Scale, which was designed to measure cosmetic side effects of medical therapy such as gingival hyperplasia and hirsutism.

In the study by Reimer and coworkers, which investigated QOL in two groups of 63 patients receiving cyclosporine or tacrolimus respectively similar results were obtained. Patients on tacrolimus immunosuppression exhibited statistically higher scores in two domains of the global test (SF-36) as well as in three subgroups of the disease specific questionnaire. The two domains of the global test with higher scores were "Physical Functioning" and "General Health", the three areas of the specific test were tacrolimus patients scored better were "Limited Physical Capacity", "Cardial and Renal Dysfunction" and "Increased Growth of Gum and Hair".

These two studies suggest that patients experience a better physical state and appearance on tacrolimus than on cyclosporine. Although the study by Oberbauer and colleagues did not compare tacrolimus to cyclosporine but rather evaluated the impact of early cyclosporine elimination from a combination regimen with sirolimus, similar results were obtained at one and two years after transplantation. Statistically significant treatment by assessment time interactions were observed for SF-36 vitality scores in patients after cyclosporine withdrawal. In the disease specific evaluation by the KTQ (kidney transplant questionnaire), patients off cyclosporine scored higher in the appearance score and felt less fatigue than those on a combination of cyclosporine and low dose sirolimus.

Besides the evaluation of the effects of different immunosuppressive protocols on HRQL after transplantation, it is feasible to discuss the potential importance of HRQL evaluations before transplantation and the probable implication of obtained scores on patient selection for transplantation. As discussed in context with the study by Jofre and colleagues, older and multimorbid patients gained less improvement after transplantation than younger subjects. It is also well known in these older subjects that the time from transplantation to the point where subjects have an advantage from the transplant procedure in terms of survival benefits compared to wait listed but not transplanted matched subjects is almost twice as long as in younger subjects [27]. These two arguments would suggest that renal transplantation is not the preferable renal replacement therapy in elderly patients with end stage disease. This hypothesis however is easy to reject. Firstly although it takes roughly one year in patients between 60 and 70 years of age until the likelihood of survival is higher than for matched wait listed dialysis patients, there is no discussion that overall survival is higher than on dialysis. Secondly, renal transplantation is more cost effective than dialysis treatment also in elderly patients if offered within a timely period after development of end stage renal failure [28]. Therefore the evaluation and results of HRQL obtained before transplantation may not be used as criterion for the selection of patients for the transplant waiting list.

The scores of a pre-transplant evaluation of HRQL may however be useful for the detection of non-compliant patients. A regular intake of the prescribed immunosuppressive drugs is key to prevent graft rejection in these subjects and a considerable number of late acute rejections are caused by non-compliant patients that stopped their immunosuppression [29]. If such patients at risk could be identified in advance for example by HRQL questionnaires, a strategy could be adopted to improve compliance. Such strategies would include more support from all members of a transplant team and also shorter follow-up intervals as outpatient to check the immunosuppressive trough levels more frequently than in compliant patients. So far however, no data exist on the feasibility of this concept. Future studies of HRQL in renal transplantation however should evaluate whether medication compliance of patients can be predicted before transplantation.

What is needed in renal transplantation is a questionnaire administered before transplantation that has predictive power for the QOL of these patients in the post-transplant period. Patients may give their preferences in terms of QOL and the results of this survey may be included into the doctors algorithm of choice for a specific post-transplant care and drug regimen. This sounds logical but was impossible in the past because only a very limited arma-

mentarium of immunosuppressive drugs were available. In the last years however several new immunosuppressive drugs were investigated in renal transplant recipients and thus a stronger incorporation of patients preferences on drug selection might be possible.

Conclusions

In conclusion, although clinical trials evaluating the HRQL in patients after renal transplantation are relatively scarce, the few published papers yielded rather similar results. In general HRQL improved after successful kidney transplantation compared to dialysis, this effect was more pronounced in male than in female patients. Although not a big surprise, these studies first document that renal transplantation is not only the cheaper renal replacement therapy in the long term and associated with less mortality but also provides a better quality of patients' life. Furthermore, these trials showed that physical activity, energy and appearance are important domains that are influenced by the mandatory immunosuppressive regimen. Thus, if equal clinical effectiveness of some commonly used immunosuppressive regimens is assumed, the physicians' algorithm of identifying the optimal regimen for a specific patient should also include the patients' preferences for individual important QOL domains.

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