Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v27i1.614_ENG

ORIGINAL PAPER

Association of Therapeutic Monitoring of Tacrolimus with Laboratory Markers of Kidney Function in Receptors of Kidney Allograft

Livia de Oliveira Albuquerque[1], Alene Barros de Oliveira[1], Francinaldo Filho Castro Monteiro[1,*], Tiago Lima Sampaio[2], Ramon Róseo Paula Pessoa Bezerra de Menezes[2]

1.Universidade Federal do Ceará – Hospital Universitário Walter Cantídio – Fortaleza (CE) – Brazil.

2.Universidade Federal do Ceará – Faculdade de Farmácia, Odontologia e Enfermagem - Departamento de Análises Clínicas e Toxicológicas – Fortaleza (CE) Brazil.

*Corresponding author: francinaldocastrof123@gmail.com

Seccion editor: Ilka de Fátima Santana F Boin

Received: July 17, 2024 | Aproved: Aug 09, 2024

ABSTRACT

Introduction: Kidney transplantation is the most commonly performed type of transplant in Brazil. Tacrolimus is one of the primary drugs used in post-transplant immunosuppressive therapy, and one of its main adverse effects is nephrotoxicity. Laboratory tests to assess renal function are of great importance in monitoring post-kidney transplant patients, helping to diagnose events indicative of graft dysfunction. **Objective:** The present study aimed to evaluate the association between laboratory changes in renal function and blood levels of tacrolimus in post-kidney transplant patients. **Methods:** Observational, analytical and cross-sectional study. The results of blood levels of tacrolimus and measurements of urea, creatinine and estimated Glomerular Filtration Rate (eGFR) were analyzed, as well as the sociodemographic data of kidney transplant recipients followed at a university hospital who underwent laboratory tests between months from January 2021 to July 2022 in a period close to 1 year after the transplant. The variables analyzed in the research were collected from the patient's medical records and subsequently analyzed; the statistical analyses considered $p < 0.05$. The project was approved by the Ethics Committee of the Walter Cantídio University Hospital under opinion number 5,436,434 and CAAE number 57396622.1.0000.5045. **Results:** The sample was mainly composed of males, mixed race, with an average age of 51.5 years (SD ± 12.5) and from cities in the interior of Ceará. Regarding the percentage of patients with laboratory changes, 50.62% (n = 45) showed changes in tacrolimus blood levels. 56.79% (n = 46) had changes in serum creatinine levels, 49.38% (n = 40) had changes in serum urea levels, and 59.26% (n = 48) had altered eGFR. The correlation analyses suggested a low significance between variations of the variables studied. **Conclusion:** The results indicate no relationship between variations in tacrolimus blood concentrations and the appearance of changes in the results of classic renal biomarkers at the end of the first year post-transplant. However, it is necessary to carry out new studies to understand better the impact of changes in blood levels of tacrolimus on the renal function of renal allograft recipients.

Descriptors: Kidney Transplantation; Tacrolimus; Drug Toxicity; Drug Monitoring.

Associação da Monitorização Terapêutica de Tacrolimo com Marcadores Laboratoriais de Função Renal em Receptores de Aloenxerto Renal

RESUMO

Introdução: O transplante renal constitui o tipo de transplante mais realizado no Brasil. O tacrolimo é um dos principais fármacos utilizados na terapia imunossupressora pós-transplante e possui como um de seus principais efeitos adversos a nefrotoxicidade. Os exames laboratoriais de avaliação da função renal possuem grande importância no acompanhamento de pacientes pós-transplante renal, auxiliando no diagnóstico de eventos indicativos de disfunção do enxerto. **Objetivo:** O presente estudo objetivou avaliar a associação entre alterações laboratoriais de função renal e os níveis sanguíneos de tacrolimo em pacientes pós-transplante renal. **Métodos:** Estudo observacional, analítico e transversal. Foram analisados os resultados dos níveis sanguíneos de tacrolimo e das dosagens de ureia, creatinina e estimativa da Taxa de Filtração Glomerular (eTFG), bem como os dados sociodemográficos de receptores de transplante renal acompanhados em um hospital universitário, que realizaram exames laboratoriais entre os meses de janeiro de 2021 e

