Therapeutic Adherence in Kidney Transplanted Adolescents

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Abstract

Introduction: Medication adherence affects the prognosis of kidney transplant recipients, since it is a determinant factor for the risk of rejection and loss of renal graft. Adolescence is a stage where many factors can influence therapeutic adherence, including cognitive development, emotional issues and family dysfunction.
The objective of this study was to evaluate therapeutic adherence in adolescents ≥ 12 years-old who were submitted to kidney transplant and are currently being followed at a Pediatric Kidney Transplantation Center.
Methods: Collection of demographic and clinical data; application of the Treatment Adherence Measure Questionnaire, between June and August 2022.
Results: There were 28 adolescents being followed. All responded to the questionnaire. The median time between transplant and questionnaire was 80 months.
Nine adolescents (32%) answered that they had already forgotten to take medication and 16 (57%) had been careless with the time of the medication. Only 11 adolescents (38%) answered that they have always complied with treatment. Of the patients who responded that they had already forgotten to take their medication, it was found that 6/9 (67%) had infra-therapeutic tacrolimus levels detected at least once and 3/9 (33%) had acute graft dysfunction. Of the patients who responded that they always adhered to therapy, it was found that only 1 (5%) had infra-therapeutic tacrolimus levels, without criteria for acute graft dysfunction.
Conclusion: Non-adherence to therapy is frequent in adolescents submitted to kidney transplant. It is crucial to develop strategies focused on adolescents to improve understanding of the disease and raise awareness of the importance of treatment adherence.

Keywords: Adolescent; Kidney Transplantation/psychology; Medication Adherence; Patient Compliance

INTRODUCTION

Adherence to therapy is defined as the process by which patients take medication according to a given prescription/medical recommendation.[1]
Therapeutic adherence is one of the main determinants of disease management in clinical practice, especially in the case of chronic diseases.[1] Non-adherence to therapy may lead to a reduction in the clinical benefits of medication, as well as the use of avoidable means of diagnosis and treatment, and may be a factor of increased morbidity and mortality.[1,2]

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Globally, it is estimated that the degree of adherence to chronic therapies, in developed countries, is only 50%, which is of great concern in terms of public health.[1]

Various methods have been used to measure adherence to therapy, including patient questionnaires/self-reports; pill count; electronic medication monitors; prescription renewal fees; use of biochemical markers, among others.[1] The various methods have advantages and disadvantages.[1,2]

In the case of the population undergoing organ transplantation, adherence to therapy is of particular importance, since non-adherence can result in graft rejection.[2] Some studies suggest that rates of non-adherence to therapy may be as high as 70% in patients undergoing transplantation.[2,3] Non-adherence to therapy may explain the lack of significant improvement in the survival rate of renal grafts in recent years despite the development of potent immunosuppressants.[2,4]

Adolescents, in particular, are at a stage in life where many factors can influence the way they see their illness and the therapy. Emotional, social, family or mental health problems as well as patient and family beliefs and attitudes are the most studied predictors of adherence.[5,6] More than the age of the adolescent itself, their developmental stage is one of the most important factors. Adolescence is a crucial time for physical, pubertal and cognitive maturation, in addition to psychosocial changes, including identity formation and the development of independent social relationships. At this stage in their life, adolescents are expected to take increasing responsibility for their health and health care.[5] Some studies show that in the adolescent population, non-adherence can vary from 10% to 90%, for chronic illnesses.[5,6] Non-adherence to treatment is a major cause of graft loss in kidney transplant adolescent recipients.[7]

The aim of this study is to evaluate the adherence to therapy in adolescents submitted to kidney transplant followed at a pediatric renal transplantation center.

METHODS

Study Design and Population

Kidney transplant recipients who were 12 years-old or older during the study period and who were being followed at the pediatric nephrology and kidney transplantation unit of an academic hospital were included in the study. All adolescents were included regarding time of follow-up, with the aim of analyzing adherence over time. Adolescents with intellectual development disorders whose caregivers actively participated in completing the questionnaire were not excluded. Adolescents whose caregivers were also unable to understand the questionnaire were excluded from the study.

