ORIGINAL RESEARCH

Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study

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Abstract

Aims. To explore the predictive value of adherence to their immunosuppressive medication in kidney transplant recipients in the first year after kidney transplantation as a determinant of graft loss and mortality up to 12 years (prospective analysis) and its association with sociodemographic and medical factors and social support (cross-sectional analysis).

Background. Poor adherence to their immunosuppressive medication in kidney transplant recipients remains the leading preventable cause of poor patient outcomes.

Design. Prospective and cross-sectional study.

Methods. At baseline, 325 patients 3–12 months posttransplantation were invited to participate. Adherence was assessed using collateral reports – a combination of patients’ self-evaluation and an estimate by their nephrologist. The patients provided sociodemographic and medical data and completed the End-Stage Renal Disease Symptom Checklist and Multidimensional scale of perceived social support. At follow-up (average 7.1 years), data on patients and graft survival were obtained. All data were collected from 2002–2013. Multinomial regression analysis and Cox regression were performed.

Results. A total of 297 patients (48.1% 12.8 years, 61.6% men) agreed to participate (response rate 91.4%); 67.4% were considered as fully adherent. Poor adherence was associated with higher risk of graft loss and mortality over 12 years. Female sex, higher education, higher perceived side effects of corticosteroids, better perceived cardiac and renal function and higher perceived family social support in the first year posttransplantation were associated with full adherence to immunosuppressive treatment.

Conclusions. Patients with poor adherence to the immunosuppressive medication in the first year after kidney transplantation showed increased likelihood of graft loss and death over 12 years compared with the adherent patients.
Introduction

Kidney transplantation (KT) is established as the best treatment modality for patients with end-stage renal disease due to its superior effect on quality of life, mortality and cost in comparison with other renal replacement therapies (Laupacis et al. 1996, Wolfe et al. 1999). However, KT requires strict adherence to a lifelong medical regimen of immunosuppressive treatment. To a great extent, adherence to such a regimen has been shown to prevent rejection and loss of a transplanted graft, consequent impairment of physical or mental functions, unnecessary pain or early death, a higher number of hospitalizations and consequently higher costs of treatment (Brickman & Yount 1996, Laederach-Hofmann & Bunzel 2000, Dickenmann et al. 2002, Butler et al. 2004, Denhaerynck et al. 2005). Nevertheless, depending on the assessment method, rates of adherence vary from 50–90% and poor adherence to immunosuppressive treatment is still the leading preventable cause of graft loss (Schafer-Keller et al. 2008, Denhaerynck et al. 2009).

Although subjective methods based on self-reporting are suspected of leading to under-reporting the levels of non-adherence when compared with other methods (Denhaerynck et al. 2005, Fine et al. 2009), Griva et al. (2012) found self-reported levels of adherence to be higher than when estimated by immunosuppression serum concentrations (Griva et al. 2012). A combination of self-reporting with clinician/pharmacist reports increases the sensitivity and specificity of this method (Schafer-Keller et al. 2008, Mitchell et al. 2011, Penn et al. 2011). The long-term accuracy of this assessment, such as future graft loss or mortality, is very rarely studied despite it being the most cost-effective way of monitoring adherence in a clinical environment.

Background

To date, the vast majority of studies exploring factors determining adherence have considered patients as either adherent or non-adherent. Recent studies, however, have stressed the consequences of subclinical non-adherence.
and have indicated that even a minor deviation from the prescribed medication is sufficient to lead to worse clinical outcomes (De Geest et al. 1995, 1998, Takemoto et al. 2007, Nevins & Thomas 2009). The World Health Organisation (2003) identified five dimensions of adherence: social/economic, therapy-related, healthcare system-related, condition-related and patient-related. Among the latter, the most consistent determinants of non-adherence are younger, living alone and poor social support (Di Matteo 2004, Denhaerynck et al. 2007). Similarly, a higher perception of adverse effects has been consistently associated with poor adherence (Denhaerynck et al. 2007, Korb-Savoldelli et al. 2010). According to Laupacis et al., patients at 3 months post-KT report new symptoms related to the side effects of immunosuppressive treatment (Laupacis et al. 1996), such as easy bruising/slow wound healing, adverse effects related to mood, sexuality and to changes in physical appearance (Moons et al. 1998, 2003, Matas et al. 2002). Non-adherence was found to appear early after transplantation and increase in the first 2 years (Couzi et al. 2013, Massey et al. 2013), affecting up to half of all patients during the first 6 months after; it was also associated with increased acute rejection rates and eventual graft loss (Nevins & Matas 2004). To explore these factors, we used the conceptual framework described by Murray, where he combines environmental factors, patient characteristics and medication adherence as a process that ultimately affects patient outcomes (Murray et al. 2004).

