Measurement of adherence to immunosuppressive drugs in renal transplant recipients

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Abstract
Objective: To measure adherence of renal transplant recipients to immunosuppressive drugs by using the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS®) and to describe sociodemographic characteristics and clinical factors in relation to immunosuppressive drugs and creatinine levels.

Methods: This retrospective, cross-sectional study was carried out from 2014 to 2015 in the post-transplantation ambulatory unit of the Kidney Hospital and Universidade Federal de São Paulo (UNIFESP).

Results: Of the 181 participants, 53.6% were men; recipients ages ranged from 18 to 74 years. Systemic arterial hypertension was the initial diagnosis of chronic renal failure in 38.7% of recipients. About 95% reported that they never forgot to take several consecutive doses of the medicine. 56.8% of recipients reported total adherence to the immunosuppressive drugs, and 41.4% did not adhere to one or more of the four assessed situations. No significant correlation was found between creatinine levels and total score and by BAASIS® items.

Conclusion: A high rate of patients not adherent to the immunosuppressive treatment was identified (41.4%). There was no significant correlation between creatinine level and receptor age at time of KTP, time after KTP, immunosuppressive separation time and total score and scores of individual BAASIS® items. This study showed that black, male recipients without a family support network, obese and autonomous are more likely not to adhere to immunosuppressive therapy. The evaluation of renal transplant recipient adherence should be considered during all phases of the nursing process actions that make up the therapeutic plan after renal transplantation.

Descritores
Transplante de rim; Cooperação do paciente; Avaliação em enfermagem; Imunossupressores

Resumen
Objetivo: Medir la adhesión a los medicamentos inmunosupresores en receptores de trasplante renal, utilizando el Basel Assessment of Adherence with Immunosuppressive Medication Scale - BAASIS® y describir las características sociodemográficas, los factores clínicos en relación a inmunossupresores y los niveles de creatinina.

Métodos: Estudio prospectivo, transversal, realizado en el período de 2014 a 2015, en el Ambulatorio Pós-Transplante del Hospital del Río (complexo hospitalar de la Universidad Federal de São Paulo (UNIFESP)).

Resultados: De los 181 participantes, 53.6% eran hombres; los receptores edades varían entre 18 a 74 años. La hipertensión arterial sistémica fue el diagnóstico inicial de insuficiencia renal crónica en 38.7% de los receptores. Aproximadamente 95% de los receptores reportaron que nunca se olvidaron de tomar medicamento; 56.8% de los pacientes reportaron adherirse totalmente a los inmunossupresores y 41.4% no adherir a una o más de las cuatro situaciones evaluadas por los ítems de BAASIS®. No se encontró correlación significativa entre el nivel de creatinina y la edad del receptor en el momento del transplantado, tiempo después del KTP, separación del inmunosupresor y total de la puntuación y por BAASIS® ítems. Este estudio mostró que los receptores negros, del sexo masculino, sin una red de apoyo familiar, obesos y autónomos son más propensos no adherirse a los inmunossupresores. La evaluación de la adhesión del receptor de trasplante renal debe considerarse durante todas las fases de las acciones del proceso de enfermería que componen el plan terapéutico después del trasplante renal.

Resumido
Objetivo: Medir la adhesión a los medicamentos inmunosupresores en receptores de trasplante renal utilizando la Basilea Evaluación de Adherencia con Inmunosupresor Medicación Escala - BAASIS® y describir las características sociodemográficas, los factores clínicos en relación con inmunossupresores y los niveles de creatinina.

Métodos: Estudio prospectivo, transversal, realizado en el período de 2014 a 2015, en el Ambulatorio de Post-Transplante del Hospital del Río (complexo hospitalario de la Universidad Federal de São Paulo (UNIFESP)).