A therapeutic adherence questionnaire was applied to the patients, which included seven questions (see Annex 1). The questionnaire was completed by the patient on the day of a clinical evaluation scheduled between June and August 2022. The questionnaire used was translated and validated by Delgado & Lima.[8] The study was approved by the Ethical Committee of Lisbon Academic Center and an informed consent was requested for participation in the study.

Clinical data were collected directly from the electronic files. Variables collected from clinical records were: sociodemographic data (sex, age); etiology of chronic kidney disease; date of kidney transplantation; donor type; prescribed immunosuppressants; serum levels of tacrolimus; estimated glomerular filtrate rate; history of acute rejection; and results of kidney biopsies, if performed.

Subsequently, the responses to the therapeutic adherence questionnaire and the clinical data were compared, namely serum levels of tacrolimus, history of acute rejection and results of kidney biopsies, if performed.

Infra-therapeutic levels of tacrolimus justified by identified clinical reasons other than non-adherence to treatment, for example diarrhea, change in somatometry or higher interval between taking the drug and measuring its levels, were not considered in this study.

Statistical Analysis

Categorical variables were presented in absolute numbers and percentages. Continuous variables were presented using the mean and standard deviation, if the distribution was normal, or using the median, minimum, maximum and interquartile range, if the distribution was not normal. The Mann-Whitney U-test was performed to compare the median frequencies of low tacrolimus levels and Chi-square test to compare the proportions of non-adherent patients according to different categories. Significant results were considered when $p<0.05$. IBM SPSS ©v.26 package was used for statistical analyses.

RESULTS

Between June and August 2022, a total of 42 kidney transplanted children were followed at our Unit, among them 28 (67%) were ≥ 12 years-old. Thirteen (46%) were male. The median time from transplant to the questionnaire was 6 years, with a minimum of 5 months and maximum of 13 years.

Congenital anomalies of the kidney and urinary tract (36%; n=10) and glomerulopathies (29%; n=8) were the most frequent causes of stage 5 chronic kidney disease (Table 1).

The median age at transplantation was 9 years-old, with a minimum of 4 and maximum of 15 years-old. The majority of transplants were from deceased donors (86%; n=24) and non-preemptive (71%; n=20).

Immunosuppression in 27 patients (96%) consisted of tacrolimus, mycophenolate mofetil and prednisolone (Table 1).

Table 1. Patient characteristics (n=28)

Male gender, n (%)	13 (46%)
Etiology of chronic kidney disease, n (%)	Uronephropathy/renal dysplasia: 10 (36%) Glomerulopathy: 8 (29%) Hereditary disease: 4 (14%) Kidney injury in the context of septic shock: 2 (7%) Vascular disease: 1 (4%) Unknown: 3 (11%)
Age at transplantation, median (min; max)	9 years-old (4; 15)
Time to transplantation, median (min; max)	80 months (5; 159)
Type of donor, n (%)	Deceased donor: 24 (86%)
Type of transplant, n (%)	Preemptive: 8 (29%)
Immunosuppression, n (%)	Prednisolone: 28 (100%) Mycophenolate mofetil/Mycophenolic acid: 27 (96%) Tacrolimus: 27 (96%) Sirolimus: 1 (4%)

Table 2. Responses to the therapeutic adherence questionnaire (n=28)