julho de 2022 no período próximo a 1 ano após a realização do transplante. As variáveis analisadas na pesquisa foram colhidas a partir dos registros dos prontuários dos pacientes e posteriormente analisadas, as análises estatísticas consideraram $p < 0,05$. O projeto foi aprovado pelo Comitê de Ética do Hospital Universitário Walter Cantídio sob o parecer número 5.436.434 e CAAE número 57396622.1.0000.5045. **Resultados:** A amostra foi composta, majoritariamente, pelo sexo masculino, cor parda, idade média de 51,5 anos (DP ± 12,5) e de cidades do interior do Ceará. Quanto ao percentual de pacientes com alterações laboratoriais, 50,62% (n = 45) deles apresentaram alterações dos níveis sanguíneos de tacrolimo; ainda, 56,79% (n = 46) apresentaram alterações na dosagem de creatinina sérica, 49,38% (n = 40) apresentaram alterações na dosagem de ureia sérica e 59,26% (n = 48) apresentaram uma eTFG alterada. As análises de correlação realizadas sugeriram uma baixa significância entre variações das variáveis estudadas. **Conclusão:** Os resultados obtidos sugerem não existir relação entre variações das concentrações sanguíneas de tacrolimo e o surgimento de alterações nos resultados de biomarcadores renais clássicos ao final do primeiro ano pós-transplante. Entretanto, faz-se necessária a realização de novos estudos para uma maior compreensão do impacto causado por alterações dos níveis sanguíneos de tacrolimo na função renal de receptores de aloenxerto renal.

Descritores: Transplante de Rim; Tacrolimo; Toxicidade de Fármacos; Monitoramento de Medicamentos.

INTRODUCTION

Over the last few decades, organ transplantation has become a therapeutic alternative, with significant growth in the number of indications, mainly due to advances that have provided a better quality of life for patients needing this procedure[1]. Brazil is a global reference when it comes to transplants[2]. Kidney transplantation, performed on patients in the terminal stage of chronic kidney disease, is the most performed procedure in the country.[3,4].

After the transplant, the patient will require, throughout his life, continuous multidisciplinary monitoring and also the use of immunosuppressive drugs, aiming to prevent the occurrence of graft rejections and increase survival after the procedure[5]. In this sense, pharmacological therapy is used to prevent acute and chronic rejections by inhibiting the actions of the organ recipient's immune system, being divided into two phases – induction and maintenance –in which immunosuppressive drugs with different mechanisms are used.of action[3].

In the context of kidney transplants, tacrolimus is one of the primary drugs used in post-transplant maintenance immunosuppressive therapy[3]. This drug belongs to the class of calcineurin inhibitors and acts to promote immunosuppression by inhibiting the activation of T lymphocytes. Despite its therapeutic effects, tacrolimus can produce several toxic effects, the nephrotoxic potential being the most notable of them[6].

Monitoring blood concentrations of tacrolimus is an essential tool for controlling the effects produced by this drug since its therapeutic concentrations are close to toxic ones. Thus, this test seeks to minimize undesirable effects in the body caused by tacrolimus in concentrations above the therapeutic window and prevent therapy failure due to subtherapeutic concentrations[6].

Laboratory tests to assess renal function are of great importance in monitoring post-kidney transplant patients, mainly when they use nephrotoxic drugs such as tacrolimus. The results of these tests are used to guide doctors in correctly diagnosing kidney complications after transplantation3; early identification of the problem is vital for a good patient prognosis[7].

However, the biomarkers for assessing renal function currently used in laboratory routines have limitations. For example, in some cases, measurements of their concentrations may not match the actual state of the individual's kidney function, which may hinder the correct diagnosis of possible kidney damage in the patient[8].

Based on the above, it is relevant to identify the behavior of laboratory markers of renal function in patients treated with tacrolimus to assist in clinical decision-making and dosage adjustment. Therefore, the present study aims to evaluate the association between laboratory changes in renal function and blood levels of tacrolimus in post-kidney transplant patients.

METHODS

Study design

The present is an observational, analytical and cross-sectional study, as it observes and analyzes relationships between variables at a given moment, without researcher intervention and using statistical methods to analyze the data collected[9]. With this, we sought to evaluate the association between changes in markers of renal function and blood levels of tacrolimus presented by post-kidney transplant patients.

The study period took place between January 2021 and July 2022.