Resultados: De los 181 participantes, el 53.6% eran hombres; la edad de los receptores varió entre 18 y 74 años. La hipertensión arterial sistémica fue el diagnóstico inicial de insuficiencia renal crónica en el 38.7% de los receptores. Aproximadamente el 95% de los receptores reportaron que nunca se olvidaron de tomar medicamento; 56.8% de los pacientes reportaron adherirse totalmente a los inmunossupresores y el 41.4% no se adhirieron a una o más de las cuatro situaciones evaluadas por los ítems de BAASIS®. No se encontró correlación significativa, a través de los ítems de BAASIS®, entre los niveles de creatinina y la puntuación total. Se identificó un alto índice de pacientes que no se adhirieron al tratamiento inmunossupresor (41.4%). No hubo correlación significativa entre el nivel de creatinina y la edad del receptor en el momento del transplantado, tiempo después del KTP, tiempo de separación del inmunossupresor y puntuación total.

Conclusión: Se identificó un alto índice de pacientes que no se adhirieron al tratamiento inmunossupresor (41.4%). No hubo correlación significativa entre el nivel de creatinina y la edad del receptor en el momento del KTP, así como tiempo después del KTP, tiempo de separación del inmunossupresor y puntuación total. La evaluación de la adhesión del receptor de trasplante renal debe considerarse durante todas las fases de las acciones del proceso de enfermería que componen el plan terapéutico después del trasplante renal.

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Conflicts to interest: Schirmer J is Editor-in-chief of Acta Paulista de Enfermagem, but he did not participate in reviewing this paper. Roza BA is Associate editor of Acta Paulista de Enfermagem, but he did not participate in reviewing this paper.
Introduction

In Brazil, more than 95% of organ transplantations are funded by the public health system, the Unified Health System, including the distribution of immunosuppressive drugs and ambulatory follow-up of recipients. Brazil has the largest transplantation program in the world, with an annual budget that increased from R$453.3 million in 2008 to R$942.2 million in 2016; if the investments in immunosuppressive drugs are considered, this budget reaches R$2.2 billion.(1-3)

Between 2010 and 2017, a mean of 5,403 (27.6 ppm) kidney transplantations (KTPs) were performed, 4,013 (20.5 ppm) of which involved deceased donors and 1,390 (7.2 ppm) of which were from living donors. These numbers place Brazil in second place in absolute number of KTPs, although it is still insufficient to address the demand of the waiting list for a kidney. Currently, the waiting list consists of 21,059 candidates (103 ppm), with the increase of effective donors in 2017 to 16.6 ppm.(4)

The global survival curve for the first and fifth years of follow-up after KTP ranged from 92% to 86% (mean, 89%) for recipients and 84% to 73% (mean, 78%) for deceased-donor grafts. For KTP with a living donor, survival ranged from 97% to 94% (mean, 95%) for patients and 93% to 86% for grafts.(4)

KTP results such as substitutive therapy depend, fundamentally, on recipients adherence to immunosuppressive drugs during follow-up after KTP. Given the high investment of transplantation, efforts to increase donation, and costs of graft rejection, researchers have recently begun focusing on adherence failures, or non-adherence, and this issue is concerning for the entire transplant community.

In this study, nonadherence to therapeutics after transplantation is understood as any deviation in the prescribed therapeutic immunosuppressive scheme that would negatively influence expected results, including mistakes in prescribed dosages and times. This is a multidimensional phenomenon determined by interaction among five factors: health system, socioeconomic level, treatment, patient, and disease.(6) According to estimates for developed countries, 50% of patients with non-communicable chronic diseases do not follow up with proposed treatment, with a negative impact on clinical evolution.(6-9) In transplantation, we estimate that the rate of nonadherence ranges from 2% to 7%, with an annual mean of around 35.6%;(5,10) non-adherence can result in graft rejection or failure, consequently increasing the cost of treatment and even leading to death.(6,11) The risk for death or recipient’s return to dialysis after graft failure is higher compared with those on the waiting list for dialysis.(12)

Studies have evaluated different strategies to identify nonadherence, including pill counts, self-report, collateral effect register, laboratory analyses of immunosuppressive drug levels, and electronic monitoring. This last is considered the gold standard for identifying adherence to immunosuppressive therapy but is not always viable because of its high cost.(13)

Self-report is the most common way to evaluate nonadherence because it can be useful in clinical practice, is low-cost, is easily and rapidly applied, moderately correlates with other strategies, and can be used to predict clinical results. However, because self-reports depend on the sincerity of recipients, they tend to overestimate adherence. Although they have low sensitivity, these instruments are highly specific and can be combined with other strategies, enabling researchers to obtain information about recipient behavior regarding medication intake, reasons for nonadherence, attitudes, beliefs, and other psychological determinants. We highlight that use of validated scales are crucial in order for results to be reliable.(14)

