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ORIGINAL ARTICLE

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

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Summary

Noncompliance with 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. A total of 161 adult kidney transplant recipients were interviewed about their self-rated health, social support, education, stress from adverse effects and compliance with the immunosuppression. The 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 successful 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, pretransplant 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]. Little is known about subclinical noncompliance, which involves violation of treatment assessed in the absence of any apparent rejection episode or graft loss. This is a consequence of 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 [2,7,10–11]. 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 cyclosporin A levels, knowledge about the amount of prescribed immunosuppressive medication).

Despite the 'minority' of subclinical noncompliance in comparison with 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 [2,4,14,15]. In addition, noncompliance is associated with significantly decreased quality of life [8,16].

The aim of this study was to examine the prevalence of subclinical noncompliance in kidney transplant recipients and to explore its characteristics. In addition, the study focused 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. Of the 171 patients, 161 agreed to participate 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 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.

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 (two to three times 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

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	≤0.05
Facial changes (moon face, hirsutism)	40.3	40.6	42.3	
Depression	34.2	26.6	42.3	≤0.05
Fear, anxiety	33.6	29.7	37.2	
Sleep disorders	30.9	25.0	35.9	
Gingival hyperplasia	23.5	12.5	32.1	≤0.001
Leg oedemas	22.8	17.2	29.5	
Skin lesions (eczema, skin tumours, warts)	20.8	12.5	26.9	
Hair loss	17.4	17.2	19.2	
Facial oedemas	17.4	15.6	19.2	
Sexual dysfunction	16.8	12.5	19.2	
Diarrhoea	11.4	9.4	14.1	
Fragile skin (easy bruises)	10.1	10.9	10.3	

Values are expressed as percentage.

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 (haemodialysis, 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–Whitney *U*-test for continuous variables (age, summary score of stress from immunosuppression, time from transplantation) and chi-square 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 <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 <6; the first and second quartiles); social support; education; and modality of dialysis before transplantation. Cut-offs 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 haemodialysis before transplantation (79.9%). The majority of organs were from cadaveric donors (97.5%). The predominant immunosuppression protocol consisted of cyclosporin, mycophenolate mofetil (MMF) and prednisone. 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 of 139 (68.3%) patients rated

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	
Haemodialysis	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, azathioprine; MMF, mycophenolate mofetil; Tac, tacrolimus; P, prednisone.

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

themselves as excellent compliers with their immunosuppressive treatment. By contrast, their nephrologist categorized 82 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 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

Table 4. Differences between compliant and noncompliant patients.

	Compliant	Noncompliant	*P*-value
Variables in χ^2-test (frequency)			
Gender			
Male	34	53	0.071
Female	30	25	
Current immunosuppressive regimen			
CsA, azathioprine, prednisone	12	8	0.111
CsA, prednisone	9	15	0.283
CsA, MMF, prednisone	26	29	0.734
Tacrolimus, MMF, prednisone	4	3	0.388†
CsA, MMF	3	13	0.049*†
Azathioprine, CsA	3	3	0.751†
CsA	4	5	0.627†
Self-rated health			
Excellent	24	13	0.011*
Good	30	41	
Fair	10	23	
Satisfaction with social support			
Excellent	38	31	0.027*
Good	22	29	
Fair	4	15	
Education			
Elementary	6	9	0.682
Secondary	47	52	
University	11	17	
Dialysis modality before transplantation			
Haemodialysis	53	59	0.570
Peritoneal dialysis	8	10	
Both methods	3	7	
Variables in *t*-test (mean ± SD)			
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‡
Total score of stress from adverse effects	6.4 ± 4.9	9.7 ± 7.5	0.003**‡

*$P < 0.05$, **$P < 0.01$.
†Fisher's exact test.
‡Mann–Whitney *U*-test.

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 [20–24]. However, paediatric 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.* [24] demonstrated that female gender and marital status is connected with noncompliant behaviour from self-reports of 241 kidney transplant recipients. 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. In contrast, Kiley *et al.* [25] found, among 105 renal allograft recipients, that male gender was associated with noncompliance with the medication. These results are in concordance with our findings, although their definition of noncompliance was based on cyclosporin 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 [22,23]. 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

Table 5. Logistic regression analysis of risk factors of noncompliance.

Variables	*P*-value	Odds ratio	95% CI
Male gender	0.001**	7.49	2.40–23.39
Immunosuppressive protocol			
CsA, azathioprine, prednisone	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	2.44–61.88
Medium stress (summary score 6–12)	0.649	1.27	0.46–3.53
Satisfaction with social support			
Fair	0.039*	4.55	1.08–19.24
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	0.92–14.83

*$P < 0.05$, **$P < 0.01$.

[20,22–25,27]. 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, similar to studies by De Geest *et al.* [2], Frazier *et al.* [24] and Raiz *et al.* [22]. Some studies found psychological factors, including depression, anxiety, patient's beliefs and coping strategies, to be predictors of noncompliance [4,28,29]. 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 decided 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 [1,30], 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 [2,4,6,11,14,19]. 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 a 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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