The study

Aims

Study aims were to explore the predictive value of adherence to immunosuppressive medication in the first year after kidney transplantation as a determinant of graft loss and mortality up to 12 years (prospective analysis) and its association with sociodemographic and medical factors and social support (cross-sectional analysis). Furthermore, we focused on the association of sociodemographic factors, medical factors (kidney function, side effects) and social support with different levels of adherence, assessed by the method most accessible in the clinical environment: patient-rated and physician-rated adherence in the first year after KT.

Design

Prospective, longitudinal and cross-sectional study.

Sample/participants

All consecutive patients from the Louis Pasteur University Hospital Transplantation centre in Kosice, Slovakia, who met the inclusion criteria were asked to participate. To be included in the study at baseline, patients had to fulfil the following criteria: to be 3–12 months after KT; to be in a relatively stable condition, such as not being hospitalized or treated for rejection at the time of interview; to have a functioning graft; and to have no psychiatric diseases, including severe dementia and mental retardation, listed in their medical records. If patients were hospitalized or unstable at 3–12 months post-KT, their assessment was deferred by 1-month. If they were still unstable at this point, they were excluded from the study due to not meeting the inclusion criteria. Patients received their immunosuppressive medication independently from this study, based solely on the decision of their transplant nephrologists, in line with standard recommendations issued by the ‘Kidney Disease Improving Global Outcomes’ (KDIGO) Clinical Practice Guideline for the care of kidney transplant recipients (Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group 2009). Of the total number of patients visiting the transplantation centre in Kosice, 325 met the inclusion criteria and were asked to participate. Of these, 8% (26) declined to participate and of the remaining 299, a further 0.6% (2) provided incomplete data; thus, the final number of participants was 297 (91.4%). The Mann–Whitney U-test and chi-square analyses did not indicate significant differences between respondents and non-respondents regarding age and sex. At follow-up, patients had to be a minimum of 4 and a maximum of 12 years posttransplantation.

Data collection

At T1, 3–12 months after transplantation, data collection of all sociodemographic, medical and psychosocial data was undertaken. T1 data collection was performed from 2002–2009 (T1). At follow-up in 2013 data on patient status (graft loss and mortality) were collected (T2) (Figure 1).

Sociodemographic data (T1)

The sociodemographic variables – age, sex, education, average income and marital status – were obtained in a structured interview by a trained interviewer. Educational background was categorized into 3 groups: primary, secondary and university education. Average income was first evaluated by dividing the household budget by the number of persons in the household and then categorized based on the minimum wage in Slovak Republic as follows: low (lower
than 1·5 times the minimum wage); average (1·5–2 times the minimum wage); and high (higher than two times the minimum wage). Marital status was represented by two options: living alone (single, divorced, widowed) and cohabitating (married/living in a cohabitating relationship). All of the sociodemographic variables were used for group comparison; however, only sex, education and marital status were used in the analysis. Female sex, postsecondary education and cohabitating were used as reference categories.

**Medical data (T1)**

Information about medical variables was taken from patient medical records. The observed medical variables were kidney function, time since transplantation (in months) and number of acute rejection episodes. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula (in millilitres per minutes) (Levey et al. 2009, Levey & Stevens 2010).

**Graft loss and mortality (T2)**

At follow-up 3–11 years after the first data collection, information about each patient’s status was taken from medical records. The observed medical variables were graft loss and patient mortality. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula (in millilitres per minutes) (Levey et al. 2009, Levey & Stevens 2010).
records, cross-checking it with the transplantation statistical report of the hospital. A patient’s status was categorized as either with functioning graft, graft loss or deceased. No patients were re-transplanted during the follow-up period.