In Brazil, studies and data on adherence to post-transplant follow-up are still scarce. However, recent studies have shown that non-adherence to immunosuppressive therapy reaches on average 58% and that the self-reported efficacy of the receptors is still very low. In this way, it is essential to develop educational strategies to reduce non-adherence.(15-18)

In randomized prospective study of incident renal transplant recipients, aimed to assess the impact of an educational/counseling program highlighting the importance of immunosuppressive medications and compliance, on treatment adherence after kidney transplantation. The non-adherence rates were
46.4 and 14.5 % in the control and treatment groups \((p = 0.001)\), respectively.\(^{18}\)

In the first multicentric, cross-sectional Brazilian study, the BASSIS questionnaire was also used, as well as other structured questionnaires. ADHERE BRAZIL study has the objective to identify the prevalence and correlates of non adherence to immunosuppressants and health behaviors in renal receptors. Data are still being evaluated.\(^{19}\)

The current study sought to measure adherence of renal transplant recipients to immunosuppressive drugs by using the Basel Assessment of Adherence with immunosuppressive medication Scale (BAASIS\(^{15}\)) and to describe sociodemographic characteristics and clinical factors in relation to immunosuppressive drugs and creatinine levels.

**Methods**

This prospective, cross-sectional study was carried out in the Post-transplantation Ambulatory unit of the Kidney Hospital of the Universidade Federal de São Paulo (UNIFESP). The convenience sample included 181 recipients who fulfilled the following criteria: age 18 years or older with minimal ambulatory follow-up of four weeks after KTP or kidney-pancreas transplantation who agreed to participate in the study from 2014 to 2015.

Data were collected from medical records and interviews conducted in the waiting room of ambulatory consultations. Interviews were conducted by nurses from the Multiprofessional Residency in Transplantation and Organ Collection Program at UNIFESP who were trained by the researchers. We included in the interview the responsible caregiver when the recipient presented literacy impairment, any physical impairment associated with compromise of reading or understanding (visual loss, deafness, low auditory and visual acuity, low cognition). And functional literacy (defined as the ability to write one’s own name, read and write simple phrases, and perform basic calculations but inability to read or write fluently in daily life activities).\(^{20}\)

To evaluate adherence, we used the Portuguese validated version of the BAASIS\(^{15}\) scale. **This easily and rapidly administered instrument evaluates adherence to drug therapy in terms of the number of dosages and times prescribed by the physician compared to the true times adopted by the recipient. The scale is composed of four “yes or no” questions with which recipients report their adherence to the immunosuppressive scheme over the last four weeks of treatment. We considered nonadherence to be any positive response (yes) to any item; when it occurred, six additional questions were asked regarding the number of times that the nonadherence occurred.**

Additional instruments were elaborated to register recipients’ sociodemographic, clinical, and transplantation variables, such as age, sex, race/ethnicity, marital status, monthly income, level of education, type of transportation used, smoking, alcohol use, initial diagnosis of chronic renal failure (CRF), type of transplantation and time since transplantation, ambulatory follow-up with pharmacist, presence or absence of caregiver, presence or absence of cytomegalovirus virus infection), creatinine level in the last year, and type and number of immunosuppressive agents in use on the day of the interview.

For statistical analysis we used SPSS software, version 20.0. For all statistical tests we adopted a significance level of 5%. Normal distribution of data was verified with the Kolmogorov-Smirnov test, and in case of violation of means we performed comparisons using the Mann-Whitney test. For analyses of associations between two categorical variables, we applied the chi-squared test; in small samples, we used the Fisher exact test. To compare means between two groups, we used the Student \(t\) test for independent samples. In violation of supposition of normality, we applied the nonparametric test by Kruskal-Wallis; if any difference on means was seen, we identified these differences by using Dunn-Bonferroni tests, thereby keeping the global significance level of 5%.

