

Strategies to improve medication adherence in kidney transplant recipients: Addressing education and pill burden

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Abstract. *Background and aim:* Adherence to immunosuppressive therapy is crucial for the success of kidney transplantation. This study aimed to evaluate medication adherence among kidney transplant recipients (KTRs) and identify factors associated with non-adherence. *Methods:* A cross-sectional study was conducted with 98 KTRs from a single transplant center. Adherence was assessed using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS). Sociodemographic and clinical data were collected through interviews and medical records. Logistic regression analysis was performed to identify factors associated with non-adherence. *Results:* The prevalence of timing non-adherence (taking medication >2 hours late) was 48.98%. Missed doses were reported by 19.39% of KTRs. Lower education levels were significantly associated with delayed medication intake ($p=0.020$). A higher number of prescribed medications was associated with a greater risk of missing consecutive doses ($p=0.027$). Logistic regression analysis identified education level (OR=0.72; 95%CI: 0.54-0.95; $p=0.020$) and number of medications (OR=1.89; 95%CI: 1.07-3.33; $p=0.027$) as significant predictors of non-adherence. *Conclusions:* Non-adherence to immunosuppressive therapy, particularly timing non-adherence, was common among KTRs. Lower education levels and a higher number of prescribed medications were associated with non-adherence. Interventions targeting these factors, such as tailored patient education, health literacy improvement, and medication regimen simplification, may enhance adherence and transplant outcomes. (www.actabiomedica.it)

Key words: kidney transplantation, medication adherence, immunosuppressive therapy, patient education, medication regimen complexity

Introduction

Chronic kidney disease (CKD), characterized by persistent abnormalities in kidney structure and function (1), has emerged as a global health concern with a rising prevalence (2). In Brazil, an estimated 133,464 individuals receive dialysis treatment, with a mere 22% on the waiting list for kidney transplantation (Tx) (3).

This limited access to transplantation, starkly contrasting with higher rates in European nations, underscores the critical need to improve transplant accessibility and organ donation rates in Brazil. Several factors contribute to this disparity, including lower rates of organ donation, socioeconomic disparities in access to healthcare, and a higher prevalence of CKD risk factors in the Brazilian population. The rise in CKD cases

is primarily attributed to the increasing prevalence of systemic arterial hypertension (SAH) and diabetes mellitus (DM), collectively accounting for 65% of dialysis patients in Brazil (3).

For patients with end-stage CKD, renal replacement therapy becomes essential, encompassing hemodialysis, peritoneal dialysis, or kidney Tx (1). Kidney Tx offers a significant advantage over dialysis, conferring longer survival and enhanced quality of life (4,5). However, post-transplantation care presents a unique challenge: ensuring the long-term viability of the transplanted organ. This hinges largely on adherence to immunosuppressant (ISS) therapy, crucial for mitigating the risk of organ rejection (6,7). Long-term use of immunosuppressants, while essential, can lead to significant side effects, impacting patients' quality of life and potentially influencing adherence.

Alarming, kidney transplant recipients exhibit the highest rates of non-adherence to ISS among solid organ transplant recipients, with reported rates fluctuating between 20% and 70% (8–11). This underscores the critical need to identify and address non-adherence to improve long-term transplant outcomes. Non-adherence to immunosuppressive therapy can lead to organ rejection, jeopardizing the success of the transplant and potentially leading to serious health complications, including graft loss and the need for return to dialysis (12).

Various strategies exist to monitor adherence, including pill counting, self-reporting, side effect documentation, laboratory analysis of immunosuppressive drug levels, and electronic monitoring (11). While electronic monitoring is considered the gold standard, its high cost often limits its feasibility (11). Consequently, self-reporting emerges as a practical and widely used method for assessing non-adherence due to its ease of implementation, low cost, and moderate correlation with other methods (13,14). However, self-reporting relies on patient honesty and may overestimate adherence. To mitigate this, combining self-reporting with other strategies can provide a more comprehensive understanding of medication adherence and reasons for non-adherence (13,14).

The Basel Assessment of Adherence Scale for Immunosuppressives (BAASIS) is a widely utilized self-report instrument for evaluating adherence to

immunosuppressive therapy (13,15). This validated questionnaire measures adherence over the past month, providing valuable insights into patients' medication-taking behaviors. Studies employing behavioral interventions to enhance adherence in kidney transplant recipients have demonstrated a reduction in non-adherence rates following counseling and targeted interventions (15,16).