**Adherence (T1)**
Evaluation of adherence was obtained in a confidential structured interview by a trained interviewer and was based on collateral reports – a combination of the self-evaluation of adherence by the patient and an estimate of the patient’s adherence by his/her nephrologist based on his/her regular check-ups and clinical results (Greenstein & Siegal 1998, Laederach-Hofmann & Bunzel 2000, Rosenberger et al. 2005, Schafer-Keller et al. 2008, Schmid-Mohler et al. 2010). In a confidential interview, patients were asked: ‘Over the last month, how often did you skip a dose, delay taking a dose by more than 2 hours or changed the timing of a dose?’ They were instructed to rate their adherence on a scale from 1–5, where excellent adherence was represented by: 1 (patient did not break the prescribed regimen over the past month); 2 (once over the past month); 3 (2–3 times over the past month); 4 (once per week over the past month); and 5 represented very poor adherence (more than twice weekly). Subsequently, the nephrologist was interviewed about each patient’s adherence to the immunosuppression therapy using the same scale while taking into consideration his/her opinion on variations in immunosuppressant levels or knowledge about prescribed and used immunosuppressants. Patients were considered to be adherent only if they declared their adherence by themselves as excellent, in agreement with their physician’s opinion.

**Side effects of treatment (T1)**
Side effects of immunosuppressive treatment were assessed using the End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD-SCL-TM) (Franke et al. 1999), which consists of 43 items making up six subscales: limited physical capacity, limited cognitive capacity, cardiac and renal dysfunction, side effects of corticosteroids, increased growth of gums and hair and transplantation-associated psychological distress. The number of the items for each subscale varies from 5–10 and for each item, patients estimate the severity of the symptom on a scale from 0 (not at all)–5 (extremely). Afterwards, an index for each symptom is computed by dividing the severity index score by the number of items in the subscales, with higher score indicating higher severity.

**Perceived social support (T1)**
Patients also completed the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al. 1988), a 12-item self-report scale that consists of three subscales, each assessing perceived availability and satisfaction with support received from either family, friends or a ‘significant other.’ Each item represents a statement, e.g. ‘There is a special person who is around when I am in need’ and the patient is asked to rate it on a 7-point scale, where 1 represents fully disagree and 7, fully agree. The totals for each subscale are added up, with a maximum 28 points per subscale; a higher score indicates more social support.

**Ethical consideration**
The local Ethics Committee approved the study.

**Data analysis**
Frequencies, means and standard deviations were calculated for the sample description. The Mann–Whitney U-test, Kruskal–Wallis test and chi-square test were used to test the differences in age and sex between respondents and non-respondents as well as between the adherence groups in patients. Then, two two-step Cox regression analyses were performed to determine the association between adherence as an independent variable in the first year post-KT and graft loss and mortality at follow-up. In first step, sex, age and education were analysed; in the second step, adherence was added to the analysis. To avoid any analysis of robustness issues, we included bootstrapping in the Cox regression analysis. The analysis used 2000 bootstrap resamples and a bias-corrected and accelerated 95% confidence interval (CI). Finally, multinomial logistical regression analysis was performed to identify the determinants of excellent and good adherence. Adherence was set as the dependent variable, with the poor adherence group set as a reference. Sex, education and family status were set as factor variables and age, number of acute rejection episodes, eGFR, ESRD-SCL-TM subscales and the MSPSS subscales were set as covariants in the main-effect model. IBM SPSS 20 for Windows was used to analyse the data (IBM Company, Chicago, IL, USA).

**Validity and reliability**
Collateral reports as as assessment of adherence have been previously used in patients after kidney transplantation (Rosenberger et al. 2005) and found to be highly accurate when compared with electronic monitoring (Schafer-Keller et al. 2008). The End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD-SCL-TM) and the Multidimensional Scale of Perceived Social Support...
(MSPSS) have been validated in the Slovak population (Nagyova et al. 2009). The Cronbach’s α of the ESRD-SCL-TM subscales was previously reported between 0.76–0.85 (Franke et al. 1999, 2003). In our sample, Cronbach’s α varied from 0.83 (for increased growth of hair and gums)–0.89 (for limited physical activity). The MSPSS (Zimet et al. 1988) has been extensively used in end-stage renal disease patients (Kimmel et al. 1998, Shidler et al. 1998, Cohen et al. 2007), with a reported Cronbach’s α ranging from 0.85–0.91 (Zimet et al. 1988). In our sample, the Cronbach’s α for the subscale ranged between 0.90–0.93.