Study location

The study was carried out at the Walter Cantídio University Hospital (Hospital Universitário Walter Cantídio-HUWC), which is linked to the hospital complex of the Federal University of Ceará (Universidade Federal do Ceará -UFC) in Fortaleza, Ceará state, Brazil.

HUWC is integrated into the Unified Health System (Sistema Único de Saúde -SUS) and plays an essential role in health care in Ceará. The hospital offers services that are divided into clinical and surgical specialties and non-medical specialties, such as outpatient and clinical pharmacy. Transplants are part of the clinical specialties offered by HUWC, considered a national reference in carrying out liver and kidney transplants, along with post-procedure patient monitoring and performing bone marrow and cornea transplants[10].

Study sample

The study included patients aged 18 years or over, kidney transplant recipients followed up at the outpatient clinic of the HUWC nephrology service, who underwent follow-up laboratory tests between January 2021 and July 2022 in a period close to 1 year after the date of transplantation and using tacrolimus as immunosuppressive therapy, totaling 81 patients. The following exclusion criteria were considered: patients using other nephrotoxic drugs, those with urological problems and a history of acute rejection after transplantation.

Variables studied

- Sociodemographic data of patients: sex, age, ethnicity, origin;
- Blood tacrolimus levels of patients, using concentration values between 3-5 ng/mL as the therapeutic range[11].
- Results of kidney function assessment tests:

Determination of serum urea concentrations (reference value 10-50 mg/dL)12, creatinine (reference value 0.6-1.3 mg/dL)[11] and estimation of the glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration – CKD-EPI equation), taking as a reference the values recommended by the organization Kidney Disease: Improving Global Outcomes (KDIGO), these being > 60 mL/min/1 .73 m^2 [12].

Assessment of laboratory parameters

The patient's renal function was analyzed using the results of serum creatinine and urea determination tests and the calculation of the estimated glomerular filtration rate (eGFR) according to the CKD-EPI equation, recommended by the guidelines on chronic kidney disease (CKD) prepared by KDIGO and published in 2013[12].

To evaluate the study's results, the average values obtained for each variable were calculated, and the individual results were categorized according to the reference values for creatinine and serum urea established by the institution's laboratory where the study was developed. The eGFR had the values recommended by KDIGO[12] as a reference.

According to the immunosuppressive kidney transplant protocol of the institution where the study was developed, the recommended tacrolimus blood levels for patients with more than one year of transplantation are 3-5 ng/mL[11].

Data collection and analysis

The collected data were tabulated in a Microsoft Office Excel® spreadsheet for subsequent statistical analysis using the IBM-SPSS v20 software. Data normality was assessed using the Shapiro-Wilk test. Non-parametric numerical data were represented as median and interquartile range; Categorical variables were expressed as absolute and relative frequencies (n, %). The Spearman correlation test was performed to check a linear relationship between continuous numerical variables. Medians were compared using Kuskall-Wallis with Dunn's post-test. As a significance criterion, $p < 0.05$ was adopted.

Ethical aspects

The project was submitted to the Ethics Committee of the Walter Cantídio University Hospital (Comitê de Ética do Hospital Universitário Walter Cantídio/CEP-HUWC) through Plataforma Brasil, being approved under opinion number 5.436.434 and CAAE number 57396622.1.0000.5045. The study was developed in full compliance with the ethical principles established in resolution 466/12 of the National Health Council (Conselho Nacional de Saúde -CNS).

RESULTS

Of the 81 kidney transplant patients evaluated during the study period, 61.7% (n = 50) were male with a mean age of 51.5 years (SD ± 12.5), with a minimum of 25 years and a maximum of 82 years old. Regarding their ethnicity, 97.6% (n = 79) were mixed race. Regarding their origin, only 21% (n = 17) of the patients lived in the city of Fortaleza, with the majority coming from the

inlands of the state of Ceará, 46.9% (n = 38), followed by those coming from other states – 30.9% (n = 25). Table 1 presents the characterization of the patient's sociodemographic profile.

Table 1. Characterization of the study population concerning sociodemographic profile.

