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Research Article

Preliminary Evaluation of Tacrolimus Impact on Glycemic Control, Renal Function, and Hematological Inflammatory Markers in Kidney Transplant Recipients

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Abstract

Background: Tacrolimus, a widely used calcineurin inhibitor in kidney transplantation, has a narrow therapeutic window and is associated with metabolic, renal, and hematological effects. ***Objective***: To evaluate the relationship between tacrolimus blood concentrations, glycemic status, kidney function tests, and hematological inflammatory indices in kidney transplant recipients. ***Methods***: This pilot study included 28 kidney allograft recipients, divided into two groups according to tacrolimus trough level (<7.5 ng/mL and >7.5 ng/mL). Fasting blood glucose, serum creatinine, blood urea nitrogen (BUN), and hematological indices, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), were measured at baseline and three months post-transplant. ***Results***: After three months, tacrolimus administration was associated with significant reductions in fasting blood glucose, serum creatinine, and BUN, particularly in female patients. Tacrolimus trough levels declined significantly in both sexes, with a more marked decrease in males. No significant changes were observed in NLR, MLR, PLR, or other hematological indices, and no significant associations were found between tacrolimus concentration groups and the studied parameters. ***Conclusions***: Tacrolimus use over three months post-transplant was linked to improvements in glycemic control and renal function parameters without significant alterations in hematological inflammatory indices. Larger, long-term studies are warranted to confirm these findings and explore potential sex-related differences in tacrolimus pharmacokinetics and clinical effects.

Keywords: Glycemic control, Inflammatory markers, Kidney transplantation, Pharmacokinetics, Renal function, Tacrolimus.

التقييم الأولي لتأثير تاكروليموس على التحكم في نسبة السكر في الدم ووظائف الكلى وعلامات الالتهاب الدموية لدى متلقي زراعة الكلى

الخلاصة

الخلفية: تاكروليموس، مثبط كالسينيورين يستخدم على نطاق واسع في زراعة الكلى، له نافذة علاجية ضيقة ويرتبط بالتأثيرات الأيضية والكلوية والدموية. **الهدف**: تقييم العلاقة بين تركيزات الدم تاكروليموس، وحالة نسبة السكر في الدم، واختبارات وظائف الكلى، والمؤشرات الالتهابية الدموية لدى متلقي زراعة الكلى. **الطرائق**: تضمنت هذه الدراسة التجريبية 28 متلقيا للطعم الخيفي للكلى، مقسمين إلى مجموعتين وفقا لمستوى حوض تاكروليموس (<7.5 نانوغرام/مل و >7.5 نانوغرام/مل). تم قياس جلوكوز الدم الصائم، والكرياتينين في الدم، ونيتروجين اليوريا في الدم (BUN)، والمؤشرات الدموية، بما في ذلك نسبة العدلات إلى الخلايا الليمفاوية (NLR)، الخلايا الوحيدة إلى الخلايا الليمفاوية (MLR)، والصفائح الدموية إلى الخلايا الليمفاوية (PLR)، في خط الأساس وثلاثة أشهر بعد الزرع. **النتائج**: بعد ثلاثة أشهر، ارتبط إعطاء تاكروليموس بانخفاض كبير في نسبة الجلوكوز في الدم أثناء الصيام، والكرياتينين في الدم، و BUN، خاصة في المريضات. انخفضت مستويات الحد الأعلى لتاكروليموس بشكل ملحوظ في كلا الجنسين، مع انخفاض أكثر وضوحا في الذكور. لم تلاحظ أي تغييرات ذات دلالة إحصائية في NLR أو MLR أو PLR أو مؤشرات الدم الأخرى، ولم يتم العثور على ارتباطات ذات دلالة إحصائية بين مجموعات تركيز تاكروليموس والمعلمات المدروسة. **الاستنتاجات**: تم ربط استخدام تاكروليموس على مدى ثلاثة أشهر بعد الزرع بتحسن في التحكم في نسبة السكر في الدم ومعلمات وظائف الكلى دون تغييرات كبيرة في مؤشرات التهاب الدم. هناك ما يبرر الدراسات طويلة الأجل لتأكيد هذه النتائج واستكشاف الاختلافات المحتملة المتعلقة بالجنس في الحرائك الدوائية لتاكروليموس والتأثيرات السريرية.

