

Research Article

Adherence to Immunosuppressive Medications in Kidney Transplant Patients at Three Centers in Khartoum State, Sudan: A Cross-sectional Hospital Study

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Abstract

Background: Graft survival post-kidney transplantation is of paramount importance to patients and nephrologists. Nonadherence to immunosuppressive therapy can be associated with deterioration of renal function and graft rejection. This study aimed to evaluate the adherence to immunosuppressive medications in kidney transplant patients at three centers in Khartoum, Sudan.

Methods: In this descriptive cross-sectional hospital-based survey, 277 post-kidney-transplant patients were recruited. Data were collected using a questionnaire and analyzed using the SPSS v.23. Our scoring method was calculated based on Morisky Medication Adherence Scale (MMAS-8) related to immunosuppressive medications and was expressed as questions in the questionnaire; every correct answer was given one mark, then the marks were gathered and their summation was expressed.

Results: Overall, 33%, 45%, and 22% of the studied participants reported high, medium, and low adherence, respectively. The major factor for nonadherence was forgetfulness affecting 36.1% of those who did not adhere. The cost of the immunosuppressive medications did not negatively affect any of the participants' adherence (100%). However, a significant association was seen between adherence and occupational status, duration of transplantation, shortage of immunosuppressants, recognizing the name of immunosuppressant, side effect, and forgetfulness (P -values = 0.002, 0.01, 0.006, 0.000, 0.022, and 0.000, respectively). Logistic regression analysis showed a significant association with occupational status, side effects, and forgetfulness.

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Conclusion: Only one-third of the participants were classed as “highly adherent” to their immunosuppressant medications. Factors that can affect adherence to immunosuppressant medications were occupational status, side effects, and forgetfulness.

Keywords: Adherence, Immunosuppressive medications , Kidney transplantation, Khartoum, Sudan

1. Introduction

Nonadherence is defined as any “deviation from the prescribed medication regimen that is sufficient to affect adversely the intended effect of the regimen.” Nonadherence to immunosuppressive therapy is associated with an increased risk of graft loss, an increased number of late acute rejections, and a significant increase in plasma level of creatinine over time. This ultimately results in higher treatment costs and poorer patient outcomes[1]. Based on the previous studies, approximately one-third of solid organ transplant recipients might have nonadherence during a year, leading to about 36% of kidney allograft rejection. At three years post-transplantation, nonadherence among the recipients of kidney transplant can cost up to \$33,000 per patient. Nonadherence to immunosuppressants results in about 125,000 deaths per year, and 33–69% of hospital admissions [2].

In the USA, a cross-sectional study among 54 kidney transplant patients showed that 81.6% of patients were adherent to their immunosuppressant medication [3]. At the Clinic of Nephrology, Clinical Centre Niš, Serbia, another cross-sectional study observed that the adherence was estimated to be 71.7% and only 28.3% did not follow the prescribed therapy. This study concluded that kidney transplant patients had a high level of adherence[4]. Another study showed that 67.4% of the 297 kidney-transplant patients were considered fully adherent to their immunosuppressive medication [5]. The duration of transplant can negatively influence adherence to immunosuppressant medication [1, 6]. A published study showed that at five months post-transplant, 95% of renal transplant patients remained adherent with their free immunosuppressant, however, by 12 months following the transplant, only 48% of the same cohort remained adherent[7]. In contrast, other studies stated that nonadherence is higher in early first post-transplant patients than the later one [8]. Importantly, nonadherence was measured by self-report and collateral reports which showed a nonadherence of 23.7% and 3.8%, respectively,

