DOI: 10.4025/cienccuidsaude.v15i1.28029

ADHERENCE TO IMMUNOSUPPRESSIVE THERAPY ADHERENCE IN KIDNEY TRANSPLANT RECIPIENTS[1]

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ABSTRACT
Kidney transplantation has advantages over other forms of kidney replacement therapies (hemodialysis and peritoneal dialysis) because it improves quality of life and increases the survival rate of recipients. However, adherence to immunosuppressive therapy after transplantation is an indispensable condition for the renal graft survival. Assessment of the adherence to immunosuppressive therapy in kidney transplant patients from a teaching hospital in São Luís - Maranhão, Brazil. Cross-sectional study of 151 kidney transplants with follow-up in the renal transplant clinic. Adherence to immunosuppressive was assessed by the self-report method Immunosuppressive Therapy Adherence Scale (ITAS): there was (60.3%) percentage of nonadherence of the transplant patients. The variables that were statistically significant with nonadherence were: being transplanted with a living donor (p=0.03), type of immunosuppressant used (p=0.04) and serum creatinine (p=0.04). We found a high rate of nonadherence to immunosuppressive therapy by the self-report method in renal transplant recipients in an outpatient follow-up. This result becomes an important risk factor for adverse clinical outcomes, such as rejection and failure of the kidney graft.

Keywords: Renal transplantation. Self-reported.

INTRODUCTION

Kidney transplantation is considered the best treatment option for chronic kidney disease (CKD) stage V because it offers a better perspective and quality of life for kidney transplanted patients(1). Such therapy requires continuous use of immunosuppressive drugs to keep the renal graft. Without effective immunosuppression, the graft is subject to adverse clinical outcomes such as rejection and shorter survival(2).

In kidney transplant, the adherence to immunosuppressive therapy is critical for the long-term graft survival(3).

In 2008, was held the Consensus Conference on nonadherence to immunosuppressive therapy in the United States. In that occasion, nonadherence to immunosuppressive therapy was defined as the deviation from the prescribed medication regimen, sufficient to negatively influence the effect of the prescribed regimen. The adherence is considered satisfactory when the gaps between the dosage taken by the patient and the prescribed dosage regimen do not affect the therapeutic outcome(4).

Kidney transplant requires continuous engagement of the transplanted person for satisfactory results of treatment and improved graft survival. Therefore, the receiver must follow a series of guidelines such as outpatient follow-up with the multidisciplinary team, adherence to medication, nutrition and regular exercise, avoid alcohol intake and smoking, maintenance of proper hygienic care and

[1] Article extracted from the dissertation titled "ADHERENCE TO IMMUNOSUPPRESSIVE THERAPY IN KIDNEY TRANSPLANT PATIENTS", presented in the Postgraduate Program in Health and Environment of the Universidade Federal do Maranhão in 2013. Manuscript presented at the XIII Brazilian Transplant Congress in 2013.

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infection control[5].

However, the nonadherence to immunosuppressive therapy of renal transplanted patients has been demonstrated in several studies, ranging from 5 to 70% depending on the method used to measure adherence[6]. The wide variation of immunosuppressant adherence is attributed to the different methodologies used to measure it[6].

There are several methods to determine the accuracy of medication intake, and they are classified as direct and indirect. No method is considered perfect, but a combination of them reaches more effective and reliable results[7].

Direct methods are based on techniques that check if medication was actually administered or taken in the required dose and frequency. Biochemical monitoring of immunosuppressant blood levels is the most used method in surveys to assess adherence in transplants[7].

Self-reporting, medication dispensing and electronic monitoring are the most used indirect methods to assess adherence to immunosuppressive medication. Self-reporting is the most used method in clinical practice and surveys because of its easy application and low cost[8].

According to the World Health Organization (WHO)[9], adherence to chronic treatment may be related to the following: socioeconomic factors, the health system, health team, disease, patient, and the therapy. Since it is a multidimensional phenomenon, patients cannot be considered solely responsible for the outcome of treatment that also extends to health professionals, specifically those who accompany these patients.