Linear association between two numerical variables was evaluated by using Pearson’s correlation. To simultaneously evaluate the effects of adherence to adjusted immunosuppressive drugs by sociodemographic, clinical, and transplantation characteristics ( explicative variables) on creatinine level (de-
ependent variable), we used multiple linear regression. Given the many explicative variables facing the size of the sample, we selected for the model those associations with dependent variables in univariate analysis that were significant.

This study followed ethical criteria of the CNS no. 466/2012 resolution approved by the Ethical and Research Committee of the UNIFESP, no. 471.626 from November 29, 2013.

Results

Of 181 interviewed patients, 53.6% were men, 46.4% were women, 53.6% were non-white, 39.2% were white. Ages ranged from 18 to 74 years (mean age, 44.2; standard deviation, 13.4 years); 53.6% of recipients were married and 46.3% were unmarried (single, 30.9%; divorced, 7.7%; separated, 4.4%; widowed, 3.3%). Participants’ education ranged between nine years (36%) and 12 years (38.7%); in addition, 13.3% of recipients were functionally illiterate and 12% had more than 12 years of education. Family monthly income, reported by 64.7% of participants, ranged from equivalent to one (R$788,00) to four (R$ 3.152,00) times the minimum wage in Brazil; 60.8% of recipients receive government aid, only 23.8% participated in paid work, and 15.5% did not have a monthly income. Types of transportation used by participants were mass transit, individual car or taxi, carpooling the types of transportation most used to get to the ambulatory service ranged from one to five (mean, 1.3; standard deviation, 07); there was a predominance of bus (38%), ambulance (31.8%) and subway (25.7%) use.

Systemic hypertension was the initial diagnosis of CRF in 38.7% of cases; other causes were seen for 47.8% of recipients, such as polycystic kidneys, traumas, infections, and immunologic disorders. Almost 93% of recipients underwent hemodialysis. Most recipients had undergone KTP for the first time (96.1%); 3.9% had had more than one KTP, and the most common reason for this was chronic rejection (57.1%). Regarding the type of KTP, 49.2% were from deceased donors, 36.5% were parental living donor transplants, and 14.4% were from no parental living donor transplants.

The mean ambulatory follow-up duration was 276.8 weeks (5.3 years); 24.3% of recipients had cytomegalovirus infection and 1.7% had cellular acute rejection confirmed by biopsy. The mean body mass index was 25.81 kg/m²; 41.4% of recipients were of normal weight. Most participants reported not drinking alcohol (98.3%) or using tobacco products (95.6%). A total 148 recipients (81.8%) used up to three immunosuppressant drugs, and 33 (18.2%) used up to two types of these drugs. The most commonly associations of immunosuppressant agents were tacrolimo, mycophenolate, and prednisone.

The need for a caregiver was reported in 4.4% of cases, 7.2% sought follow-up with and guidance from a pharmacist, and the mean time required for separation of the immunosuppressant was four minutes.

When recipients were considered individually according to the items evaluated using BAASIS®, we observed that 94.5% of them reported that they did not ingest different consecutive doses, 87.8% did not forget to take their medications sometimes, and 64.1% never took the immunosuppressant drug more than two hours from the time prescribed within the past four weeks (Table 1).

In general scores of BAASIS®, calculated from arithmetic sum of the score attributed to questions 1a, 1b, 2, 3 and 4, 58.6% of recipients reported total adherence to the immunosuppressant drug and 41.4% did not adhere to one (18.8%) or more than four of evaluated situations at least once in the last four weeks (Table 2).

In correlation between recipients who forgot to take immunosuppressant drugs sometimes (1a) with sociodemographic variables, the highest score for adherence to treatment was seen for recipients who were married (94.8%), non-white (94.9%) and retired (90.9%). Inversely lower scores were seen between singles (80.4%) and divorced (64.3%) recipients, black (78.9%) recipients, and those in an autonomous profession (76.9%). Among those who did not take several consecutive doses (1b), non-white (100%) and married (99%); the most
frequent occurrence of this type of nonadherence occurred among white (11.3%), separated (25%), obese (20%) and autonomous professional (30.8%) recipients.

Nonadherence in the context of taking the immunosuppressant drug more than two hours after the prescribed time (2) was most common among white (40.8%), separated (62.5%), and divorced (42.9%) recipients; those with more than 12 years of education (45%); and those who used tacrolimo (67.7%). For the remaining variables and items assessed by using BAASIS®, the correlations were not significant.