1.	Have you ever forgotten to take your medicine for your illness? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 1 (4%) Rarely: 8 (29%) Never: 19 (68%)
2.	Have you ever been careless with the timing of taking medication for your illness? , n (%)	Always: 0 (0%) Often: 1 (4%) Frequently: 0 (0.0) Sometimes: 4 (14%) Rarely: 11 (39%) Never: 12 (43%)
3.	Have you ever stopped taking medication for your illness because you feel better? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 0 (0%) Rarely: 1 (4%) Never: 27 (96%)
4.	Have you ever stopped taking medication for your illness, on your own initiative, after feeling worse? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 0 (0%) Rarely: 0 (0%) Never: 28 (100%)
5.	Have you ever taken one or more pills for your illness on your own after feeling worse? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 0 (0%) Rarely: 0 (0%) Never: 28 (100%)
6.	Have you ever stopped therapy for your illness because you ran out of medication? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 0 (0%) Rarely: 1 (4%) Never: 27 (96%)
7.	Have you ever stopped taking medication for your illness for any reason other than your doctor's advice? , n (%)	Always: 0 (0%) Often: 0 (0%) Frequently: 0 (0%) Sometimes: 0 (0%) Rarely: 0 (0%) Never: 28 (100%)

We obtained 28 responses to the questionnaire- 100% of the patients (Table 2). Nine patients (32%) answered that they had already forgotten to take their medication; 16 (57%) had already been careless with the time of taking the medication; 1 (4%) had already stopped taking medication for his illness because he felt better; 1 (4%) had interrupted the therapy because he had run out of drugs; and 11 (38%) reported always complying with the therapy (Table 2).

When analyzing blood levels of tacrolimus in patients who answered that they had already forgotten to take their medication (9/28) it was found that six (67%) had, at least, one infra-therapeutic tacrolimus trough level. Between those, three (50%) had acute graft dysfunction, with one requiring renal biopsy (33%), without criteria for graft rejection.

Of the patients who responded that they always complied with the therapy, including the time to take the medication (11/28), it was found that only one (5%) had infra-therapeutic tacrolimus trough levels, without criteria for acute graft dysfunction. There was no statistically significant difference between the two groups ($p = 0.78$).

Among patients who only reported being careless with the time of taking the medication (7/28), but never forgot or stopped to take it, none had infra-therapeutic tacrolimus trough levels or criteria for acute graft dysfunction.

Concerning age at transplantation, we verified that between those who were < 10 years-old at time of transplantation (17/28; 61%), five (29%) answered that they had already forgotten to take their medication, nine (53%) had already been careless with the time of taking the medication, and five had infra-therapeutic tacrolimus trough levels (29%); those who were ≥ 10 years-old at time of transplantation (11/28; 39%), two (18%) had already forgotten to take their medication, three (27%) had already been careless with the time of taking the medication, and one had infra-therapeutic tacrolimus levels (9%). Within this last age group, between patients with age ≥ 15 years-old at time of transplantation (3/28; 11%), one (33%) revealed they had already forgotten to take their medication, two (66%) had already been careless with the time of taking the medication, but only one had infra-therapeutic tacrolimus trough levels (33%). There was no statistically significant difference between the groups.

Regarding previous status at time of transplantation, between those who were preemptive (8/28; 29%), three (38%) revealed they had already forgotten to take their medication, four (50%) had already been careless with the time of taking the medication, and two had infra-therapeutic tacrolimus levels (25%); and those who had previously undergone renal replacement techniques (20/28; 71%), six (30%) revealed they had already forgotten to take their medication, 12 (60%) had already been careless with the time of taking the medication, and four

had infra-therapeutic tacrolimus levels (20%). There was no statistically significant difference between the groups.
Comparing therapeutic adherence according to the time between kidney transplant and the questionnaire, from those who had been transplanted less than 5 years ago (60 months) 2/10 (20%) had already forgotten to take their medication, 3/10 (30%) had already been careless with the time of taking the medication, and 1/10 had infra-therapeutic tacrolimus trough levels (10%); between those who had been transplanted more than 5 years ago 8/18 (44%) had already forgotten to take their medication, 9/18 (50%) had already been careless with the time of taking the medication, and 6/18 had infra-therapeutic tacrolimus levels (33%). There was no statistically significant difference between the groups.