Given this context, this study aimed to assess adherence to immunosuppressive therapy in kidney transplant recipients in outpatient follow-up.

METHODS

This is a descriptive cross-sectional study of quantitative approach. It was performed between May/2012 and April/2013 in the outpatient clinic of the Renal Transplant Service of a teaching hospital located in the city of Maranhão. The study included 151 kidney transplant recipients aged 18 years or over, of both genders, and over a year since the transplant. The convenience sample was collected while waiting for the follow-up outpatient consultation scheduled according to the time since transplant.

Two instruments were used for data collection. The first was a questionnaire with sociodemographic (age, gender, color/race, marital status, labor activity, family income, educational level) and clinical variables (underlying disease, duration of hemodialysis, transplant time, donor type, dialysis in the first week of transplant, post-transplant complications, type of immunosuppressant used, and number of immunosuppressant tablets ingested).

The second instrument used was the Immunosuppressive Therapy Adherence Scale (ITAS). It was developed and validated by Chisholm et al.[10] to measure the adherence to immunosuppressant use by self-report in the three previous months.

The ITAS contains four situations on the use of immunosuppressive drugs (forgetfulness, carelessness, stop for feeling bad and stop for any reason) and four alternatives of choice for the previously reported situations (never, rarely, most times, always) with the respective scores of 3, 2, 1, 0. This method considers as adherence when the patient's score is equal to 12, and nonadherence when patient's score is lower than 12[10].

The categorical variables were described by frequencies and percentages, and the numerical variables by mean ± standard deviation. At the intersection of the adherence variable, a categorical dichotomous variable, with metrical, continuous and normally distributed variables, was applied the t test for independent samples, and the Mann-Whitney test for variables without normality. The chi-square test was used for categorical data comparisons. The significance level was set at $p < 0.05$. The Data Analysis and Statistical Software (STATA®) version 12.0 was used for statistical analyzes.

The study was conducted in compliance with the ethical standards, and approved by the Research Ethics Committee of the teaching hospital Unidade Presidente Dutra (HUUPD) on May 7th, 2012 under number 0076/2012. The transplanted patients who agreed to participate signed the informed consent form in accordance with the current legislation on research involving human beings, Resolution number 466/12 of the National Health Council.

RESULTS AND DISCUSSION

Table 1 displays data about the sociodemographic characteristics of the studied universe. Of the 151 transplanted patients, 51.7% were male, 74.8% of mixed race, 55.6% were married, 59% without work activity, 77.5% with family income above a minimum wage, with 62.9% more than eight years of study and the average age was 40.33 ± 11.7 years.

There were no significant differences (p <0.05) between adherence by self-report method and the surveyed sociodemographic variables.

Regarding clinical characteristics, 49% had undetermined underlying disease, average time of hemodialysis of 32.41 ± 29.64 months, average time of transplant of 68.19 ± 43.53 months, 72.8% were receivers of live donors, 56.3% had complications after transplantation and the immunosuppressive average intake was of 6.15 ± 1.74 tablets (Table 2).

According to the ITAS items, 60.3% (91 individuals) of receptors were non-adherent to immunosuppressive therapy. The high rates of nonadherence in studies using this instrument can be explained by the fact that according to it, the presence of any failure in the use of immunosuppressive is considered nonadherence, regardless of the frequency at which it occurs (Table 3).

In the self-report assessment method, the statistically significant variables with nonadherence were the following: type of donor (p = 0.03), type of immunosuppressant used (p = 0.04) and serum creatinine (p = 0.04). Among non-adherent patients, those transplanted with live donors and with higher serum creatinine values (1.7 ± 1.3) stood out. Regarding the type of immunosuppressant used, 40.6% used tacrolimus, and 28.7% used sirolimus (Table 3).