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INTRODUCTION

A kidney transplant is still considered the most appropriate treatment for end-stage renal disease (ESRD), and patients have a much higher probability of both living longer and feeling better with a transplant than with dialysis [1]. However, successful long-term outcomes rely on effective immunosuppressants to prevent allograft rejection. Tacrolimus, a calcineurin inhibitor (CNI), is considered a cornerstone in current immunosuppressive therapies [2]. Tacrolimus is associated with a narrow therapeutic index and a wide range of adverse effects. Even though it can affect patients negatively and lead to complications for the transplant, affecting morbidity, metabolic, and hematological systems [3]. Tacrolimus is the most common and widely used calcineurin inhibitor (CNI) in kidney transplant patients. It has been strongly associated with the impairment of blood glucose metabolism and the development of post-transplant diabetes mellitus [4]. One of the well-documented side effects of calcineurin inhibitors is their effect on blood glucose, which may result in new-onset diabetes after transplantation (NODAT) or worsen pre-existing diabetes mellitus [5]. Calcineurin inhibitor (CNI) affects diabetes by reducing insulin production from pancreatic β-cells and increasing insulin resistance [6]. Appropriate glycemic control is essential for those who have received a transplant [7] since high blood sugar levels increase the risks of cardiovascular complications [8,9], infections, and organ failure [7]. High rate of tacrolimus metabolism (calculated by low concentration/dose ratios) is notably connected with deterioration of kidney function one or two years post-graft transplant; exhibiting variability in individual pharmacokinetics in tacrolimus metabolism can affect lifelong kidney graft survival [10]. In addition, tacrolimus is known to be toxic to the kidneys, and it can still cause chronic kidney disease (CKD) in transplant patients, even when their blood levels are within the recommended range [11]. For the earlier diagnosis of nephrotoxicity in kidney transplant patients, tacrolimus concentration/dose (C/D) ratio estimation can be utilized as a predicting value of graft toxicity and acute rejection [12]. As a result of nephrotoxicity, glomerular filtration rate (GFR) may reduce. Creatinine and blood urea nitrogen (BUN) levels may increase; it is especially important to observe the patient and adjust doses to keep the graft functioning [13]. Minimizing rejection and nephrotoxicity caused by tacrolimus metabolism requires carefully observing kidney function tests and individualizing the dose regimen [14]. At the same time, indices such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could be labeled as biomarkers for signaling inflammatory responses in transplant patients [15,16]. As well as predictive, the value of neutrophil, lymphocyte, and platelet ratios could be essential in the diagnosis of acute rejection during the early post-transplant period [17]. These blood indices gained from complete blood count (CBC) could be used as helpful indicators for infection, organ rejection, and cardiac complications in transplant patients [18]. Besides the effect of tacrolimus on blood glucose and renal systems, there are signs that tacrolimus may have a role in controlling the systemic inflammatory response. Alterations in the ratios of complete blood count parameters could reflect the inflammatory environment in kidney transplant recipients and potentially be influenced by tacrolimus concentration. This study aims to show how tacrolimus blood levels are related to blood glucose, kidney function, and a set of novel hematological inflammatory indicators in patients who underwent kidney transplants. Learning how these markers work can lead to a better understanding of optimizing immunosuppressant therapy regimens and improve the patient's long-term outcome.

METHODS

Study design and setting

This case-control pilot study included a total of 28 kidney allograft recipients. This study was performed between June and August 2025 at Dr. Bryar Clinical Lab in the Sulaimani province of Iraqi Kurdistan. Clinical evaluation and laboratory testing are performed at baseline 0 and after 90 days of treatment with tacrolimus.

Inclusion criteria

All kidney allograft recipient patients treated with tacrolimus as an immunosuppressive agent.

Exclusion criteria

Patients with age <18 years, thyroid or parathyroid disorders, postmenopausal women, diabetes mellitus, and gastrointestinal disease were excluded from this study.

Outcome measurements

Baseline data such as age, sex, and tacrolimus concentration level according to the number of days post-graft transplant were included in this study. The patients were divided into two groups according to the tacrolimus serum concentration. 13 patients showing high serum concentration of TAC (TAC>7.5 ng/ml). While another 15 patients with low levels of TAC (TAC < 7.5 ng/ml). Blood samples were collected by a trained phlebotomist using 5 ml gel tubes, centrifuged at 4000 rpm for 10 minutes, and serum was separated by micropipettes, then added to cuvettes to be run by the automated biochemistry analyzer (Roche Diagnostics Cobas c311) (Roche Diagnostics GmbH, Mannheim, Germany).