Thus, this research aims to measure adherence to immunosuppressants in kidney transplant recipients using the BAASIS scale, contributing to a better understanding of adherence patterns in this population. By identifying factors associated with non-adherence, this study can inform the development of targeted interventions to improve medication adherence and, ultimately, enhance long-term transplant outcomes.

Methods

This is a descriptive, cross-sectional, prospective study with a quantitative approach conducted in post-kidney transplant patients treated at the Nephrology Outpatient Clinic of a teaching hospital in the interior of São Paulo - Brazil. A convenience sample of 98 kidney transplant patients treated at the nephrology outpatient clinic from November 2021 to May 2022 was used.

Clinical data were collected from electronic medical records, and de-identified for analysis, after acceptance by the patient for inclusion in the research, as well as completion of the informed consent form. Creatinine values, serum levels of immunosuppressants, and complementary exams were collected at the time of the interview, which occurred at least three months post-transplantation. The interviews were conducted by the nurses of the Hospital's Transplant Service, in a specific office, with privacy and personalized care for the purpose of better understanding adherence to immunosuppressants. While the interviews were conducted in person, the data were anonymized before analysis to ensure patient confidentiality.

The responsible caregiver was included in the interview when the patient had impaired reading ability.

Assessment of treatment adherence was made using the validated Portuguese version of the BAASIS®

scale (17). This scale was originally developed by Dobbels et al. (2010) and validated for use in Portuguese by Marsicano et al. (2013) (17,18). This easily administered instrument assesses adherence to drug therapy in terms of the number of doses and times prescribed by the physician. The scale consists of four “yes or no” questions, with which recipients report their adherence to the immunosuppressive regimen in the last four weeks of treatment. Non-adherence will be considered as any positive (yes) response to any item of the instrument (17,18).

Inclusion criteria were patients of both sexes, aged over 18 years at the time of the interview, kidney transplant recipients with at least 3 months of transplantation, and who were being treated at the transplant outpatient clinic, who agreed to participate in this research and who signed the Informed Consent Form.

Patients who withdrew authorization or no longer wished to participate in the research were excluded; who were absent for reasons that prevented them from participating at the time of data collection or who did not meet the inclusion criteria.

An instrument was constructed for the collection of sociodemographic data with factors that impact the patient’s risk of adherence to immunosuppressive therapy. This instrument was designed in a questionnaire style, containing questions about age, sex, color, origin, marital status, education, occupation, which people and how many of them lived in the same residence, monthly income, medications in use, and whether they were responsible for the medication, questions that according to the current literature demonstrate the potential to influence adherence or not to health treatments. Then, the BAASIS scale was applied. Both the

BAASIS scale and the sociodemographic questionnaire are included as supplementary material to this manuscript.

Regarding data analysis, the programs MiniTab, Stats Direct, and GraphPad were used. Qualitative variables were analysed using Fisher’s test or Chi-square test (χ^2). For quantitative variables with Gaussian distribution, the unpaired t-test was used for comparison between two groups. For quantitative variables without Gaussian distribution, the Mann-Whitney test was used for two groups. Additionally, logistic regression analysis was performed to identify factors associated with non-adherence. An alpha error of 5% was admitted, considering values of $P \leq 0.05$ as significant.

Results

Ninety-eight patients were interviewed, with a mean age of 50.06 years (range 18 to 79 years), mostly male (51.02%), from other cities in the state of São Paulo (78.57%), and more frequently white (63.27%) and married (58.16%).

Table 1 presents the results of the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) administered to the 98 kidney transplant recipients.

The data reveal varying levels of non-adherence across different aspects of medication-taking behavior. Notably, nearly half of the participants (48.98%) reported taking their immunosuppressants more than 2 hours late in the preceding 4 weeks, indicating a significant prevalence of timing non-adherence.

Table 1. BAASIS Scale Questions and Percentage of “YES” Responses.