This study assessed the adherence to immunosuppressive therapy through the self-report method using the ITAS and found a high percentage of nonadherence in kidney transplant recipients. The study conducted by Brahm[11] in a teaching hospital located in south of Brazil with 288 kidney transplant patients found 61.8% of nonadherence in the self-report, which is data similar to our study. The study by Brahm also used the ITAS to assess adherence.

The high nonadherence rates found in studies that used the ITAS self-report can be explained by the fact that according to this method, the presence of any failure in the use of medication is considered nonadherence, regardless of the frequency at which it occurs.

Table 1. Sociodemographic data of kidney transplant patients.

Variables	Frequency (n)	%	p<0.05
Gender			0.74
Male	78	51.7	
Female	73	48.3	
Age in years (mean ±SD)	40.33 ±11.71		
Color/race			0.84
White	16	10.6	
Black	22	14.6	
Mixed race	113	74.8	
Marital status			0.64
Married*	84	55.6	
Single*	67	44.4	
Work activity			0.58
Active	62	41.0	
Inactive	89	59.0	
Family income			0.31
≤1 minimum wage	34	22.5	
≥1 minimum wage	117	77.5	
Educational level			0.54
≤8 years	56	37.1	
≥8 years	95	62.9	

*The married category also included widowed, divorced and common-law marriage.

Table 2. Clinical data of kidney transplant patients.

Variables	Frequency (n)	%
Transplant time - months (mean ± SD)	68.19 ±43.53	
Hemodialysis time - months (mean ± SD)	32.41 ± 29.64	
Donor type		
Live	110	72.8
Deceased	41	27.2
Dialysis in the first post-transplant week		
Yes	29	19.2
No	122	80.8
Post-transplant complications		
Yes	85	56.3
No	66	43.7
Immunosuppressant used		
Tacrolimus	70	46.4
Cyclosporine	20	13.2
Azathioprine	28	18.5
Sirolimus	35	23.2
Number of ingested immunosuppressant (mean ± SD)	6.15 ± 1.74	
Underlying disease		
Hypertension	14	9.3
Diabetes Mellitus	11	7.3
Glomerulonephritis	26	17.2
Indeterminate	74	49
Others	26	17.2

Table 3. Association between adherence in the self-report and variables included in the univariate analysis.

Variables	Self-report (ITAS)				
	Non adherent		Aderent		
	N	%	N	%	p(<0.05)
Donor type					0.03
Live	72	79.1	38	63.3	
Deceased	19	20.9	22	36.7	
Immunosupressant					0.04
Tacrolimus	37	40.6	30	50	
Cyclosporine	15	16.4	5	8.3	
Sirolimus	26	28.7	9	15	
Serum Creatinine (average)	1.7 ±1.3		1.4 ±0.6		0.04

*T test;# Mann Whitney

The living donor recipients were less adherent than deceased donor recipients. This finding was similar to other studies investigating adherence to immunosuppression therapy in kidney transplantation[11].

The transplantation from living donor reaches better results when compared to transplantation from deceased donor because of the better Human Leukocyte Antigens (HLA) compatibility between donor and recipient, shorter dialysis time, the younger age of the recipient, and the shorter cold ischemia time. All these factors contribute to the improvement of clinical conditions and the recipient's sense of well-being, which could justify the low adherence among the living donor recipients[11,12].

The kidney transplant program at the teaching hospital of the Universidade Federal do Maranhão (HUUFMA) began operations in 2000 with live donor transplants only. In 2005 was performed the first kidney transplant with deceased donor. Hence the high percentage of living donors in the studied sample. Moreover, the capture of organs by the Center of Notification, Organ Procurement and

Distribution of Maranhão (CNCDO/MA - Central de Notificação, Captação de Distribuição de Órgãos do Maranhão) was low in this period.

The low capture of organs at national and state levels can be attributed to several factors, namely: the difficulty to detect brain death, clinical contraindications, problems in maintaining the potential donor, and family refusal to allow the donation in case of deceased donors[13]. Therefore, the poor performance of CNCDO/MA is explained by the already mentioned reasons, plus the lack of state government support.