The mean value of the last creatinine dosage ranged significantly (p=0.001) only between types of renal transplantation: 2.41 (not parental living donor), 1.54 (parental living donor), and 1.99 (deceased donor). There was no significant correlation between level of creatinine and patients’ age at the time of KTP, time after KTP, time of separation of immunosuppressant, and total score and individual item scores of BAASIS®.

In the adjusted multiple linear regression model with the dependent variable of creatinine level value, we considered as explicative variables (significant to 20% in the univariate analysis) transportation using a bus, immunosuppressive scheme, type of transplantation, use of cyclosporine, use of azathioprine, age at transplantation, time between transplantation and ambulatory consultation. And the time to separate medications, number of transportation types used, frequency of forgetting to take the immunosuppressant drugs sometimes (1a), and frequency of forgetting to take consecutive doses (1b) of immunosuppressant drugs within the four last weeks. The categories “every two weeks,” “every week” and “more than once per month” were clustered in a single category called “more than once per month” because of the low number of cases. We observed that the variables that remained significant in this model were bus transportation (p=0.043), parental living donor transplantation (p=0.006), and forgetting to take immunosuppressant drugs once within the last four weeks and more than once per month (p=0.043).

**Discussion**

The contribution of the study shows that the BAASIS® scale has been applied, not alone, in clinical practice in the follow-up of renal receptors, identifying in which moments and what type of nonadherence the use of immunosuppressants occurs. Reinforced action by a systematic review of self-reported instruments to identify noncompliance with medication, where BAASIS® was recommended as a reliable, valid and sensitive tool.[21]

Measurement of adherence has implications for nursing and interdisciplinary practice, and it is relevant because of the high investment of the public health system—more than 50% of the annual transplantation budget is directed to immunosup-
Measurement of adherence to immunosuppressive drugs in renal transplant recipients

Pressant drugs. Therefore, the evaluation of adherence in recipients who have undergone transplantation must be considered to support actions for the therapeutic plan after KTP and in this way will help reduce investment in treatment of complications due to nonadherence.

To evaluate non-adherence to immunosuppressant drugs, we recommend assessing four dimensions: ingestion, time, dose, and voluntary interruption (drug holiday) because even small changes in therapeutic regimens in any of them (e.g., reducing ingestion of medications to less than 98% or interrupting ingestion voluntarily, ranged in time >2 h) can increase the risk for late rejection, loss of graft and reduction in renal function.

In our study, although isolated results of items assessed by BAASIS® indicate an adherence of 94.5%, the general score showed that 41.4% of patients did not adhere to one or more of the four situations evaluated, at least within the last four weeks, thereby representing an estimated loss in 3% of prescribed doses.

The International literature evidenced factors as determinants of post-transplant noncompliance. A review based on 38 articles estimated that the non-adherence rate is between 28% and 52%. In a meta-analysis, the chances of graft failure were seven times higher in non-adherent patients compared to adherent patients and a study that used BAASIS® to evaluate 74 patients found 14.3% nonadherence.

However, the general score for nonadherence found would be higher than cited, with a score similar to results of a Brazilian randomized study that used an education intervention and found adherence of 46.4% in the control group and 14.5% in the intervention group (p=0.001).

A prospective cohort study with 1,505 patients in which 924 (61.4%) underwent KTP showed that non-adherence increased continually from six months until three years of follow-up; this finding supports the early adoption of measures supporting adherence to immunosuppressive therapy.

Even considering that free release per se does not justify a greater adherence to immunosuppressant drugs, it is possible to suggest that the influence of a number of health and treatment systems in Brazil helps improve adherence, once therapy is established in legislation by clinical protocols and guidelines, establishing the triple scheme of immunosuppressant drugs as the better therapeutic proposal, assuring the access and free distribution of immunosuppressant to all transplanted individuals, and avoiding the negative financial impact on adherence.

The complex therapeutic regimen and with the excessive number of medications ingested daily, directly influence the adherence to the treatment. Unfortunately, nonadherence to immunosuppressants is common among renal recipients. And if that was not enough, there are some reports showing that these are the most non-compliant among all recipients. Inversely, a more simple immunosuppressant therapy in relation to both number of drugs and prescribed dose per day can increase the chances of better adherence.