BAASIS Scale Questions	Percentage of “YES” Responses
1. In the last 4 weeks, have you missed taking your immunosuppressants as prescribed?	19.39%
2. In the last 4 weeks, have you missed taking consecutive doses of your immunosuppressants?	3.06%
3. In the last 4 weeks, have you taken your immunosuppressants more than 2 hours late?	48.98%
4. In the last 4 weeks, have you taken a lower dose of immunosuppressants than prescribed?	4.08%

Source: The Authors.

Table 2. The relationship between the question: “Did you fail to take several consecutive doses of your immunosuppressive medication in the last 4 weeks?” with taking the medication without the help of third parties and the number of prescribed medications.

Did you fail to take several consecutive doses of your immunosuppressive medication in the last 4 weeks?							
Information	Total		Yes		No		P-value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
		98	100.00	3	3.06	95	
Taking medication without the help of third parties							
Yes	86	87.76	2	66.67	84	88.42	0.260
No	12	12.24	1	33.33	11	11.58	
Medications (quantity)							
1. Medication	1	1.02	0	0.00	1	1.05	0.027
2. Medications	4	4.08	1	33.33	3	3.16	
3. Medications	93	94.90	2	66.67	91	95.79	

Source: The Authors.

Approximately one-fifth of the participants (19.39%) admitted to missing doses of their immunosuppressants during the same period. Conversely, lower rates of non-adherence were observed for taking consecutive missed doses (3.06%) and reducing prescribed dosages (4.08%). These findings underscore the multifaceted nature of medication adherence and highlight areas requiring targeted interventions to improve immunosuppressant adherence in this patient population.

The underlying diseases of the participants were primarily chronic glomerulonephritis (33.6%) and diabetes mellitus (19.3%).

Regarding the characteristics of this sample, most patients had completed high school (45.92%), with a family income between one and three thousand reais (50%) and were retired (54.08%). These demographic factors showed no statistically significant association with non-adherence as measured by the first question of BAASIS.

The majority of kidney transplants were from deceased donors with standard criteria (53.06%). From the date of transplantation to the time of the survey, 61.22% had changes in prescribed immunosuppressive medications. The prevalence of graft renal function with creatinine up to 1.5 mg/dL was 57.14%. These factors did not show a statistically significant relationship with non-adherence in the last 4 weeks.

Most patients had Systemic Arterial Hypertension (SAH) concomitant with other diseases (32.65%), isolated SAH (27.55%), or no associated

diseases (24.48%). The majority of patients (87.76%) administered their own medication without assistance. The number of medications ranged from one (1.02%) to three (98.98%) for daily use, with a statistically significant association ($P=0.027$) observed between the number of medications and non-adherence as measured by the second question of BAASIS (Table 2).

Education level was found to have a statistically significant impact on medication timing adherence ($p = 0.020$). The time since kidney transplantation varied, with the majority of patients being less than five years post-transplant (48.98%), followed by eleven to fifteen years (19.39%), but this factor did not significantly contribute to poor adherence.

The logistic regression analysis (Table 3) identified education level and the number of medications as significant predictors of non-adherence, with adjusted odds ratios of 0.72 (95% CI: 0.54-0.95, $p=0.020$) and 1.89 (95% CI: 1.07-3.33, $p=0.027$), respectively. Other factors, including age, gender, time since transplantation, and creatinine levels, did not show statistically significant associations with non-adherence in this model.

Discussion

This research aimed to measure adherence to immunosuppressants in kidney transplant recipients (KTR) using the BAASIS scale (17), characterize and

Table 3. Logistic Regression Analysis of Factors Associated with Non-Adherence.

Variable	Adjusted OR	95% CI	P-value
Age (per year increase)	0.98	0.96-1.01	0.235
Gender (Male vs. Female)	1.22	0.65-2.29	0.537
Education Level (per level increase)	0.72	0.54-0.95	0.020
Number of Medications (per additional medication)	1.89	1.07-3.33	0.027
Time Since Transplantation (per year)	1.03	0.98-1.08	0.251
Creatinine Level (per mg/dL increase)	1.31	0.89-1.93	0.173

Source: The Authors.

analyse clinical and sociodemographic characteristics, and analyse clinical factors in relation to immunosuppressants and creatinine levels. The relevance of this study is underscored by the limited body of research specifically examining medication adherence among kidney transplant recipients. This scarcity of literature is evident in recent reviews such as Gandolfini et al. (2022), who provide a comprehensive overview of the complexities and challenges in this area (19). Additionally, studies like Villeneuve et al. (2020) further highlight the need for more research on adherence profiles and their causes and consequences in kidney transplant patients (20).