Variable	Mean ± Standard Deviation
Age	51.5 ± 12.5 years old
Variable	**n (%)**
Sex	**n = 81**
Female	31 (38.3%)
Male	50 (61.7%)
Ethnicity	**n = 81**
Yellow	1 (1.2%)
White	1 (1.2%)
Brown	79 (97.6%)
Origin	**n = 81**
Fortaleza-CE	17 (21%)
Within Ceará state	38 (46.9%)
Other states	25 (30.9%)
No data	1 (1.2%)

Source: Elaborated by the authors.

Therefore, the results of the patients' tacrolimus blood levels were analyzed, obtaining a mean concentration of 5.39 ng/mL (SD ± 2.71), IC95 = 4.80 – 5.98. Regarding the individual distribution of patients according to their blood concentrations of tacrolimus and the values of the therapeutic range of this drug, 49.48% (n = 40) of patients had serum levels of tacrolimus within the therapeutic range. In comparison, 45.68% (n = 40) n = 37) had tacrolimus blood concentrations above this range, as shown in Table 2.

Table 2. Individual distribution of patients according to their tacrolimus blood concentrations and therapeutic range values.

Tacrolimus Blood Concentration	n (%)
Below therapeutic range (< 3 ng/mL)	4 (4.94%)
Within the therapeutic range (≥ 3 ≤ 5 ng/mL)	40 (49.38%)
Above the therapeutic range (> 5 ng/mL)	37 (45.68%)
Total	81 (100%)

Source: Elaborated by the authors.

Concerning serum creatinine, an average concentration of 1.56 mg/dL (± 0.97) was observed, with 56.79% (n = 46) of patients presenting measurements outside the reference values. As for serum urea, an average concentration of 53,60 mg/dL (± 21.81) was calculated, with 49.38% (n = 40) of patients presenting changes in their dosages. For eGFR, an average of 54.31 mL/min/1.73 m^2 (± 21.24) was found, with 59.26% (n = 48) of patients presenting results below reference values. The results obtained are shown in Table 3.

Table 3. Mean values of kidney function biomarkers in kidney transplant patients and the number of changes presented.

Variable	Reference Values	Mean ± Standard Deviation	Patients with results outside the reference values n (%)
Serum creatinine (mg/dL)	0.6 – 1.3	1.56 (± 0.97)	46 (56.79%)
Serum urea (mg/dL)	10 – 50	53.60 (± 21.81)	40 (49.38%)
eGFR (mL/min/1.73 m^2)	> 60	54.31 (± 21.24)	48 (59.26%)

Source: Elaborated by the authors.

An attempt was made to establish a correlation between the values of tacrolimus blood levels and the results of the renal function biomarkers analyzed. For this purpose, the Pearson correlation test was applied. When examining the correlation between the

results of tacrolimus blood concentration measurement and the values found for serum creatinine and urea concentrations, no significant result was observed, finding $p = 0.120$ and $p = 0.569$, respectively. No significance was also seen when analyzing the correlation between the tacrolimus blood concentration variable and the eGFR values obtained, finding $p = 0.172$. Table 4 presents the Spearman correlation coefficient (Rho) values and the p values obtained for each variable after applying the Pearson correlation test.

Table 4. Results of the Spearman correlation test between tacrolimus blood concentration values and the results of renal function biomarkers.

Variable	Rho	*p*
Serum creatinine	-0.174	0.120
Serum Urea	-0.064	0.569
eGFR	0.153	0.172

Source: Elaborated by authors .

The patients were then separated according to the classification of their tacrolimus blood concentration results, according to the therapeutic range stipulated by the study (3-5 ng/mL), into three groups: patients with results below, within and above the therapeutic concentrations of the drug. A comparison was made between the median values of the renal function biomarker dosages of patients stratified in each group using the Kruskal-Wallis test and the Dunns post-test. When carrying out the analysis, no significant result was found. Table 5 shows the results obtained after carrying out the tests.

Table 5. Results of the Kruskal-Wallis test with Dunns post-test applied between the groups with different tacrolimus blood concentrations and the average results in the renal function assessment tests.

