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Original/Research Paper

Medication adherence in kidney transplant recipients: A cross-sectional study from a nursing clinical practice perspective

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https://doi.org/10.32598/JNRCP.23.50

Abstract

Medication non-adherence is implicated as one of the major causes of early and late kidney transplant rejection. The present study aimed to evaluate medication adherence in kidney transplant recipients. The study design was cross-sectional and descriptive. The sample was 144 kidney transplant patients, and sampling was by convenience. The researchers collected data using a three-part questionnaire, including demographic characteristics, clinical features, and simplified medication adherence questionnaire (SMAQ). Findings suggest that medication adherence in participants was at the desired level (94.4%; 95% CI: 89.8-97.3; P<0.001) and the number of hospitalizations was a predictor of medication adherence in kidney transplant recipients (95% CI: 0.236-1.009; OR:0.488; P=0.053). The mean serum levels of Tacrolimus, Sirolimus, Cyclosporine, and Everolimus in kidney transplant recipients were 8.22 (SD=4.75), 59.66 (SD=82.71), 138.25 (SD=74.99), and 5.7, respectively. Glomerular filtration rate and serum levels of Tacrolimus and Cyclosporine were higher in patients with appropriate medication adherence than those with poor medication adherence (P>0.05). With the increasing number of hospitalizations, medication adherence in these patients decreased. Overall, the medication adherence in kidney transplant recipients at the Kidney Transplantation Referral Center was at the desired level. Therefore, medicating related training programs are a promising approach to improve the quality of life in kidney transplant recipients and potentially reduce the incidence of transplant rejections among kidney transplant patients.

Keywords: Medication Adherence, Kidney Transplantation, Nursing, Kidney, Chronic Kidney Disease.

1 │ Introduction

Chronic kidney disease (CKD) is a significant challenge in public health that affects 8 to 16% of the general population [1]. This disease imposes a heavy burden on the health care system, the patient, and the family due to the chronicity and cost of all forms of therapies [2]. In Iran, the prevalence of CKD is 6.5 to 18.9% [3], and the trend of this disease in Iran is increasing [4].

Among the methods used to manage patients with renal failure, the preferred choice is kidney transplantation because of patients' improved quality of life after a kidney transplant and the comparatively lower cost of a transplant compared to lifelong dialysis [5]. However, regardless of the use of dialysis or kidney transplantation, a standard feature for optimal management of CKD is adherence to the prescribed treatment regimen [6]. The concept of medication adherence is complex and dynamic and may change over time [7]. Patients' adherence to treatment strategies goes beyond medication adherence and non-adherence and includes abiding with all other forms of treatment recommendations such as fluid intake, rest, and dietary recommendations. Therefore, ensuring treatment and medication adherence in patients with chronic conditions such as end-stage renal disease (ESRD) is critical to medical staff, managers, and health system policymakers due to the negative impact and burden of non-adherence in patients with CKD [7]. Proper medication adherence

can improve the quality of life of patients, especially in chronic diseases, such as ESRD [8, 9]. It is often determined by other patient and community factors, such as age, sex, knowledge, side effects, quality of life, self-efficacy, and mental health status. Patients with ESRD and kidney transplant recipients have higher potential for poor medication adherence as a result of the increased number of medications to be taken on regularly, the cumulative side effects of these drugs, and negative impacts on quality of life [6]. According to the results of previous studies, medication adherence among CKD patients varies from 8 to 33% [6, 10, 11].

Poor medication adherence is one of the most important reasons for rejecting early and late kidney transplantation. Medication non-adherence predisposes to significant complications in kidney transplant recipients, such as increased morbidity, the exponential cost to the health care system, disease side effects, and increased mortality. In addition, failure to use immunosuppressive drugs as prescribed leads to kidney transplant failure in the long term [12]. Therefore, kidney transplant recipients should use immunosuppressive drugs as prescribed to prevent early and late transplant rejection [13].