while the combination of the two showed a total nonadherence of 26.4%. This study showed that forgetfulness was the greatest cause of non-adherence [9]. It is worth mentioning that education, employment, and country of origin were also significantly associated with adherence, also predictors of nonadherence included a greater period of time since transplant[10]. One study showed that 75% of nonadherent patients were found to have low calcineurin inhibitor levels. However, when this cohort of patients were provided with free medication, they became more adherent [11]. It is important to mention that the cost associated with immunosuppressant medication is an important factor in adherence in some situations, and may lead to increased risk for acute allograft loss [12–14]. Different factors can be related to nonadherence such as increased serum creatinine levels – a marker of decreased kidney function; noncompliant patients had a significantly higher increase in the plasma level of creatinine over time compared with compliant patients ($P < 0.001$) [15]. Besides, with respect to the effect of demographic status on medication adherence, some studies suggest male to be more likely to be nonadherent [16], while others show a higher risk of nonadherence in females [17]. However, many studies have found no association between medication adherence and gender[18–20]. In addition, some studies have shown younger age to be associated with nonadherence [16, 21, 22], while others have found older kidney-transplant patients to have a greater extent of nonadherence [23]. Nevertheless, some studies have found no association between them[19, 24, 25].

The patients' level of education is another factor. Some studies have found no association between nonadherence and education level following renal transplantation [18, 24], while others suggest that higher level of education is associated with better adherence or vice versa [16]. Moreover, some research has been conducted on the relationship between immunosuppressants adherence and ethnicity – while most studies found no association[18, 19, 24], some have found White Americans to have higher adherence than African Americans[26]. Some research have established that higher socioeconomic status is associated with high adherence[27]; however, others found no association between them [18, 19, 24]. Nonadherence Consensus Conference summary reported that decreased adherence to immunosuppressive medications directly contributes to allograft injury and induces chronic dysfunction [28]. Nevins *et al.* showed that excellent post-transplant medication adherence is critical to improved outcomes and the later consequences of medication nonadherence [29]. Therefore, the current study aimed to assess the adherence to immunosuppressant medication among Sudanese kidney transplant patients.

2. Materials and Methods

2.1. Study setting

The current study was a hospital-based descriptive cross-sectional survey carried out in the department of nephrology at Ahmed Gasim Hospital, Ibn Sina Hospital and Dr. Salma Center for Kidney Disease between May and August 2018.

2.2. Inclusion and exclusion criteria

Patients who had kidney transplantation and were receiving immunosuppressant post-surgery were included. Patients taking immunosuppressive medication for non-transplant purposes and those who had not exceeded one month post-transplant were excluded.

2.3. Sample size and sampling technique

The sample size was estimated using the following equation:

$$n = N/1 + N(e)^2,$$

where:

n = Sample size to be computed

N = Total population size

e = Degree of accuracy desired (or accepted margin error and it is usually set to be 0.05)

Using the above formula, a sample size of 281 was calculated.

$$n = 948/(1 + 948(0.05)^2) \quad n = 281.$$

We used stratified sampling technique and considered each center as a stratum and the number of patients in each center was calculated from their total capacity in one month according to their proportion in the centers.

The number of patients collected from Ahmed Gasim, Ibn Sina, and Dr. Salma Center for Kidney was 180, 59, and 42, respectively. Accordingly, Ahmed Gasim Hospital represented 64%, Ibn Sina represented 21%, and Dr. Salma represented 15% of patients. The patients within each center were selected by simple random sampling method.

2.4. Data collection tool

Patients who came to the follow-up outpatient clinic were invited to participate in the study. Twenty questionnaires were collected as a pilot study from Ahmed Gasim Hospital and Ibn Sina Hospital, and the questionnaires were standardized and modified until the last version was obtained.

The questionnaire consisted of a set of sociodemographic characteristics, length of time post-transplant, and treatment using eight-items of Morisky medication adherence scale. The questionnaires were filled during face-to-face interviews with the participants.

2.5. Morisky Medication Adherence Scale (MMAS)

The MMAS-8 is a questionnaire with eight questions whose wording is formulated to avoid the “yes” bias seen in chronic care patients. This is important as it allows the patient to respond to questions and to fully disclose to a clinician about their nonadherence. Items 1 through 7 have response choices yes or no whereas item 8 has 5-point Likert response choices. Each no is rated as 1 and each yes is rated as 0 except for item 5, in which each yes is rated as 1 and each no is rated as 0. For item 8, if a patient chooses response 0 the score is 1, and if they choose response 4 the score is 0. Responses 1, 2, 3 are respectively rated as 0.25, 0.75, 0.75. The total MMAS-8 scores can range from 0 to 8 and have been categorized into three levels of adherence: high adherence (score = 8), median adherence (score of 6 to <8), and low adherence (score <6) [30].