Variable	< 3,0 ng/mL (n = 4)	Between 3.,0 and 5.0 ng/mL (n = 40)	> 5,0 ng/mL (n = 37)	*p*
Serum creatinine (mg/dL)	2.15 (1.05 – 2.43)	1.50 (1.20 – 1.80)	1.30 (1.05 – 1.70)	0.1701
Serum urea (mg/dL)	71.50 (47.75 – 82.50)	49.50 (37.75 – 63.75)	50.00 (36.50 – 57.00)	0.3221
eGFR (mL/min/1,73 m²)	27.80 (26.05 – 88.80)	48.70 (36.20 – 67.65)	58.30 (44.15 – 70.45)	0.1574

Source: Elaborated by the authors.

DISCUSSION

Tacrolimus is one of the main medications used in the immunosuppressive regimen of post-kidney transplant patients[3]. However, due to its nephrotoxic nature, constant monitoring of the concentrations that this substance reaches in the patient's body is necessary, as well as a continuous assessment of renal function parameters to avoid conditions that lead to graft loss[6,7]. However, the main biomarkers of renal function used in laboratory routines recently are limited. They are subject to interference from various factors and have low sensitivity and specificity[8]. Therefore, it is crucial to investigate the relationship between tacrolimus blood concentrations and the frequency of laboratory changes in renal function to identify patterns of changes capable of assisting in clinical decision-making and dosage adjustments.

Analysis of the sociodemographic profile of patients undergoing post-renal transplant follow-up provides more significant knowledge about the portion of the population that most commonly needs to undergo this type of procedure. These data provide support to health professionals so that they can provide care targeted to this patient profile. In the present study, male patients were predominant (61.7%), with a mean age of 51.5 years (SD ± 12.5). A similar profile was found in the study by Oliveira et al.[13], carried out in Florianópolis, which analyzed the sociodemographic and clinical profile of 122 kidney transplant patients in a philanthropic hospital, where 68,9% of transplant recipients were male and had an average age of around 50 years. Mota's study[14], carried out in Fortaleza and which evaluated the quality of life of 197 kidney transplant patients in a university hospital, also found within the analyzed population a predominance of male patients (52%), with the percentage found being lower than that obtained in the present study, with an average age of approximately 48 years old – data that corroborates the findings of this research.

According to the Ministry of Health, the male population is more vulnerable to the development of diseases, particularly chronic illnesses, such as systemic arterial hypertension and diabetes mellitus, which constitute significant risk factors

for the development of chronic kidney disease. Adding to this factor, it is observed that males seek less care in health establishments than females[15]. Thus, the factors presented confirm the presence of most male patients who required the kidney transplant procedure.

Regarding their ethnicity, 97.6% of the patients in the study were brown. Mota[14], in research carried out with transplant patients in Ceará, found that 69% of the patients in his study declared themselves black or brown, with a result similar to that found in the present study. In contrast, Oliveira et al.[13], in a survey with transplant patients from Santa Catarina, presented divergent results, with the majority of patients analyzed (92.5%) belonging to white ethnicity. Thus, it was possible to observe that the ethnic characteristics of the population of kidney transplant patients are subject to variation depending on the characteristics of the region where they reside since studies carried out in the Northeast region showed a predominance of black and brown patients. In contrast, in the survey carried out in the country's southern region, white patients were predominant.

When assessing their origin, most kidney transplant recipients (77.8%) had to travel from their city of origin to undergo follow-up exams. In Mota's study[14], 55% of the sample analyzed underwent treatment outside the city of origin, presenting a result below that found in the present study, which still represents the majority of patients analyzed, corroborating what was found in the present study. This finding represents a factor that significantly impacts the transplant patient's quality of life due to the need to travel constantly to carry out follow-up care or even change their city of origin.

Regarding the analysis of the results of tacrolimus blood concentrations of the patients under study, a mean value of 5.39 ng/mL (SD ± 2.71) was found, IC95 = 4.80 – 5.98. This finding differs from the study by Alghanem et al.[16], which analyzed the results of tacrolimus therapeutic monitoring of 232 post-kidney transplant patients over one year using the therapeutic range of 5-8 ng/mL. In this study, the authors obtained an average tacrolimus concentration of 7.0 ng/mL when measuring the drug one year after the transplant. Despite the discrepancies between the mean values of tacrolimus dosed in patients, both studies found mean concentrations close to or within the therapeutic range stipulated for each.