Results

Both the patients’ reports of their own adherence and their physicians’ estimates were slightly skewed, as over 80% of patients and physicians scored 1 (no deviation from the prescribed regimen). In previous research using self-reports, the cut-off score for non-adherence varies as either skipping one or more doses a month (Siegal & Greenstein 1997, Greenstein & Siegal 1999, Rosenberger et al. 2005) or two or more doses a month (Raiz et al. 1999, Vasquez et al. 2003). Accordingly, our sample was split into three adherence groups: Group 1: ‘Excellent adherence’ (67.4% of the sample) consisting of patients where both patients and nephrologists reported not missing any doses over the past month; Group 2: ‘Good adherence’ (26.3% of the sample): one or both reported 2; and Group 3: ‘Poor adherence’ (6.3% of the sample): one or both scored 3 or over. (Figure 2).

When comparing the three adherence groups (Table 1), no significant differences were present regarding sociodemographic or medical factors. Significant differences were found when comparing the Excellent adherence and Good adherence groups in the self-reported adverse effects in three scales of ESRD-SCL-TM: Limited Cognitive capacity (P ≤ 0.01), Increased Gum and Hair Growth (P ≤ 0.01) and Transplantation-related Psychological Distress (P ≤ 0.05) and all subscales of Perceived Social Support Scales (P ≤ 0.01) (Table 2). The basic characteristics of the sample are shown in Tables 1 and 2.

Graft loss and mortality

Information on graft loss and on patient mortality was collected 3–11 years after the first data collection, with an average follow-up period of 7.1 (2.2) years. The χ² of the Cox regression model 1 for graft loss was 16.77. According to the bootstrap analysis, age (HR 0.9, P ≤ 0.05), sex (HR 0.02, P ≤ 0.001) and poor adherence (HR 6.03, P ≤ 0.05) contributed significantly to this model. Younger age, male sex and poor adherence significantly increased the odds of future graft loss. The χ² of the Cox regression model 1 for mortality was 12.1, with poor adherence as the single factor significantly contributing to this model (HR 3.07, P ≤ 0.05) (Table 3, Figure 3).

Factors associated with excellent and good adherence

When analysing the factors associated with excellent and good adherence, the model produced by multinomial regression explained 42.7% of variance. Female patients with higher education, a higher number of perceived side effects of corticosteroids (ESRD-SCL-TM), better perceived cardiac and renal function (ESRD-SCL-TM) and higher perceived family social support in their first year post-KT were more likely to belong to the excellent adherence group than to the poor adherence group. Similarly, patients reporting a higher number of perceived side effects of corticosteroids (ESRD-SCL-TM), better perceived cardiac and renal function (ESRD-SCL-TM) and higher perceived family social support in their first year post-KT were more likely to belong to the good adherence group than to the poor adherence group (Table 4).

Discussion

This study explored the different levels of adherence as reported by patients and physicians in the first year after kidney transplantation and the long-term clinical consequences of poor adherence in terms of graft loss and mortality and factors associated with adherence as well. We found that poor adherence predicted mortality, but not graft loss. Regarding factors associated with excellent adherence, we found that female patients with higher education, a higher number of perceived side effects of corticosteroids, better perceived cardiac and renal function and higher perceived family social support in their first year post-KT were more likely to belong to the excellent adherence group than to the poor adherence group. The last three factors also made it more likely for patients to belong to the good adherence group than to the poor adherence group.

In line with the literature, the vast majority of the patients (67.4%) rated themselves and were considered by their physicians as fully adherent to their prescribed immunosuppressive regimen, with only 26.3% admitting to skipping/or being suspected of skipping or changing one dose over the past month and only 6.3% admitting/being sus-
Adherence after KT and its impact on graft loss and mortality

Table 1 Sociodemographic and medical characteristics of the sample.