A study in Iran showed a significant relationship between adherence to immunosuppressive drugs and the quality of life of kidney transplant recipients [14]. However, another study demonstrated that 55% of patients do not adhere to their prescribed immunosuppressive therapy and other treatment regimens [15].

1.1 | Literature review

Medication adherence is an essential requirement for successful treatment outcomes and is a critical imperative for successful organ transplantation. Non-medication adherence is a severe organ transplant problem which has adverse outcomes for patients, health care providers, health systems, and the community [16]. Previous evidence has shown a wide variation in the prevalence of non-medication adherence in kidney transplant recipients from 5 to 50% [17, 18]. A study in the United States found that non-adherence to immunosuppressive drugs was more common in kidney transplant recipients compared to recipients of other types of solid organ transplants [19]. Also, a study in India showed that non-medication adherence in kidney transplant recipients is the third leading cause of allograft transplant rejection [20]. Therefore, medication adherence in kidney transplant recipients needs special attention. However, despite several studies on the perception and prevalence of non-medication adherence in kidney transplant recipients, most research has focused on barriers [21], beliefs [22], predictors [23], and interventions aimed at improving

medication adherence in these patients [24, 25]. There is limited evidence regarding the perception and incidence of medication adherence or non-adherence among kidney transplant recipients and their impact on treatment outcomes for these patients.

Health care providers can adopt some strategies in supporting and intervening when a patient exhibits non-adherence. These supportive measures require understanding the determinants and the adherence patterns of kidney transplant recipients in any community [20]. Therefore, an in-depth perception of medication-adherence-related factors is essential before any intervention and can play a unique role in diagnosing non-adherence and the risk factors for such behaviors. Therefore, this study aimed to evaluate medication adherence among kidney transplant patients in Iran.

2 | Methods

2.1 | Study design and sample

This cross-sectional and descriptive study evaluated kidney transplant recipients referred to the Kidney Transplantation Referral Center in Iran. The researchers calculated the sample size required to assess medication adherence among kidney transplant recipients 180 based on a study by Lalić et al. with a power of 0.8 [26]. The researchers collected data using convenience sampling from July 2018 to January 2019.

2.2 | Ethical consideration

The Institutional Ethics Committee of Guilan University of Medical Sciences approved this research (IR.GUMS.REC.1397.127). The researchers visited kidney transplantation referral center and invited patients to participate in the present study. After explaining the study's objectives, the researchers obtained written and oral consent from the participants. The researchers used anonymous questionnaires to ensure participants' confidentiality information.

2.3 | Inclusion and exclusion criteria

The researchers included stable patients with kidney transplant surgery, age over 18 years, at least three months after kidney transplant, and who signed the informed consent to participate in the present study. In addition, patients with life-threatening conditions who underwent kidney transplant surgery within the last three months were excluded from the study due to difficulty collecting data.

2.4 │ Data collection

The researchers collected data using a three-part questionnaire, including demographic characteristics, clinical features, and simplified medication adherence questionnaire (SMAQ). Demographic characteristics included age, sex, weight, marital status, and level of education. Clinical features included a history of the underlying disease, duration of kidney transplantation, number of kidney transplants, type of immunosuppressive drugs, number of consumable medications, number of medications per day, number of hospitalizations, serum level of immunosuppressive drugs, blood pressure, and glomerular filtration rate (GFR).

The SMAQ tool was a modified Morisky-Green questionnaire developed to assess adherence to antiviral therapy in the patients of acquired immunodeficiency syndrome. The SMAQ was adapted and used to assess the medication adherence of kidney transplant patients. This tool consists of six items with dimensions of forgetfulness, routine, side effects, and quantification of omissions [27, 28]. Participants responded to the first four items using a two-choice Likert (yes/no) and the fifth item using a five-choice Likert (from never to more than ten times). In item six, participants answered a closed-ended question about the number of days that patients take not the drug since the doctor's visit. As presented in Table 1, participants were divided into medication adherence and non-medication adherence groups based on response to items.