Alghanem et al.[16] also analyzed the results of recipients' blood concentrations according to the stipulated therapeutic range and found that 11.6% of the patients examined had tacrolimus blood concentrations below the therapeutic range, 60.3% had blood concentrations within the therapeutic range and 28 % had blood concentrations above the determined therapeutic range. The present study found percentages of patients with blood concentrations of the drug analyzed at subtherapeutic levels and within the therapeutic range, as did the study mentioned above, these being 4.94% and 49.48%, respectively. The percentage of patients with tacrolimus blood concentrations above the therapeutic range was higher when compared to the literature analyzed, 45.68%.

The high percentage of patients with blood concentrations outside the stipulated therapeutic range for tacrolimus, with blood levels above or below this window, represents a reason for attention for health professionals when monitoring these patients. There is a need to pay greater attention to preventable factors that can cause these variations in drug concentration, such as low patient adherence to treatment or even the lack of guidance so that the patient only administers the medication after collecting the sample on exam day.

In the analysis of the results of the biochemical parameters of the patients under study, mean concentrations for serum creatinine and serum urea were found to be 1,56 mg/dL (SD ± 0.97) and 53.60 mg/dL (SD ± 21.81), respectively. The data found corroborates the results obtained by the study of Lira[17], carried out with 58 kidney transplant patients at a university hospital in Fortaleza, where mean concentrations for serum creatinine and serum urea were obtained of 1.63 mg/dL and 55.89 mg/dL, respectively. In both studies, the mean serum urea and creatinine concentration values found were slightly above the reference values used by each study. Concerning eGFR, the average value found for the patients under study was 54.31 mL/min/1.73 m^2 (DP ± 21.24), this result being outside the values recommended by KDIGO[12], where eGFR values based on serum creatinine concentration below 60 mL/min/1.73 m^2 should be reported as decreased. The average eGFR value of the patients under study was also below that found in the study by Alghanem et al.[16], who, when using the CKD-EPI equation to estimate patients' eGFR one year after the transplant, obtained an average value of 66 mL/min/1.73 m^2.

Concerning the correlation analysis between the results of tacrolimus blood concentration measurement and the values of serum concentrations of creatinine and urea, as well as the values obtained in the eGFR of the analyzed patients, no statistically significant result was found, with the analyzed correlation presenting p values more remarkable than 0.05. Therefore, the present study did not observe a relationship between tacrolimus blood concentrations and the results of kidney function assessment tests. By performing, using the Kruskal-Wallis test with Dunns post-test, the comparison of the mean values of the dosages of renal function biomarkers of patients stratified into groups according to their blood concentration of the drug concerning the therapeutic range, no significant results were observed, as occurred in the test previously carried out.

Creatinine is a substance from muscle metabolism that is freely filtered by the glomerulus and does not undergo reabsorption or metabolism by the kidney. Due to these characteristics, creatinine is commonly used to evaluate the filtration function performed

by the kidneys. However, serum levels of this biomarker may not match the patient's actual condition since concentrations adopted by most laboratories as above average (1.3 mg/dL) may be associated with reductions of around 50% - 60% of the glomerular filtration rate, which impairs the early diagnosis and treatment of possible injuries[18].

Another biomarker traditionally used to assess kidney function is urea, a nitrogenous metabolite of protein degradation in the body. Like creatinine, this is a substance freely filtered by the glomerulus. Still, it is a weak predictor of glomerular filtration, as between 40% and 70% of this molecule returns to the plasma by passive tubular diffusion after being filtered by the kidneys. Due to this factor, serum urea concentrations are commonly evaluated in association with creatinine levels. Due to these limitations, it is of great importance to combine tests that assess other aspects of kidney function and structure, which are often not associated with the filtration mechanism of this organ[19]. Among these, we can highlight the assessment of the presence of electrolyte disorders or other changes resulting from tubular injuries, urinary sediment abnormalities and the use of markers of renal parenchymal damage such as proteinuria and microalbuminuria[7]. In the population analyzed, there was a low frequency of requesting these last tests, raising the need for their inclusion so that monitoring renal function in post-kidney transplant patients is more complete and adequate.

Therefore, due to the limitations of the leading classic biomarkers used in assessing renal function, developing new biomarkers for renal evaluation has become one of the leading research themes aimed at the renal system. Molecules such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18), among others, have been evaluated to promote more excellent early diagnosis of kidney injury and a better prognosis for the patient[8].