Laboratory analysis

The routinely recorded preoperative laboratory test results were used for the reference interval analysis. The laboratory tests included serum biochemical parameters: fasting blood glucose (60-110 mg/dL), creatinine (Cr) (male 0.7-1.3 mg/dL, female 0.5-1.2 mg/dL), and blood urea nitrogen (BUN) (6.0-24 mg/dL) levels were measured. Hematology parameters such as white blood cell count (4.0-11.0 x 10^9/L) with absolute neutrophil count (2.0-8.0 x 10^9/L), lymphocytes (0.5-5.0 x 10^9/L), monocytes (0.05-1.0 x 10^9/L), red blood cell (RBC) count (4.5-6.0 x 10^{12}/L), hemoglobin (Hb) (12.5-17.0 g/dL), platelet count (130-450 x 10^9/L), and mean platelet volume (MPV) (6.0-11.0 fL) were determined by the automated biochemistry analyzer (Roche Diagnostics Cobas c311) (Roche Diagnostics GmbH, Mannheim, Germany).

Ethical considerations

Approval of the study protocol was achieved by the Local Research Ethics Committee of the University of Sulaimani, College of Pharmacy (Certificate No: PH157-25 on June 29, 2025). All participants provide their consent before enrolling in the study.

Statistical analysis

The results were expressed as frequency and percentage for nonparametric variables, and as mean ± SD for the parametric variables. Unpaired t-test was used to compare the difference between two groups. Statistical analysis was performed using GraphPad Prism version 7.0 software (GraphPad, La Jolla, California, USA). Values with $p < 0.05$ are considered significantly different.

RESULTS

In this study, a total of 28 patients with kidney graft recipients participated. Figure 1 showed tacrolimus significantly reduced blood glucose, serum creatinine, and blood urea nitrogen (BUN) ($p< 0.001$) after three months of kidney transplantation. Furthermore, there was a significant reduction in blood glucose level, serum creatinine, and blood urea ($p< 0.05$), respectively, after three months of kidney transplantation in the female gender. Additionally, tacrolimus trough levels are significantly decreased in males ($p< 0.001$) and females ($p< 0.05$) following three months post-transplant. In contrast, there was no significant change in blood glucose level, creatinine, and urea following three months of transplantation in the male gender. There was no significant difference in the level of RBC, Hb, platelets, WBC, NLR, PLR, MLR, LMR, NMR, and MNR in both genders after three months following administration of tacrolimus (Figure 2). Table 1 showed that among 28 patients with kidney graft recipients, 13 patients had a TAC level < 7.5 ng/ml, and 15 patients had a TAC level > 7.5 ng/mL. There was no significant gender difference (p= 1.000) or age difference (p = 0.307) between high TAC and low TAC levels.