In this study, the SMAQ was translated to Persian, and the reliability, Cronbach's alpha of the tool was 0.89. The face and content validity of the SMAQ was approved by a 13-member panel consisting of nursing faculty members in private and collective sessions with a content validity ratio and content validity index above 0.9. Serum levels of Tacrolimus, Sirolimus, Cyclosporine, and Everolimus were measured in a private laboratory with ABBOTT 2000 device. An OMRON HN268 digital scale with an accuracy of 100 g was used to measure participants' weight. The researchers measured patients' blood pressure using an OMRON digital sphygmomanometer. Other demographics of the participants were collected through interviews. The research team also collected other clinical information of the participants via medical records.

2.5 │ Data analysis

We used the SPSS software package (version 19.0, SPSS Inc., Chicago, IL, United States) for data analysis. Continuous and categorical variables were presented using the mean (standard deviation) and frequency (percentage), respectively. Based on the Kolmogorov-Smirnov test, all variables had a normal distribution except serum levels of Tacrolimus and Cyclosporine. Fisher's exact test evaluated demographic variables with medication adherence. Mann-Whitney and Kruskal-Wallis tests assessed the significance of the study variables with quantitative and qualitative variables. Spearman Correlation Coefficient evaluated the correlation of quantitative variables. We used multiple logistic regression (backward method) to assess factors related to medication adherence. We used the 95% confidence interval (CI) to estimate the precision of odds ratios (OR). In addition, we considered $P < 0.05$ as a significance level for all study variables.

3 │ Results

3.1 │ Participants' characteristics

Of the 180 kidney transplant recipients, 144 participants were willing to participate. Thirty-six patients did not participate in the present study due to a lack of laboratory kits. Finally, we conducted the final analysis on 144 kidney transplant recipients (response rate=80%). The mean age of eligible patients was 45.86 (SD=12.35). Of the kidney transplant recipients, 59% were male, 52% had a history of hypertension, 96.5% had only one kidney transplant, 100% had a multidrug regimen, and 47.9% had more than five medications. The mean weight and time of kidney transplant were 72.30 (SD=13.07) kg and 6 (SD=5.26) years, respectively. Most drugs used in patients were Prednisolone (95.83%) and Cyclosporine (68.75%), respectively. GFR and diastolic and systolic blood pressures had a normal distribution, but serum levels of Tacrolimus and Cyclosporine had not a normal distribution. Demographic characteristics and clinical features of kidney transplant recipients are presented in Tables 2 and 3.

3.2 │ Medication adherence in kidney transplant recipients

The mean medication adherence in kidney transplant recipients was 94.4% (95% CI: 89.8 to 97.3; $P < 0.001$). The mean serum levels of Tacrolimus, Sirolimus, Cyclosporine, and Everolimus in kidney transplant recipients were 8.22 (SD=4.75), 59.66 (SD=82.71), 138.25 (SD=74.99), and 5.7, respectively. Also, serum levels of Tacrolimus and Cyclosporine, and GFR were higher in patients with higher medication adherence than in patients with non-medication adherence ($P > 0.05$) (Table 3). According to Table 2 and 3, there was no statistically significant relationship between medication adherence and variables such as age, sex, weight, marital status, level of education, history of the underlying disease, duration of kidney transplantation, number of kidney transplants, type of immunosuppressive drugs, number of consumable medications, number of medications per day, serum level of immunosuppressive drugs, blood pressure, and GFR. On

the other hand, the number of hospitalizations was a predictor related to medication adherence in kidney transplant recipients (95% CI: 0.236 to 1.009; OR: 0.488; P=0.053). With the increasing number of hospitalizations, medication adherence to these patients decreased.

Table 1. Simplified medication adherence questionnaire.