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Excellent adherence N = 200</th>
<th>Good adherence N = 78</th>
<th>Poor adherence N = 19</th>
<th>Whole Sample N = 297</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>N (%)/AM (sd)</td>
<td>N (%)/AM (sd)</td>
<td>N (%)/AM (sd)</td>
<td>N (%)/AM (sd)</td>
</tr>
<tr>
<td>Men/Women</td>
<td>113 (56.5)/87 (43.5)</td>
<td>55 (70.5)/23 (29.5)</td>
<td>15 (78.9)/4 (21.1)</td>
<td>183 (61.6)/114 (38.4)</td>
</tr>
<tr>
<td>Age</td>
<td>46.71 (12.81)</td>
<td>50.64 (11.97)</td>
<td>52.22 (14.36)</td>
<td>48.11 (12.8)</td>
</tr>
<tr>
<td>Education</td>
<td>19 (9.5)/94 (47)/87 (43.5)</td>
<td>16 (20.5)/37 (47.4)/25 (32.1)</td>
<td>6 (31.6)/8 (42.1)/5 (26.3)</td>
<td>41 (13.81)/139 (46.8)/117 (39.39)</td>
</tr>
<tr>
<td>Primary/Secondary/Postsecondary</td>
<td>Low/Average/High</td>
<td>107 (53.5)/40 (20)/53 (26.5)</td>
<td>58 (74.4)/2 (2.6)/18 (23)</td>
<td>12 (63.2)/2 (10.5)/26 (26.3)</td>
</tr>
<tr>
<td>Income*</td>
<td>67 (33.5)/133 (66.5)</td>
<td>33 (42.3)/45 (57.7)</td>
<td>8 (42.1)/11 (57.9)</td>
<td>108 (36.4)/189 (63.6)</td>
</tr>
<tr>
<td>Family status†</td>
<td>Living alone/Cohabitating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from KT (months)</td>
<td>7.69 (3.49)</td>
<td>7.69 (3.39)</td>
<td>8.13 (4.35)</td>
<td>7.74 (4.21)</td>
</tr>
<tr>
<td>Kidney function (eGFR – Levey, mL/minutes)</td>
<td>55.7 (18.57)</td>
<td>56.86 (20.43)</td>
<td>49.23 (16.88)</td>
<td>54.73 (20.16)</td>
</tr>
<tr>
<td>Number of acute rejection episodes</td>
<td>0.44 (0.57)</td>
<td>0.67 (0.63)</td>
<td>0.33 (0.65)</td>
<td>0.49 (0.6)</td>
</tr>
<tr>
<td>Type of acute rejection episodes</td>
<td>None/Cellular/</td>
<td>131 (65.5)/17 (8.5)/35 (44.9)/9 (11.5)/15 (79)/2 (21.1)</td>
<td>181 (60.9)/26 (8.8)/19 (6.4)/6 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Humoral/Combined/</td>
<td>7 (3.5)/4 (2)/41 (20.5)</td>
<td>12 (15.4)/2 (2.6)/20 (25.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy not performed</td>
<td>12 (15.3)</td>
<td>3.5 (2.83)</td>
<td>3.12 (2.33)</td>
<td>3.37 (2.57)</td>
</tr>
<tr>
<td>Deceased/Living</td>
<td>183 (91.5)/17 (8.5)</td>
<td>75 (96.2)/3 (3.8)</td>
<td>19 (100)/–</td>
<td>277 (93.3)/20 (6.7)</td>
</tr>
<tr>
<td>Haemodialysis/Peritoneal dialysis/Both</td>
<td>146 (73)/33 (16.5)/21 (10.5)</td>
<td>64 (82.1)/2 (2.6)/12 (15.3)</td>
<td>17 (89.5)/2 (10.5)/33 (11.1)</td>
<td>227 (76.4)/37 (12.5)/33 (11.1)</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>3.34 (2.52)</td>
<td>3.5 (2.83)</td>
<td>3.12 (2.33)</td>
<td>3.37 (2.57)</td>
</tr>
<tr>
<td>Glimeralonephritis/Tubointerstitial nephritis/polycystic kidneys/diabetes mellitus/other or unknown causes</td>
<td>80 (40)/35 (17.5)/3 (3.8)/12 (15.3)</td>
<td>30 (38.5)/20 (25.6)/3 (3.8)/11 (14.1)/3 (15.8)/4 (21.1)/8 (42.1)</td>
<td>112 (37.7)/57 (19.2)/19 (6.4)/29 (9.8)/80 (26.9)</td>
<td></td>
</tr>
<tr>
<td>Current immunosuppressive protocol</td>
<td>Pred + Csa + MMF/Pred</td>
<td>134 (67.4)/44 (22)/45 (57.7)/23 (29.5)/17 (89.5)/2 (10.5)/196 (66.6)/67 (22.5)/20 (6.7)/14 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ MMF + Tac/Csa</td>
<td>12 (6)/10 (5)</td>
<td>6 (7.7)/4 (5.2)</td>
<td>7.69 (2.14)</td>
<td>7.82 (2.17)</td>
</tr>
<tr>
<td>+ MMF/Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Average follow-up (years)</td>
<td>7.59 (2.11)</td>
<td>8.5 (2.23)</td>
<td>7.69 (2.14)</td>
</tr>
<tr>
<td>Patient mortality/Graft loss</td>
<td>23 (11.5)/9 (4.5)</td>
<td>12 (15.4)/2 (2.6)</td>
<td>7 (36.8)/2 (10.5)</td>
<td>42 (14.1)/13 (4.4)</td>
</tr>
</tbody>
</table>