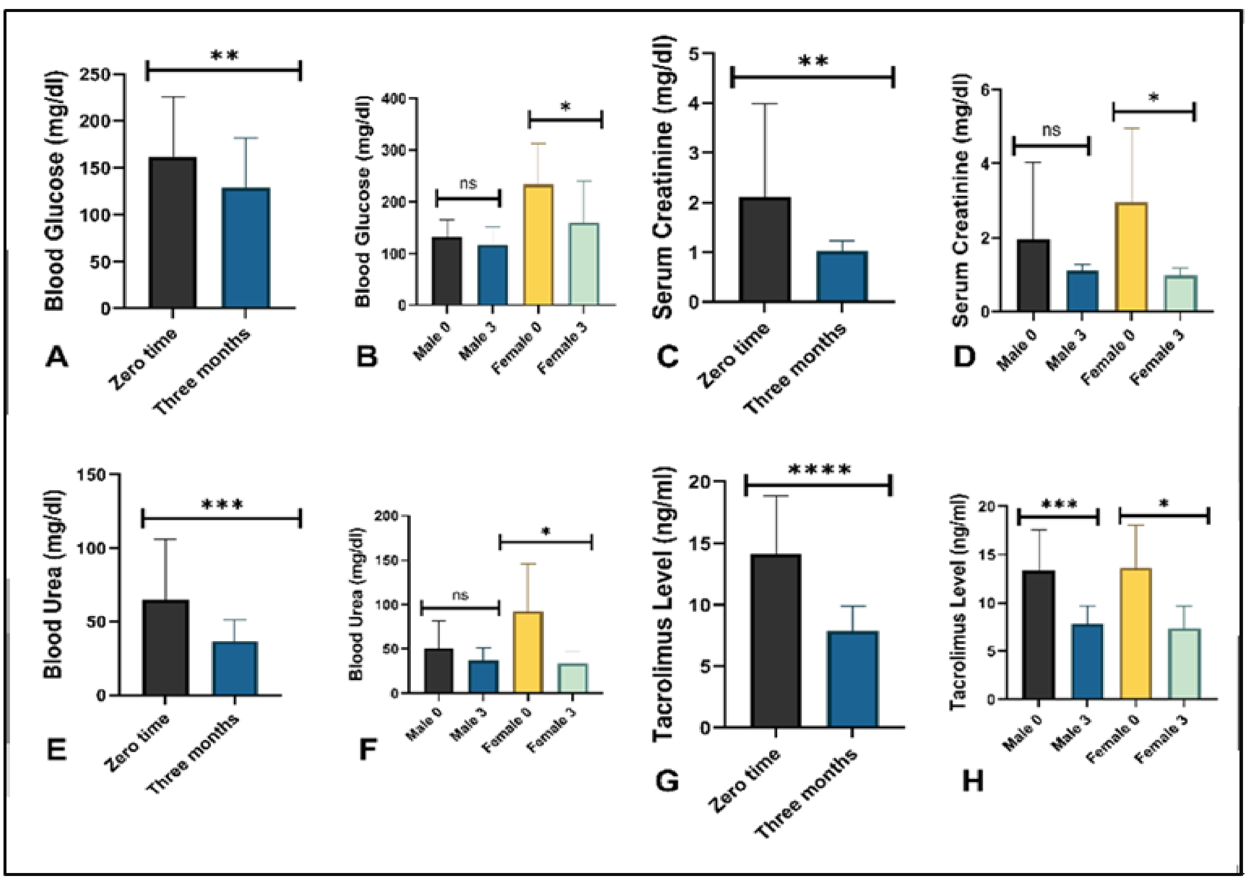

Figure 1: Effect of tacrolimus on blood glucose, serum creatinine, and BUN after three months of kidney transplantation with the differences in their levels in different genders. * (p <0.05), ** (p <0.01), *** (p <0.001), **** (p <0.0001).