No.	Items			Groups	
				Medication adherence	**Non-medication adherence**
1	Did you take the medication on time?	1.	Yes	Yes	No
		2.	No		
2	Did you stop taking the medication when you felt unwell?	1.	Yes	No	Yes
		2.	No		
3	Have you ever forgotten to take your medicine?	1.	Yes	No	Yes
		2.	No		
4	Have you ever forgotten to take your medicine on the weekends?	1.	Yes	No	Yes
		2.	No		
5	How many times in the past week have you not taken prescription drugs?	1.	Never	1. Never	1. 3 to 5 times
		2.	1 to 2 times	2. 1 to 2 times	2. 6 to 10 times
		3.	3 to 5 times		3. More than 10 times
		4.	6 to 10 times		
		5.	More than 10 times		
6	Since the last visit, what is the total number of days you did not take your medicine/medicines?	Participants answered a closed-ended question		Less than two days	More than two days

Table 2. Demographic characteristics and medication adherence in the kidney transplant recipients (N=144).

	Kidney transplant recipients (N=144)	Adherence		P-value
		Medication adherence	**Non-medication adherence**	
Age (y)	45.86 (SD=12.35)			
≤ 30	20 (13.9)	18 (90)	2 (10)	0.723*
31-50	59 (41)	56 (94.9)	3 (5.1)	
> 50	65 (45.1)	62 (95.4)	3 (4.6)	
Sex				
Male	85 (59)	80 (94.1)	5 (5.9)	0.999
Female	59 (41)	56 (94.9)	3 (5.1)	
Marital Status				
Single	22 (15.3)	21 (95.5)	1 (4.5)	0.999
Married	122 (84.7)	115 (94.3)	7 (5.7)	
Level of Education				
Illiterate	11 (7.6)	9 (81.8)	2 (18.2)	
Less than a diploma	59 (41)	56 (94.9)	3 (5.1)	0.102
Diploma	52 (36.1)	51 (98.1)	1 (1.9)	
Above the diploma	22 (15.3)	20 (90.9)	2 (9.1)	
Weight (Kg)	72.30 (SD=13.07)			
≤ 60	28 (19.4)	27 (96.4)	1 (3.6)	
61-70	39 (27.1)	37 (94.9)	2 (5.1)	0.961
71-80	37 (25.7)	35 (94.6)	2 (5.4)	
> 80	40 (27.8)	37 (92.5)	3 (7.5)	

SD: Standard Deviation.

Data are presented as number (percentage) and mean (standard deviation).

* P-value was obtained with Fisher's exact test.

Table 3. Clinical features and medication adherence in the kidney transplant recipients (N=144).

	Kidney transplant recipients (N=144)	Adherence		P-value
		Medication adherence	Non-medication adherence	
Underlying Disease				
Renal failure	18 (12.5)	1 (5.56)	17 (94.44)	
Hypertension	75 (52.08)	3 (4)	72 (96)	
Nephrotic syndrome	3 (2.08)	0 (0)	3 (100)	
Polycystic kidney	9 (6.25)	1 (11.11)	8 (88.89)	
Diabetes	8 (5.56)	0 (0)	8 (100)	0.052*
Pregnancy poisoning	7 (4.86)	0 (0)	7 (100)	
Increase Creatinine and Urea	2 (1.39)	1 (50)	1 (50)	
Kidney atrophy	3 (2.08)	1 (33.33)	2 (66.67)	
Proteinuria	3 (2.08)	1 (33.33)	2 (66.67)	
Other	16 (11.12)	0 (0)	16 (100)	
Number of kidney transplants				
Once	139 (96.53)	132 (94.96)	7 (5.04)	0.252
Twice	5 (3.47)	4 (80)	1 (20)	
Duration of kidney transplantation (y)	6 (SD=5.25)			0.279*
≤ 4	69 (47.92)	67 (97.1)	2 (2.9)	
> 4	75 (52.08)	69 (92)	6 (8)	
Multi-drug regimen	144 (100)	136 (94.44)	8 (5.56)	
Number of consumable medications per day				
Three times	25 (17.36)	23 (92)	2 (8)	0.393
Four times	50 (34.72)	46 (92)	4 (8)	
More than five times	69 (47.92)	67 (97.1)	2 (2.9)	
Number of hospitalizations after kidney transplantation				
No hospitalization	72 (50)	71 (98.61)	1 (1.39)	0.300
Once	41 (28.47)	36 (87.8)	5 (12.2)	
Two and three times	25 (17.36)	25 (100)	0 (0)	
More than three times	6 (4.17)	4 (66.67)	2 (33.33)	
Type of drug/ immunosuppressive drugs				
Tacrolimus	54 (37.5)	51 (94.44)	3 (5.56)	0.999
Sirolimus	3 (2.08)	3 (100)	0 (0)	
Cyclosporine	86 (59.72)	81 (94.19)	5 (5.81)	
Everolimus	1 (0.7)	1 (100)	0 (0)	
GFR	61.29 (SD=18.68)	61.37 (SD=18.42)	59.94 (SD=24.17)	0.834**
Blood Pressure				
Systolic	130.32 (SD=14.35)	130.01 (SD=14.53)	135.63 (SD=10.01)	0.283**
Diastolic	83.48 (SD=10.92)	83.26 (SD=11.02)	87.25 (SD=8.81)	0.317**