According to studies that assess adherence to immunosuppressants in transplant recipients, they are characterized as complex and multifaceted, influenced by factors such as age, gender, socioeconomic status, medication side effects, social support, patient-physician communication, and beliefs about treatment (18). Our findings align with this multifaceted nature, particularly highlighting the significant impact of education and medication complexity on adherence. While our findings highlight the importance of health literacy in medication adherence, it's crucial to acknowledge that knowledge alone might not always translate into consistent medication management. This gap between knowledge and practice underscores the need for comprehensive interventions that address both cognitive and behavioral aspects of medication adherence.

Our findings align with a recent meta-analysis by Lee et al. (2020), which shows a significant and positive relationship between health literacy and medication adherence across various chronic conditions, including transplant recipients (21).

Practical skills and support mechanisms, particularly for patients with conditions like stroke who may require significant caregiver assistance, are equally vital.

Studies have demonstrated the effectiveness of structured training programs in enhancing medication adherence. For instance, Stirparo et al. (2022) emphasized the importance of educating patients and caregivers about stroke symptoms and the urgency of seeking immediate medical attention (22). Similarly, Bellini et al. (2023) found that cardiopulmonary resuscitation training at workplaces significantly improved employees' knowledge and skills in providing immediate assistance during cardiac events (23). Furthermore, Avau et al. (2022) demonstrated that using simulated patients in basic first-aid training significantly enhanced laypeople's knowledge, skills, and self-efficacy in responding to emergencies (24). These findings not only underscore the potential of targeted training programs to bridge the gap between theoretical knowledge and practical application but also suggest that similar approaches could be adapted for improving medication adherence in KTR. Implementing simulation-based training or interactive educational sessions specifically tailored to immunosuppressant management could potentially yield significant improvements in adherence rates and, consequently, transplant outcomes.

Inadequate self-management of medication impairs transplantation and other health outcomes. Some authors believe that adherence is related to self-care and self-management of this therapy and that it should be performed by the transplant recipient, as autonomy and empowerment are fundamental for the success of the therapy. The results of the current study showed

that the majority of the researched population administers their medications without the help of third parties (25,26). This finding highlights the importance of patient empowerment in medication management, but also raises questions about the potential benefits of involving caregivers or support systems in certain cases, especially for patients with complex regimens or cognitive impairments.

In the present study, it was evidenced that education directly influences the delay in taking medication, with statistical significance ($p = 0.020$). It has been published in a scientific article that lower levels of health literacy are linked to lower medication adherence in KTR (27). Our findings highlight the challenges of medication adherence in kidney transplant recipients, a concern echoed in a recent meta-analysis by Lee, Shin, & Seo (2020) (21). This meta-analysis, focusing on organ transplant recipients, underscores the potential of eHealth interventions to significantly improve medication adherence rates. The intersection of our findings with the potential of eHealth solutions presents an intriguing avenue for future research and intervention development. Integrating digital health literacy training with eHealth adherence tools could potentially address both the educational and practical aspects of medication management. While our findings highlight the importance of health literacy in medication adherence, it's crucial to acknowledge that knowledge alone might not always translate into consistent medication management. Practical skills and support mechanisms, particularly for complex medication regimens or patients with cognitive impairments, can be equally important. Non-adherence rates were 1.33 times higher in those with limited health literacy (28–31). In a randomized study with KTR, medication adherence was assessed before and after the application of an educational plan on immunosuppressive drugs. The authors concluded that they significantly improved short-term therapy adherence (25,32). This underscores the potential of incorporating practical training components, such as medication reminder strategies, dosage demonstrations, and open communication channels for addressing concerns, into patient education programs.

In a study conducted, patients were evaluated using the Health Literacy Questionnaire tool. An

association of low medication adherence with an inadequate level of health literacy was observed, in the same way, we can observe in our own results (33). This consistent finding across studies reinforces the critical need for tailored health literacy interventions in transplant care. Future research could explore the effectiveness of literacy-sensitive medication education materials and their impact on long-term adherence rates.