The research results allowed us to get the average values of tacrolimus blood levels and the biomarkers for evaluating the renal function of the population under study, slightly outside the recommended reference values for each variable. It was also possible to measure the percentage of patients analyzed who presented some change in the results of their exams, with this percentage being 50.62% regarding tacrolimus blood levels, adding up the percentages of patients above and below the therapeutic range stipulated for the drug.

Regarding the percentages of patients with changes in the results of renal function assessment tests, 56.79% showed changes in serum creatinine levels, 49.48% showed changes in serum urea levels, and 59,26% showed altered eGFR. Regarding the correlation analyses between tacrolimus dosages and the results of renal assessment tests, no statistically significant results were obtained, indicating no relationship between the variables. Comparing patients stratified into groups according to their blood concentration of the drug concerning the therapeutic range was also not statistically significant, suggesting no significant difference between the groups regarding the results of kidney function assessment tests.

As the study's main limitation, the variation in tests requested by medical professionals to evaluate the renal function of each post-kidney transplant patient can be highlighted. The lack of a more significant number of target patients for the research who underwent assessment of blood electrolyte concentrations, as well as the determination of proteinuria, microalbuminuria and measurement of creatinine clearance using the laboratory method, made it impossible to analyze the results of these biomarkers and the relationship between the same and blood levels of tacrolimus. Therefore, there needed to be more assessment of the actual relationship between tacrolimus blood concentrations and the potential damage caused to patients' renal function.

CONCLUSION

The study's results suggest no relationship between variations in tacrolimus blood concentrations and the emergence of changes in the results of classic biomarkers of renal function measured at the end of the first year post-transplant. These parameters currently used in laboratory routines as tools for assessing renal function have limitations, and their concentrations may, in some cases, not match the actual state of the individual's renal function. Therefore, it is suggested that new studies evaluate the correlation between tacrolimus blood concentrations and the dosage of innovative biomarkers of renal function, which have shown greater specificity and sensitivity compared to classic biomarkers in recent studies.

The data obtained by the research can support offering better assistance to post-kidney transplant patients. However, new studies are necessary to help better understand the impact caused by changes in the blood concentration of tacrolimus, used in the post-transplant immunosuppressive regimen, on the kidney function of these patients, aiming to improve the quality of life and increase survival.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Albuquerque LO, Barros A, Monteiro FFC, Sampaio TL, Menezes RRPB; **Data analysis and interpretation:** Albuquerque LO, Sampaio TL, Menezes RRPB; **Article writing:** Albuquerque LO, Barros A, Sampaio TL, Menezes RRPB; **Critical revision:** Albuquerque LO, Barros A, Monteiro FFC, Sampaio TL, Menezes RRPB; **Final approval:** Monteiro FFC.

DATA AVAILABILITY STATEMENT

All dataset were generated/analyzed in the current study.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

Not applicable.