The donations from living donor have declined every year in almost all regions of Brazil, accounting for only 26.7% of kidney transplants in 2012, when it was around 50% five years ago[14].

The consolidation of the National Transplant Program has raised Brazil to the second position worldwide in absolute numbers of kidney transplants through the implementation of measures to increase its efficiency and the number of deceased donors. However, the regional disparities in demand and allocation of organs for transplantation are still great.

In Brazil, approximately 40% of the estimated annual need for kidney transplantation is met. In 2012, were performed 5,385 transplants, when the estimated need was 11,445. In that same year, the estimated need for kidney transplant in Maranhão was 394, but only 28 transplants were performed[14].

The finding that kidney transplant recipients from a living donor are more likely not to adhere to immunosuppressive treatment reinforces the current attempts of the National Transplant System (SNT - Sistema Nacional de Transplante) through the CNCDOs and Organ Procurement Organizations (OPO) to increase the number of organ capture of deceased donors and increasingly reduce the capture of living donors.

Regarding the type of immunosuppressant, the recipients taking tacrolimus showed higher percentages of nonadherence. The immunosuppression protocols vary according to the transplant centers, but a three-drug combination is normally prescribed for the graft maintenance phase. The immunosuppressive regimen may be composed of a calcineurin inhibitor (cyclosporine or tacrolimus) associated with an antimetabolic drug (sodium mycophenolate or mycophenolate mofetil or azathioprine) or an mTOR inhibitor (sirolimus or everolimus) in combination with prednisone.

The nonadherence percentage among patients using sirolimus is noteworthy, since this immunosuppressant is taken once a day, whereas tacrolimus and mycophenolate are taken twice daily. This result may be related to the fact that in our service this drug is not taken in combination with another immunosuppressant, as it happens with the tacrolimus and mycophenolate association, which are administered together to minimize missed doses.

The study performed by Rodrigues et al.[15] with 127 kidney transplant recipients in outpatient follow-up found that using tacrolimus once daily (extended release) or the formulation twice daily had comparable results, the renal function remained stable.

Kuypers et al.[16] demonstrated better compliance rates in kidney transplantation with use of the extended-release tacrolimus formulation.

In the literature, we have not found studies assessing adherence in adult kidney transplant recipients who used sirolimus to correlate with our results.

The indeterminate etiology for CKD was found in approximately half of the studied sample. Similar results were obtained in the study by Oliveira et al.[17], demonstrating the need to implement the National Policy of Care to Patients with Renal Disease[18] to better identify the determinants of major diseases leading to kidney disease, and introduce and implement prevention and control measures for this disease in the three levels of health care.

The Kidney Disease Prevention Center of the HUUFMA was established in 2009 as part of public policies for the prevention of CKD. It has played an important role in enabling early detection, proper handling, and delay of CKD progression through conservative treatment for this disease, thus improving the quality of life of the population in outpatient follow-up in this service.

The weak correlation between socioeconomic factors and nonadherence suggests the focus of the multidisciplinary team attention should be on

other variables of greater influence such as factors related to patients, the treatment, system and the health team.

Higher levels of creatinine were found among non-adherent receptors (p <0.04), clearly showing the negative impact on the renal allograft when there are failures of immunosuppressive therapy. The extended follow-up of patients in the sample is necessary to assess the late consequences of nonadherence to immunosuppressive medication, such as chronic rejection and graft loss.

The significantly higher levels of serum creatinine (p <0.001) in kidney transplant recipients that did not adhere to immunosuppressive therapy were an important finding of our study. Lalić et al.[19] have found similar results, corroborating our research.

CONCLUSION

After assessing adherence to immunosuppressive therapy by self-report in kidney transplant recipients in outpatient follow-up, was found a high percentage of nonadherence in the studied sample. The study results demonstrated no influence of sociodemographic variables in the outcome.