Low (≤1.5 times the min. wage), Average (1.5–2 times the min. wage), High (≥2 times the min. wage).

†Cohabiting (Married/In a cohabitating relationship), Living alone (Single/Divorced/Widowed).

Pred, prednisone; Csa, cyclosporin A; MMF, mycophenolate mofetil; Tac, tacrolimus.

Expected of skipping or changing more than two doses over the past month (Butler et al. 2004, Denhaerynck et al. 2005). Clinical consequences such as graft loss have been confirmed as being linked to poor adherence (Nevins & Matas 2004, Morrissey et al. 2007, Denhaerynck et al. 2009); this was also confirmed in our sample – patients who admitted or were considered as delaying, skipping or altering their medication twice a month in the first year.
after kidney transplantation were more likely to lose their graft or to die in the future. In this study, we found no association between subclinical adherence (delaying, skipping or altering their medication once a month) and poor long-term patient outcomes. The ‘poor adherence’ group of patients did contain a higher percentage of patients with diabetes, polycystic kidneys or systemic diseases listed as their primary kidney disease and although these differences were not significant, we cannot rule out that the burden of their primary disease could have affected their survival. It is also quite possible that patients who are not adhering to their immunosuppressive treatment have a tendency to skip their other medications, too, which in turn can increase their odds of dying. Unfortunately, in this study, we only focused on the immunosuppressive treatment and were not able to verify this theory.

Contrary to our results, some previous studies found age to be positively associated with adherence, favouring the group of patients between their late 40s and early 60s over patients in their twenties (Chisholm-Burns et al. 2012, Dharancy et al. 2012, Couzi et al. 2013, Russell et al. 2013), while others contradict these results (Russell et al. 2013), while others contradict these results (Russell et al. 2012, Couzi et al. 2013).
In spite of the slight differences between the groups regarding their adherence, multinomial regression produced models with some differences between the excellent and good adherence group. The excellent adherence group consisted of significantly more females and patients with higher education. Both groups reported a higher number of perceived side effects of corticosteroids (ESRD-SCL-TM) and better perceived cardiac and renal function (ESRD-SCL-TM) along with higher perceived family social support in their first year post-KT in comparison with the poor adherence group. It appears that patients in their first year post-transplant are able to tolerate some negative side effects of immunosuppressive treatment and not deviate from the prescribed regimen more than once a month, as long as they are able to also perceive the positive impact it has on their overall health. On the other hand, patients not receiving sufficient social support from their family were more likely to show less adherence. It is possible that family support provides additional benefits to maintaining adherence, benefits that a ‘friend’ or ‘significant other’ may not be able to facilitate, whether it is instrumental support with immunosuppression – collecting medication from the pharmacy, daily reminders to take medication or being available when dealing with the physical and psychological side effects of treatment.