GFR: Glomerular Filtration Rate; **SD:** Standard Deviation.

Data are presented as number (percentage) and mean (standard deviation).

* P-value was obtained with Fisher's exact test.

** P-value was obtained with t-test.

4 │ Discussion

Based on the results of the present study, medication adherence in kidney transplant recipients was at the desired level. GFR and serum levels of Tacrolimus and Cyclosporine were higher in patients with medication adherence than those with non-medication adherence. The number of hospitalizations was a predictor of medication adherence in kidney transplant recipients. With the increasing number of hospitalizations, medication adherence in these patients decreased. There was no significant relationship between variables, such as age, sex, weight, education, blood pressure, GFR, underlying disease, and duration of kidney transplantation.

The main result of the present study was the desired medication adherence (94.4%) in kidney transplant recipients, which similar studies have been found in Brazil [29], the Czech Republic [30], Serbia [26], and the United States [16], with a range between 64.2 to 94.5%. Inconsistent with the present study, the results of studies in Brazil [31] and France [32] reported high medication non-adherence in kidney transplant recipients (70.5% and 68%, respectively). Moreover, the lack of a proper and standardized definition of medication adherence in the different studies may cause heterogeneity [33, 34]. On the other hand, many

diagnostic methods cause stress and anxiety in kidney transplant recipients due to frequent monitoring [18, 35] and may be related to inaccurate medication adherence reports in these patients. Overall, several studies evaluated the improvement and understanding of medication adherence in kidney transplant recipients in Georgia [18], Germany [36], Brazil [37], Australia [38], and the United States [16]. However, the unreliability of the sensitivity and specificity of the different approaches to medication adherence assessment can cause problems in investigating medication adherence in kidney transplant recipients [39].

In the present study, GFR, Tacrolimus, and Cyclosporine serum levels were higher in patients with higher medication adherence than those exhibiting non-medication adherence. However, patients often take several immunosuppressive drugs that make it difficult to distinguish between them. A study in the United States found that adherence to Cyclosporine was greater when free drugs were given to patients than Tacrolimus [40]. Therefore, health care providers should exercise caution in assessing medication adherence through serum levels of Cyclosporine and Tacrolimus. In line with the present study, a study in Brazil showed that GFR levels were higher in patients with better adherence [41]. Regular use of drugs leads to maintenance of renal function and reduction of allograft failure, followed by GFR maintained at a higher level [42]. Therefore, we suggest that researchers in future studies evaluate the association of medication adherence and serum levels of Cyclosporine and Tacrolimus in kidney transplant recipients to reinforce the present study's findings.