2.6. Data analysis

Data were analyzed using the statistical package for social sciences (SPSS) version 23 and Excel 2010. We used descriptive statistics (frequency tables, means, standard deviation, median) as well as inferential statistics (Chi-square test and logistic regression test).

2.7. Ethical consideration

Approvals were obtained from Omdurman Islamic University, the Ministry of Health, Ahmed Gasim Hospital, Ibn Sina Hospital, and Dr. Salma Center for Kidney. Verbal

consent was also obtained from selected participants after explaining the purpose of the study and the right to refuse or withdraw at any time during the study.

3. Results

A total of 281 kidney transplant patients were recruited in the study. Of them, 4 declined and 277 accepted to complete the study. The median age of the participants was 42 years, and a majority of them were male (71.1%) and married (69.3%). In addition, 54.2% of the participants lived in their own homes. Most patients were educated at least up to the high school level, however, more than half were unemployed.

The median duration of years post-kidney transplantation was three years. Out of the 277 patients in the study, 13.7% had their kidney transplants less than three months ago; 27.1% between three months and a year; 36.5% between one and six years, 11.6% between seven and ten years, and 11.2% longer than 10 years. Moreover, 71.8% of the participants reported having comorbid diseases – of them, 83% had hypertension pre-transplantation and 17% post-transplantation, while only 28.3% had developed diabetes pre-transplantation and 71.7% post-transplantation (Table 1).

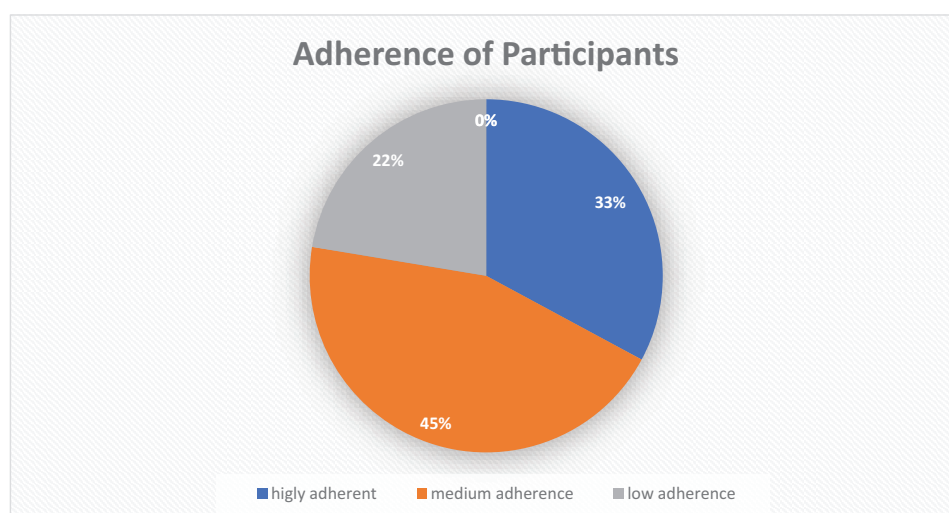


Figure 1: High, medium, and low adherence among the participants.