In our sample, more than 90% of the patients were treated with a protocol containing a corticosteroid or prednisone, which are commonly associated with higher side effects (Reimer et al. 2002, Franke et al. 2006). Surprisingly, patients reporting more corticosteroid-related side effects also tended to be more adherent. These patients, however, also perceived their cardiac and renal function as better, which could hypothetically mean that patients can endure side effects without altering their adherence as long as they are convinced that the treatment is effective. As the literature suggests increased rates of non-adherence over time, it is possible that this effect eventually wears off (Butler et al. 2004, Denhaerynck et al. 2005, Morrissey et al. 2007).

In line with previous findings, family social support was found to be associated with better adherence (DiMatteo 2004). Similarly, in our study, the more support patients received from their families, the more likely they were to fully adhere to their prescribed medication and vice versa – the less support from family patients perceived, the more likely they were to break their prescribed regimen.

**Strengths and limitations**

The main strength of this study is the combination of sociodemographic, medical and psychosocial variables in a prospective follow-up for a minimum of 3 and a maximum of 12 years. We used collateral reports to assess adherence, as the most cost-effective way of monitoring adherence in a clinical environment (Schafer-Keller et al. 2008). Another strength of this study is the fact that the average number of patients undergoing kidney transplant at the Louis Pasteur University Hospital Transplantation centre in Kosice, Slovakia, during the observation period was 31.4 per year – representing about one-fourth of all kidney transplantations carried out in Slovakia. Therefore, our cohort contained a substantial proportion of national transplant recipients and for this study, all consecutive patients fitting the inclusion criteria were asked to participate to prevent selection bias. However, this may also be considered as one of the limitations of the study – all of our patients were enrolled from a single centre and the sample consisted of rather younger and predominantly Caucasian patients and the number of patients who lost their graft or died was quite small; therefore, our findings cannot be generalized without further consideration. Similarly, we have limited information on patients who dropped out prior to the start of this study due to graft loss or mortality. Similarly, it is difficult to determine the adherence rates in patients who did not agree to participate in the study. Finally, as this was an experimental observational study, causal associations between predictors and outcomes cannot be definitely confirmed.

**Conclusions**

We found that older males with lower education, lower social support from family and worse perceived kidney function were more likely to skip/alter two or more doses of their prescribed immunosuppressive medication per month in their first year after successful kidney transplant. In our sample, subclinical non-adherence was not associated with worse patient outcomes. However, poor adherence in the first year posttransplantation was associated with increased risk of poor future graft and patient outcomes in the following 12 years. The results show that medical staff and intervention programmes need to target patients who admit to skipping/changing even as little as one dose every 2 weeks in their first year after transplantation due to the potential severe consequences. Special attention should be paid to the side effects reported by patients and to their social support network, especially their family. Further research is needed to determine the pathways between adherence and future patient outcomes and other factors that come into play in this process, such as depression, functional status and overall health-related quality of life.
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### Conflict of interest

No conflict of interest has been declared by the author(s).

### Author contributions

All authors have agreed on the final version and meet at least one of the following criteria [recommended by the ICMJE (http://www.icmje.org/ethical_1author.html)]:

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

### References


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Table 4 Multinomial regression analysis (main-effect model): factors associated with excellent and good adherence in the first year post-KT.

<table>
<thead>
<tr>
<th>Factors associated with excellent adherence</th>
<th>Wald</th>
<th>Exp (B)</th>
<th>95% CI</th>
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<td>Limited cognitive capacity</td>
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<td>Social support – Significant Other (MSPSS)</td>
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</table>

Nagelkerke pseudo $R^2 = 42.7%$

* $P \leq 0.05$; ** $P \leq 0.01$.

1Reference category: poor adherence group.

2Reference category: Female sex.

3Reference category: University.

ESRD-SCL-TM, End-Stage Renal Disease Symptom Checklist; MSPSS, Multidimensional Scale of Social Support.


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