The results of systematic review and meta-analysis in patients with heart failure showed that interventions related to promoting medication adherence reduce the rate of readmission and mortality in these patients [43]. Another result of the present study was a decrease in medication adherence due to an increase in the number of hospitalizations of patients in the hospital, supported by a study in the United States [44]. Taber et al. 2013, demonstrated that with the implementation of a comprehensive interdisciplinary intervention in kidney transplant recipients, the readmission of these patients was reduced by 50%. Therefore, patients' responsibility for disease management and overcoming medication non-adherence increases by improving patients' knowledge and awareness [45].

There was no significant relationship between variables, such as age, sex, weight, education, blood pressure, GFR, history of the underlying disease, and duration of kidney transplantation with medication adherence in the present study. A study in the United States [46] showed that older adults exhibited lower medication adherence when compared with younger patients. In contrast, the results of other studies in the United States and Switzerland showed that younger people have less medication adherence [33, 47]. A systematic review study found that risk factors for medication non-adherence can be considered under five categories. These include demographic factors (age less than 50 years, low social support, men, unemployment, and poor education), disease-related factors (more than three months after transplantation, re-transplantation, and the presence of more than six underlying diseases), medication-related factors (taking more than five drugs per day, and treatment with cyclosporine), patient-related factors (negative thoughts, negative behaviors, and inadequate satisfaction), and psychological factors (depression and anxiety) [48].

4.1 │ Limitations

The present study had several limitations. The study evaluated medication adherence in kidney transplant recipients referred to a Kidney Transplantation Referral Center in Iran. The use of only patients referred to this center can threaten the generalizability of the study. Also, a group of patients declined to participate in the present study, which has no knowledge of their medication adherence. In the present research, adequately accounting for passive attrition, was not completed to ensure the 180 required for adequate power. Therefore, the study was not fully powered and the results should be considered preliminary. Future work is needed in larger samples to further validate these findings.

4.2 │ Implications for nursing clinical practice

Non-adherence in clinical practice is always a possibility with all patients. Medications are most effective when patients take them as prescribed. Based on the present study's findings, kidney transplant recipients had a high level of medication adherence. However, health care providers have a pivotal role in maintaining and promoting medication adherence in kidney transplant recipients. Patients with a history of multiple hospitalizations had less medication adherence that required special attention. Hence, health care providers need to be vigilant in identifying patients who may have difficulty with medication adherence and develop supportive measures to improve medication adherence. Such interventions will prevent the likelihood of rejections, reduce the cost of treatment, and improve these patients' quality of life and health outcomes. Therefore, kidney transplant recipients should be aware of the importance of drug use and its impact on their clinical outcomes and quality of life. Regular medication intake according to prescription is essential to maintain adequate levels of GFR in kidney transplant recipients.

5 │ Conclusions

Overall, the medication adherence in kidney transplant recipients at the Kidney Transplantation Referral Center was at the desired level. Serum levels of Tacrolimus and Cyclosporine, and GFR were higher in patients who had medication adherence compared with patients who had medication non-adherence. The number of hospitalizations was a predictor of medication adherence in kidney transplant recipients. With the increasing number of hospitalizations, medication adherence in these patients decreased. Therefore, medicating related training programs are a promising approach to improve the quality of life in kidney transplant recipients and potentially reduce the incidence of transplant rejections among kidney transplant patients.

Ethics approval and consent to participate
The Institutional Ethics Committee of Guilan University of Medical Sciences approved this research (IR.GUMS.REC.1397.127). The researchers visited Kidney Transplantation Referral Center and invited patients to participate in the present study. After explaining the study's objectives, the researchers obtained written and oral consent from the participants. The researchers used anonymous questionnaires to ensure participants' confidentiality information.

Competing interests
We do not have potential conflicts of interest with respect to the research, authorship, and publication of this article.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on request.

Using artificial intelligent chatbots
None.

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