TABLE 1: Demographic characteristics of the participants ($n = 277$).

| Demographic data | Percentage |
|---------------------------------------|------------|
| Gender | |
| Male | 71.10% |
| Female | 28.90% |
| Marital status | |
| Married | 69.30% |
| Single | 28.50% |
| Divorced | 2.20% |
| Widowed | 0% |
| Educational level | |
| Illiterate | 5.80% |
| Primary school | 42.20% |
| High school | 35% |
| Bachelor degree | 15.90% |
| Postgraduate | 19.10% |
| Occupational status | |
| Employed | 37.50% |
| Retired | 9.70% |
| Unemployed | 52.70% |
| Accommodation Status | |
| Own a house | 54.20% |
| Did not own a house | 45.80% |
| Duration since transplantation | |
| <3 months | 13.70% |
| 3 months to 1 year | 27.10% |
| 2–6 years | 36.50% |
| 7–10 years | 11.60% |
| >10 years | 11.20% |
| Co-morbid diseases | |
| Hypertension (before transplantation) | 54.50% |
| Hypertension (after transplantation) | 10.80% |
| Diabetes (before transplantation) | 5.40% |
| Diabetes (after transplantation) | 13.70% |

3.1. Factors affecting the adherence of patients to immunosuppressive medications

Overall, 85% of the patients recognized the name of the immunosuppressant that they had taken. All patients had bought their medication from the centers using health insurance, so the price was not an issue. However, medications can sometimes be in short supply in Sudan. About 17% of the participants reported having experienced a

TABLE 2: Morisky scale results for immunosuppressant's among studied participants ($n = 277$).

| Questions | Percentage (%) | |
|--|----------------|-------|
| | Yes | No |
| Do you sometimes forget to take your medications? | 36.8% | 63.2% |
| People sometimes miss their medication for reason other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medications? | 30.7% | 69.3% |
| Have you ever cut back or stopped taking your medications without telling your doctor because you felt worse when you took it? | 2.2% | 97.8% |
| When you travel or leave home, do you sometimes forget to bring along your medications? | 13.7% | 86.3% |
| Did you take all your medications yesterday? | 98.2% | 1.8% |
| When you feel like your symptoms are under control, do you sometimes stop taking your medications? | 0.4% | 99.6% |
| Taking medications every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? | 19.9% | 80.1% |
| How often do you have difficulty remembering to take all your medications? | | |
| A. Never / Rarely | 67.5% | |
| B. Once in a while | 14.8% | |
| C. Sometimes | 14.8% | |
| D. Usually | 2.5% | |
| E. All the time | 4% | |

shortage of immunosuppressants. Of them, 42% bought their medication from another pharmacy out of health insurance, while 29% reported ordering them from outside Sudan.

What governs adherence in patients is adequate education and counselling. Therefore, as part of the study, we also looked at the topics and tactics used by health providers in Sudan regarding adherence and compliance. The most popular topic discussed by doctors (65%) were investigations and blood tests. About 48.7% of participants reported that doctors discussed the medication regimens with them. While treatment compliance and medications side effects were discussed with 36.5% and 39% of patients, respectively.

With regards to the barriers that prevent patients from taking their immunosuppressants medication, 59.2% reported that nothing can prevent them from taking their medications while only 36.1% complained of forgetfulness as a barrier to adherence and only 8.3%, 4%, 3.2% reported immunosuppressant's unavailability, cost (when there is shortage within health insurance), and side effects as barriers to adherence, respectively.

TABLE 3: Associations between adherence and demographic data using the Chi-square test.

| | Immunosuppressant's adherence | | | Immunosuppressant's adherence |
|---|-------------------------------|------------------|---------------|-------------------------------|
| | High adherence | Medium adherence | Low adherence | |
| Occupational status | | | | |
| Employed | 25.00% | 39.40% | 35.60% | 0.002 |
| Retried | 40.70% | 44.40% | 14.80% | |
| Unemployed | 37.00% | 48.60% | 14.40% | |
| Duration of transplantation | | | | |
| <3 months | 57.90% | 28.90% | 13.20% | 0.01 |
| 3 months to 1 year | 34.70% | 49.30% | 16.00% | |
| 2–6 years | 22.80% | 48.50% | 28.70% | |
| 7–10 years | 37.50% | 34.40% | 28.10% | |
| >10 years | 25.80% | 51.60% | 22.60% | |
| Shortage of immunosuppressants | | | | |
| Yes | 12.80% | 57.40% | 29.80% | 0.006 |
| No | 37.00% | 42.20% | 20.90% | |
| Recognizing the name of immunosuppressant | | | | |
| Yes | 28.00% | 47.00% | 25.00% | 0.000 |
| No | 61.00% | 31.70% | 7.30% | |
| Presence of side effects | | | | |
| Yes | 0.00% | 44.40% | 55.60% | 0.022 |
| No | 34.00% | 44.80% | 21.30% | |
| Forgetfulness as a barrier | | | | |
| Yes | 1.00% | 45.00% | 54.00% | 0.00 |
| No | 50.80% | 44.60% | 4.50% | |