According to research on medication simplification to promote better adherence, it shows us that patients taking two medications reported more frequently having missed a dose compared to those who only took one medication. The main finding was that KTR on monotherapy were more likely to adhere to medication management compared to patients on dual therapy (26). As shown in the data presented in this research, it is noted that the greater the number of prescribed medications, the greater the chance of not taking consecutive doses ($p = 0.027$). This finding aligns with the broader literature on medication adherence across various chronic conditions, suggesting that simplification of regimens could be a universal strategy for improving adherence. However, it's important to note that in transplant care, the complexity of immunosuppression regimens is often clinically necessary, highlighting the need for innovative approaches to support adherence even in complex medication schedules.

According to a study conducted, there was better implementation of a monotherapy regimen because an additional dose each day was eliminated. In this way, it was also seen that simplifying the regimen eliminates nighttime doses, which have a higher incidence of missed doses compared to morning doses in the twice-daily regimen. Patients' morning activities are relatively more structured than nighttime activities, making it easier to associate dose intake with certain habits or rituals (31,32). This observation points to the potential benefit of aligning medication schedules with patients' daily routines and circadian rhythms. Future interventions could explore the use of chronotherapy principles in designing immunosuppressant regimens that not only meet clinical requirements but also align with patients' natural behavioral patterns.

Regarding health professionals, it is of utmost importance that they recognize the main factors that contribute to non-adherence to drug treatment, as it

is of great value for the development of strategies. It is worth noting that adherence should not be restricted to medical consultations; it should involve the participation of a multidisciplinary team, where nurses can act in an integrated manner in the approach to risk assessment, adoption of health promotion measures, and continuing education, ensuring qualified care for KTR (32). This multidisciplinary approach is crucial, and our findings suggest that it could be further enhanced by incorporating specialized health literacy training for healthcare providers. Equipping the entire transplant care team with skills to effectively communicate complex medical information and support patients in developing practical medication management strategies could significantly improve overall adherence rates and transplant outcomes.

This study has several limitations that should be considered when interpreting the results. Firstly, there is potential for selection and inclusion bias in our patient cohort. The study was conducted at a single center, which may limit the generalizability of our findings to other transplant populations or healthcare settings. Additionally, patients who agreed to participate in the study may have different characteristics or attitudes towards medication adherence compared to those who declined, potentially skewing our results.

The use of the BAASIS scale, while validated and widely used, has its own limitations. As a self-reported measure, it is subject to recall bias and social desirability bias, where patients may underreport non-adherence. Furthermore, the scale does not capture the reasons behind non-adherence, which could provide valuable insights for developing targeted interventions.

Our study design was cross-sectional, which limits our ability to establish causal relationships between the factors we identified and medication adherence. Longitudinal studies would be necessary to better understand how adherence patterns change over time and what factors predict long-term adherence.

Finally, we did not assess all potential confounding factors that could influence medication adherence, such as psychological factors, social support, or healthcare system-related barriers. Future studies should aim to incorporate a broader range of variables to provide a more comprehensive understanding of adherence behaviors in kidney transplant recipients.

Despite these limitations, our study provides valuable insights into the complex issue of medication adherence in kidney transplant recipients and highlights important areas for future research and intervention development.

Conclusion

Considering kidney transplantation as a treatment option for chronic kidney disease, which brings a better quality of life, adherence to immunosuppressive treatment is essential for the success of this process.

The present study showed that reducing daily doses, such as prescribing fewer pills for treatment, can improve medication adherence. This finding draws attention to the need for caution when prescribing medications to patients, as not only the number of medications should be taken into account but also the number of pills per schedule.

It was possible to conclude that education levels can directly influence the delay in taking medication. This result should alert us to the pre- and post-kidney transplantation process, such as the performance of the multidisciplinary team according to the patient's level of education, with the objective of providing tools according to each patient's understanding.

The delay of 2 hours in taking the medication with a relevant percentage demonstrates inadequate adherence to the essential post-kidney transplant therapy. Through all the results, we can see the need for interventions and reorientations for this public with the performance of the multidisciplinary team.

Ethic Approval: This work was carried out with the approval of the Research Ethics Committee of the Faculty of Medicine of São José do Rio Preto under number CAAE: 46825421.2.0000.5415.

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