The high rates of nonadherence found in this study emphasize the need for further research related to kidney transplant patients, immunosuppressive therapy, the health service and team in cases when patients are linked to adherence to immunosuppressive therapy for the identification of barriers hindering the compliance with immunosuppressive treatment.

It is necessary to invest in multidisciplinary educational activities since the beginning of the assessment process to perform the transplant, in order to increase engagement of kidney transplant recipients with immunosuppressive therapy.

Thus, the planning and implementation of actions by the multidisciplinary team responsible for monitoring the kidney transplant patient should be done through an individualized approach, educational interventions and motivational strategies sustained over time to prevent and minimize nonadherence, and consequently improve adherence and increase survival of the graft and kidney transplant recipients.

ADERÊNCIA À TERAPIA IMUNOSSUPRESSORA EM TRANSPLANTE RENAL

RESUMO

O transplante renal apresenta vantagens sobre as outras formas de terapias renais substitutivas (hemodiálise e diálise peritoneal), visto que melhora a qualidade de vida e aumenta a sobrevida dos receptores. Contudo, a adesão à terapia imunossupressora, após o transplante, é uma condição indispensável para a sobrevida do enxerto renal. Avaliar a adesão à terapia imunossupressora em transplantados renais de um hospital de ensino na cidade de São Luís – Maranhão. Estudo transversal, cujos dados foram coletados no período de maio de 2012 a abril de 2013 com aplicação de instrumentos junto a 151 transplantados renais acompanhados no ambulatório de Transplante renal. A adesão aos imunossupressores foi avaliada pelo método autorrelato com a Escala de Aderência à Terapia Imunossupressora (ITAS). Encontrou-se um percentual de não adesão de (60,3%) dos transplantados. As variáveis que tiveram significância estatística com a não adesão foram: ter sido transplantado com doador vivo (p= 0,03), tipo de imunossupressor usado (p=0,04) e creatinina sérica (p=0,04). Houve uma taxa elevada de não adesão à terapia imunossupressora pelo autorrelato em receptores de transplante renal no seguimento ambulatorial. Tal resultado torna-se um importante fator de risco para desfechos clínicos negativos, como rejeição e falência do enxerto renal.

Palavras-chave: Transplante renal. Autorrelato.

ADHERENCIA AL TRATAMIENTO INMUNOSUPRESOR EN TRASPLANTE RENAL

RESUMEN

El trasplante renal presenta ventajas sobre otras formas de terapias de reemplazo renal (hemodiálisis y diálisis peritoneal), ya que mejora la calidad de vida y aumenta la tasa de supervivencia de los receptores. No obstante, la adherencia al tratamiento inmunosupresor, después del trasplante, es una condición indispensable para la supervivencia del trasplante renal. El objetivo del estudio fue evaluar la adherencia al tratamiento inmunosupresor en el trasplante de riñón de un hospital universitario en São Luís - Maranhão, Brasil. Se trata de un estudio transversal, cuyos datos fueron recolectados en el período de mayo de 2012 a abril de 2013 con la aplicación de instrumentos a 151 trasplantados renales acompañados en el ambulatorio de Trasplante renal. La adhesión a los inmunosupresores se evaluó a través del método autoinforme con la Escala de Adherencia al Tratamiento Inmunosupresor (*ITAS*). Se encontró un porcentaje de no adhesión (60,3%) de los trasplantados.

Las variables que resultaron estadísticamente significativas con la no adherencia fueron: haber sido trasplantado con donante vivo (p = 0,03); el tipo de inmunosupresor utilizado (p = 0,04) y la creatinina sérica (p = 0,04). Hubo una tasa grande de falta de adherencia al tratamiento inmunosupresor por el autoinforme en receptores de trasplante renal en el seguimiento ambulatorio. Este resultado se convierte en un importante factor de riesgo para los resultados clínicos adversos, como el rechazo y el fallo del trasplante renal.

Palabras clave: Trasplante renal. Autoinforme.

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Submitted: 12/08/2015
Accepted: 20/02/2016