TABLE 4: Predictors for immunosuppressant's adherence among studied participants using logistic regression test ($n = 277$).

| Variable | P-value | Odd ratio (OR) | 95% C.I. for OR | |
|--|---------|----------------|-----------------|--------|
| | | | Lower | Upper |
| Time since transplant | 0.283 | 0.953 | 0.874 | 1.040 |
| shortage of your immunosuppressant? | 0.926 | 1.045 | 0.409 | 2.670 |
| Recognizing the names of immunosuppressant | 0.359 | 0.514 | 0.124 | 2.131 |
| Forgetfulness | 0.000 | 30.718 | 12.038 | 78.388 |
| Occupational status | 0.026 | 4.389 | 1.197 | 16.090 |
| Side effect | 0.042 | 8.153 | 1.075 | 61.814 |

Tacrolimus, mycophenolate, and prednisolone regimen was used by 45.1% of the patients, while tacrolimus, azathioprine, and prednisolone was used by 37%.

Calcineurin inhibitors level was reported within therapeutic range among 75% of the participants. Moreover, in more than three quarters of the studied participants, the lipid panels (TG, LDL, cholesterol) and renal function tests (serum creatinine, blood urea nitrogen) were reported within the normal range, while fasting blood glucose and hemoglobin levels were reported controlled in 71% and 63% of the participants, respectively.

3.2. Morisky Scale results

More than one-third of the participants reported that they sometimes forget to take their medications, and only about 20% reported that they rarely feel hassled about sticking to their treatment plan (Table 2).

Moreover, 33% of the study participants reported high adherence, 45% reported medium adherence, and low adherence was reported by 22%. While categorizing the participants into a binary category, we found that 78% adhered (high adherence + medium adherence) to their immunosuppressive medications while 22% did not (low adherence) (Figure 1).

3.3. Tests of significance

We performed the Kruskal–Wallis test to compare the mean rank of total adherence score with occupational status and duration of transplantation and found that there was a significant difference among these groups (P -values = 0.001, 0.001).

3.4. Test of associations

3.4.1. Chi-square test

When this test was performed to determine the associations between the adherence and other variables, we found a significant association between immunosuppressant's adherence with occupational status, duration of transplantation, shortage of immunosuppressants, recognizing the name of immunosuppressant, side effect, and forgetfulness (Table 3).

3.4.2. Logistic regression analysis

By using logistic regression to determine the factors that predict the adherence, forgetfulness, presence of side effects, and occupational status had a statistically significant association with adherence. Adhering participants were not likely to forget taking their medications by 31 times than those who did not adhere ($P = 0.000$, CI for OR = 12.038–78.388). Moreover, those who were unemployed adhered to their medications by 4.5 times than those who were not ($P = 0.026$, CI for OR = 11.197–16.090). Furthermore, adhering participants were not likely to stop taking their medications when they experience side effects by eight times than those who did not ($P = 0.042$, CI for OR = 1.075 – 61.814) (Table 4).

4. Discussion

Adherence to medications post-transplant is important for both graft and patient survival. The adherence was assessed using Morisky scale eight-items questions. This study showed a high rate of nonadherence to immunosuppressant medication (67.1%). The duration of transplantation, knowledge of the name of immunosuppressive medications, and shortage of drugs were found to be statistically significant with the degree of adherence to immunosuppressive medications. Importantly, patients with less than three months of renal transplantation were significantly adherent compared to those who had had transplantation more than three months prior. This result was similar to other studies [1, 5, 6]. In our study, unemployed patients were more adherent to medications than those who were employed. This result is similar to that of Denhaerynck *et al.*'s [10] and contrary to Kiley *et al.*'s [16].