REFERENCES

1. Tessmer MGS, Mielke GI, Barcellos FC, Moraes BP de, Gatto CST. Doação de órgãos: opinião e entendimento sobre morte encefálica de estudantes universitários. Braz J Transplant. 2011; 14(1): 1466–1471. https://doi.org/10.53855/bjt.v14i1.192
2. Soares LSS, Brito ES, Magedanz L, França FA, Araújo WN, Galato D. Transplantes de órgãos sólidos no Brasil: estudo descritivo sobre desigualdades na distribuição e acesso no território brasileiro, 2001-2017. Epidemiol Serv Saude 2020; 29(1): e2018512. https://doi.org/10.5123/S1679-49742020000100014
3. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Imunossupressão em Transplante Renal. Brasília, 2020. [access on 15 Jun 2022]. Available in: https://gov.br/conitec/pt-br/midias/consultas/relatorios/2020/relatorio_pcdt_imunossupressao_em_transplante_renal_cp_28_2020.pdf.
4. Associação brasileira de transplante de órgãos. Dimensionamento dos Transplantes no Brasil e em cada estado (2014-2021). Registro Brasileiro de Transplantes. São Paulo, Ano XXVIII, 2021 [access on 16 Jun 2022]; 4: 8. Available in: https://site.abto.org.br/wp-content/uploads/2022/03/leitura_compressed-1.pdf.
5. Silva JM, Fialho AVM, Borges MCLA, Silva LMS. Perfil epidemiológico dos pacientes transplantados renais em hospital universitário e o conhecimento sobre o uso de drogas imunossupressoras. Braz J Transplant 2011; 14(1): 1456–1459. https://doi.org/10.53855/bjt.v14i1.190
6. Bentata, Y. Tacrolimus: 20 years of use in adult kidney transplantation. What we should know about its nephrotoxicity. Artif Organs 2020; 44(2): 140-152. https://doi.org/10.1111/aor.13551
7. Porto JR, Gomes KB, Fernandes AP, Domingueti CP. Avaliação da função renal na doença renal crônica. Rev Bras Anal Clínic 2017; 49(1): 26-35. https://doi.org/10.21877/2448-3877.201500320
8. Dusse LMS, Rios DRA, Sousa LPN, Sousa RMMS, Domingueti CP, Gomes KB. Biomarcadores da função renal: do que dispomos atualmente? Rev Bras Anal Clínic 2017; 49(1): 41-51. https://doi.org/10.21877/2448-3877.201600427
9. Marconi MA, Lakatos EM. Metodologia do trabalho científico. São Paulo: Atlas; 2003.
10. Universidade Federal do Ceará (UFC). Hospital Universitário é referência no Norte e Nordeste na política de transplantes do Brasil. Notícia. 2023. [acess on 15 Ago 2024]. Available in: https://ufc.br/noticias/noticias-de-2023/18136-hospital-universitario-e-referencia-no-norte-e-nordeste-na-politica-de-transplantes-do-brasil#:~:text=Em%202020%2C%20o%20HUWC%20havia,totalizando%20151%20cirurgias%20dessa%20natureza.
11. Universidade Federal do Ceará (UFC). Hospital Universitário Walter Cantídio (HUWC). Protocolo do Transplante Renal. Fortaleza, 2019.
12. Kidney Disease: Improving Global Outcomes (KDIGO). CKD WORK GROUP. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int (Suppl), 2013; 3(Issue 1): 1–150.
13. Oliveira LSV, Vietta GG, Kretzer MR, Machado JS. Perfil sociodemográfico e clínico de pacientes com transplante renal e os fatores associados à rejeição do órgão transplantado em um hospital filantrópico de Florianópolis. Dissertation [Graduation in Nursing] - Universidade do Sul de Santa Catarina; 2020. https://repositorio.animaeducacao.com.br/handle/ANIMA/4886

14. Mota MU. Qualidade de vida em pacientes transplantados renais assistidos em um hospital universitário. Dissertation [Master in Public Health] – Universidade Estadual do Ceará; 2015. https://siduece.uece.br/siduece/trabalhoAcademicoPublico.jsf?id=84254

15. Batista CMM, Moreira RSL, Pessoa JLE, Ferraz AS, Roza BA. Perfil epidemiológico dos pacientes em lista de espera para o transplante renal. Acta Paulist Enferm 2017; 30(3); 280–286. https://doi.org/10.1590/1982-0194201700042

16. Alghanem SS, Soliman MM, Alibrahim AA, Gheith O, Kenawy AS, Awad A. Monitoring Tacrolimus Trough Concentrations During the First Year After Kidney Transplantation: A National Retrospective Cohort Study. Front in Pharmacol 2020; 11(8); 1–10. https://doi.org/10.3389/fphar.2020.566638

17. Lira ALBC. Diagnósticos de enfermagem em pacientes transplantados renais de um hospital universitário de Fortaleza-CE. Dissetation [Master in Nursing] – Universidade Federal do Ceará; 2005. http://repositorio.ufc.br/handle/riufc/1953

18. Kashani K, Rosner MH, Ostermann M. Corrigendum to Creatinine: From physiology to clinical application. Eur J Intern Med 2023; 116: 168–169. https://doi.org/10.1016/j.ejim.2023.07.025

19. Liu F, Guanhui M, Chao T, Shan Z, Xinghua Y, Cong X, Weihao Y, Guobao X, Mingliang L. Elevated Blood Urea Nitrogen-To-Creatinine Ratio Increased the Risk of Coronary Artery Disease in Patients Living with Type 2 Diabetes Mellitus." BMC Endocr Disord 2022; 22(1): 1-10. https://doi.org/10.1186/s12902-022-00954-3