A recent study did not find a significant correlation between levels of creatinine and patient age at KTP, time after KTP, time of separation of immunosuppressant drugs, and total score of BAASIS® items.

Sociodemographic variables showed a higher score for adherence among married recipients (94.8%) than among single (80.4%) or divorced (64.3%) recipients and autonomous professionals (76.9%). Although the influence of the existence of a conjugal partner is not conclusive in some publications, a recent study showed that being separated or divorced was a factor associated with nonadherence.

We can suggest that variables that cover family, social, work, and domestic context directly influence the lives of individual recipients and consequently their adherence. Absence of a daily routine can contribute to nonadherence with any treatment, such as in cases in which the family and social resources are poor, or even among autonomous professionals who do not follow a routine.

Limitations of this study include the use of a cross-sectional design with a convenience sample and adoption of a self-report instrument to measure the level of adherence; the results may not be applicable beyond this sample. However, the contributions of this study deserve to be considered because...
these results show we can incorporate measures of adherence in clinical nursing practice in the greatest KTP service in the world, which performs on average 900 KTPs yearly, a model for other reference centers in the area.

Conclusion

A high rate of patients not adherent to the immunosuppressive treatment was identified (41.4%). There was no significant correlation between creatinine level and receptor age at time of KTP, time after KTP, immunosuppressive separation time and total score and scores of individual BAASIS® items. This study showed that black, male recipients without a family support network, obese and autonomous are more likely not to adhere to immunosuppressive therapy. The evaluation of renal transplant recipient adhesion should be considered during all phases of the nursing process actions that make up the therapeutic plan after renal transplantation.

Collaborations

Leite RF, Silva AC, Oliveira PC, Silva LMG, Pestana JMA, Schirmer J and Roza BA declare participating in the conception of the study, data analysis and interpretation, drafting the manuscript, critical review of the content and approval of final version to be published.

References

16. Brito DC, Marsicano EO, Grincenkov FR, Colugnati FA, Lucchetti G, Sanders-Pinheiro H. Stress, coping and adherence to


Erratum

In the article published in Acta Paul Enferm. 2018; 31(5):489-96, Leite RF, Silva AC, Oliveira PC, Silva LM, Pestana JM, Schirmer J, Roza BA; “Measurement of adherence to immunosuppressive drugs in renal transplant recipients”, the authors requested to publish the following erratum:

Table 1. Distribution of adherence to immunosuppressant drugs of renal transplant recipients according to BAASIS® items (n=181)

<table>
<thead>
<tr>
<th>Analyzed items</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Taking nonadherence</td>
<td></td>
</tr>
<tr>
<td>Yes / No</td>
<td>22(12.2) / 159(87.8)</td>
</tr>
<tr>
<td>On one occasion</td>
<td>17(9.4)</td>
</tr>
<tr>
<td>On two or more occasion</td>
<td>5(2.8)</td>
</tr>
<tr>
<td>1b. Drug-holidays</td>
<td></td>
</tr>
<tr>
<td>Yes / No</td>
<td>10(5.5) / 171(94.5)</td>
</tr>
<tr>
<td>On one occasion</td>
<td>7(3.9)</td>
</tr>
<tr>
<td>On two or more occasion</td>
<td>3(1.6)</td>
</tr>
<tr>
<td>2. Timing non-adherence</td>
<td></td>
</tr>
<tr>
<td>Yes / No</td>
<td>65(35.9) / 116(64.1)</td>
</tr>
<tr>
<td>On one occasion</td>
<td>28(15.5)</td>
</tr>
<tr>
<td>On two occasion</td>
<td>13(7.2)</td>
</tr>
<tr>
<td>Every 2 – 3 days</td>
<td>21(11.6)</td>
</tr>
<tr>
<td>Almost every day</td>
<td>3(1.6)</td>
</tr>
<tr>
<td>3. Dose alteration</td>
<td></td>
</tr>
<tr>
<td>Yes / No</td>
<td>3(1.7) / 178(98.3)</td>
</tr>
<tr>
<td>4. Discontinuation</td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td>0(0,0) / 181(100)</td>
</tr>
</tbody>
</table>

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