Zelikovsky *et al.* showed that better knowledge was associated with high adherence to immunosuppressive medications [31]. Knowledge about immunosuppressants in our study was also significantly associated with adherence. The availability was not considered a barrier for immunosuppressive medications adherence; however, this study revealed a significant association between drug shortage and immunosuppressant's adherence. This may be explained by the fact that medication is offered free of charge in renal transplant centers. Shortage of medication is likely to occur in those who do not regularly follow-up in outpatients' clinics. The issue of age and adherence to immunosuppressant medication showed different opinions. For instance, some studies show older patients to have good adherence, while others show younger patients to be more adherent, and some show no association between age and nonadherence [16,

18, 21–23]. In this study, we found no association between age and adherence. We also found no association between gender and adherence of immunosuppressive medication, although the number of male participants was higher than the females, there was no significant difference. This was also shown in other studies [19, 20]. However, some studies suggest that male kidney transplant recipients are more likely to be nonadherent [16, 23], while others show female recipients to have a higher risk of nonadherence [17]. Similar result was also observed for the role of education. For instance, education was shown to have no association with adherence, some studies have shown education to be associated with good adherence [16, 18, 23, 24, 32]. Interestingly, our study showed that the number of educated patients was the largest group with no significant association with medications adherence.

Forgetfulness was the most common barrier that affects immunosuppressive medications adherence ($P = 0.000$). Similar to our results, some studies found that forgetfulness has been examined qualitatively and established as the main reason for intermittent nonadherence [33–35]. Since medication was offered free of charge in all the three transplant centers, it is not surprising that medication cost was not significantly associated with adherence. It is worth mentioning, studies outside Sudan showed that medication cost is an important factor in patients' adherence [13, 14, 36]. In our study, side effects was significantly associated with immunosuppressive medications adherence ($P = 0.022$); this can be attributed to the fact that only 36.5% of the participants stated that their doctors counseled them about the importance of medications compliance, and this may be contributed to the higher percentage of nonadherent patients which was found in this study.

This study is not without limitations. First, the study is a descriptive cross-sectional survey as adherence is a dynamic process and difficult to be assessed objectively using cross-sectional study. Also, the study might be associated with recall bias compared with pill count, the effective method for assessing adherence. Moreover, the sample size was collected from three public centers in Khartoum state by convenience random sampling; therefore, the results of this study cannot be generalized in other geographical areas in Sudan. A prospective study is necessary to study the natural history of nonadherence. Despite these limitations, the study is novel and provided an accurate estimate of the prevalence and risk factors associated with nonadherence to immunosuppressant medication in kidney transplant patients in Sudan.

5. Conclusion

Only one-third of the participants were highly adherent to the immunosuppressants. Occupational status, duration of transplantation, shortage of immunosuppressants, recognizing the name of immunosuppressant, side effects, and forgetfulness were significantly associated with adherence.

5.1. What is already known on this topic

1. Graft survival post kidney transplantation is of paramount importance to patients and nephrologists.
2. Nonadherence to immunosuppressive therapy can be associated with deterioration of renal function and graft rejection.
3. Globally, nonadherence to immunosuppressive medication can occur in young and old patients.

5.2. What this study adds

1. Only one-third of participants were classed as "highly adherent" to their immunosuppressant medication.
2. Factors that can affect adherence to immunosuppressant medication were occupational status, side effects, and forgetfulness.
3. A prospective future study is necessary to study the impact of nonadherence to immunosuppressant medication in renal transplant patients in all states of Sudan.

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Ethical Considerations

Approvals were obtained from Omdurman Islamic University, the Ministry of Health, and Ahmed Gasim Hospital, Ibn Sina hospital, and Dr. Salma Center for Kidney. Verbal consent was also obtained from selected participants after explaining the purpose of the study and the right to refuse or withdraw at any time.

Competing Interests

The authors declare no competing interest.

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