DISCUSSION

In our cohort, approximately one third of patients forgot to take their medicine at some point in their illness, which represents a high percentage of patients. When looking exclusively for the time of taking the medication, the percentage of failures was even higher with more than half stating they had already been careless with the time of taking the medication.
Other studies found a rate of non-adherence to therapy of approximately 9%-44% in kidney transplant recipients.[2] However, none of these studies were conducted among pediatric patients.
When a comparative analysis was performed between the responses to the questionnaire and the measurement of tacrolimus levels, it was found that two thirds of the non-compliant patients had infra-therapeutic levels at least once, with criteria of acute graft dysfunction in half, which can have many clinical implications including kidney graft loss. In clinical practice, it is often found that patients only admit therapeutic failures or even other relevant complications when something goes wrong in the medical examinations.
Among patients who only reported being careless with the time of taking the medication but never forgot or stopped to take it, none had infra-therapeutic tacrolimus levels or criteria for acute graft dysfunction.
When we evaluated therapeutic adherence according to the time of transplantation, we verified that patients submitted to a kidney transplant five or more years before the questionnaire had more failures to therapy, with greater number of infra-therapeutic levels of tacrolimus. Although these results were not statistical significant, it may suggest that patients may become more careless with chronic therapy with time, so it is important to maintain a tight follow-up.
As limitations of this study, we point out that the size of the sample may limit some results and the statistical analyses, particularly when comparing subgroups of patients. The adolescents completed the questionnaires, but the responsibility for taking the therapy may not lie entirely with the adolescent and there may be at least supervision by caregivers, which was not evaluated on this study. As a strength of the study, it was not limited to the application of a questionnaire, but it also included the comparison of the adolescents' responses with clinical and laboratorial data.
Despite the limitations mentioned, this study contributed to increasing knowledge about adherence to therapy in adolescents submitted to a kidney transplant.
New technologies, should be considered to improve communication between patients and health institutions, facilitating the follow-up of transplant patients, avoiding the difficulties of travel reported by patients in accessing transplantation centers, reducing the costs and maximizing health care in the national territory. Some studies show that people who use medication reminder apps are significantly more likely to adhere to their medications.[9,10]
Transition of adolescents to adult care may also be a challenging process and may worsen therapeutic adherence,[7] therefore it is important to be alert to this risk at this stage. Nonetheless, in some cases, there may be an improvement in therapeutic adherence, as adult clinic settings may better fit some patients.[7] It is important to understand if the adolescent, despite having turned 18 years-old, is not prepared for transition, or if a new environment and new health team may be more suitable for him.
In conclusion, non-adherence to therapy is frequent, so it is crucial to develop strategies focused on adolescents to improve the understanding of the disease and raise awareness to the importance of therapy adherence.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
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Contributorship Statement

ABR: Material preparation, data collection and analysis, writing the original draft.
ARC, ASV and SC: Material preparation, data collection.
PJM: Material preparation, data collection and analysis, reviewing and editing the original draft.
AZ, FD, PCR and ARS: Conceptualization and supervision
JES: Conceptualization, supervision and final approval.
All authors approved the final version to be published.

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Annex 1

Questionário de Adesão à Terapêutica (Traduzido)

Alguma vez se esqueceu de tomar os medicamentos para a sua doença?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez foi descuidado com as horas da toma dos medicamentos para a sua doença?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez deixou de tomar os medicamentos para a sua doença por se sentir melhor?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez deixou de tomar os medicamentos para a sua doença, por sua iniciativa, após se ter sentido pior?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez tomou um ou vários comprimidos para a sua doença, por sua iniciativa, após se ter sentido pior?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez interrompeu a terapêutica para a sua doença por ter deixado acabar os medicamentos?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6

Alguma vez deixou de tomar os medicamentos para a sua doença por alguma outra razão que não seja a indicação do médico?

Sempre	Quase sempre	Com frequência	Por vezes	Raramente	Nunca
1	2	3	4	5	6