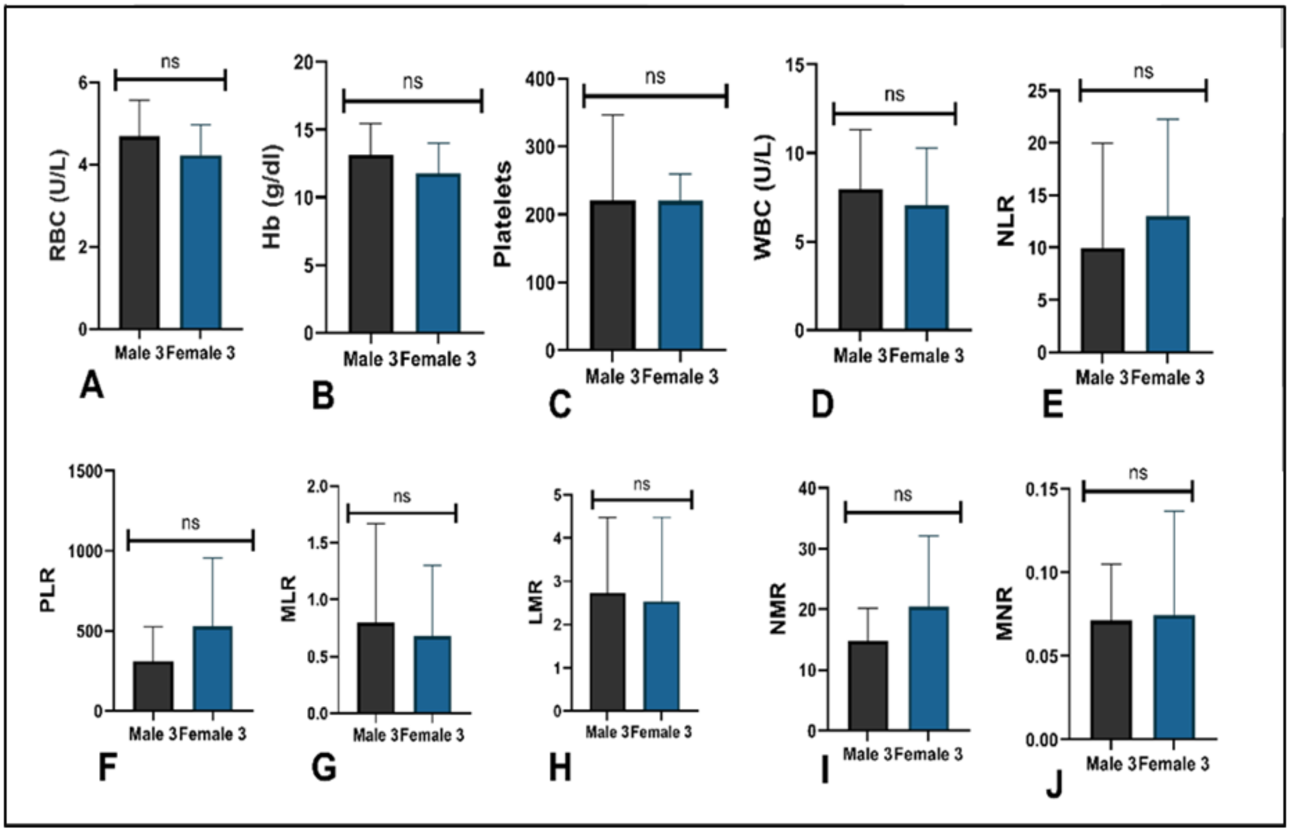

Figure 2: Effect of Tacrolimus on hematological markers in different genders after three months of kidney transplant. ns: non-significant ($p > 0.05$).

Table 1: Comparison between different blood levels of tacrolimus with respect to characteristic features and laboratory findings

Parameter		TAC level (< 7.5 ng/ml)	TAC level (> 7.5 ng/ml)	*p*-value
Gender	Male	8.0	10	1.0
	Female	5.0	5.0	
Age (year)		44.3±10.4	39.1±11	0.307
Glucose level (mg/dL)		137±65	116±34	0.28
S. creatinine (mg/dL)		0.96±0.16	1.09±0.2	0.07
BUN (mg/dL)		33.6±16	39±12	0.2
Hb (g/dL)		12.7±2.1	12.1±2.4	0.86
RBC x 10^{12}/L		4.49±0.8	4.4±0.9	0.81
WBC x 10^{9}/L		7.9±2.9	7.4±3.2	0.75
MPV (fL)		9.2±0.86	8.9±1.1	0.503
Platelets x 10^{9}/L		254±105	201±76	0.21

Values were expressed as mean±SD.

Furthermore, there were no significant differences in glucose level (p= 0.28), serum creatinine (p= 0.07), BUN (p= 0.2), Hb (p= 0.86), RBC (p= 0.81), WBC (p= 0.75), MPV (p= 0.503), and platelets (p= 0.21) between patients with high TAC levels and patients with low TAC levels. Figure 3 displayed no statistically significant difference in NLR, PLR, MLR, LMR, NMR, and MNR parameters in patients with low tacrolimus (TAC) levels compared to patients with high tacrolimus (TAC) levels after three months following administration of tacrolimus.

DISCUSSION

Post-transplant diabetes mellitus (PTDM) is a common and serious complication following kidney transplantation [19,20]. However, its underlying pathophysiological mechanisms are still a subject of debate [19]. PTDM occurs in approximately 15–25% of recipients and is linked to elevated cardiovascular risk and increased healthcare expenditures [21]. The diabetogenic properties of tacrolimus (TAC) are still being explored, with research examining its effects on β-cell regeneration, insulin production, and insulin resistance. While intestinal glucose absorption is a key factor in maintaining glucose balance, its role in TAC-induced diabetes has not yet been clarified [22]. However, the present study showed that fasting blood sugar was significantly reduced after 3 months, which is in contrast with other studies, which found that using tacrolimus after 3 months increased the level of fasting blood sugar [20,23].

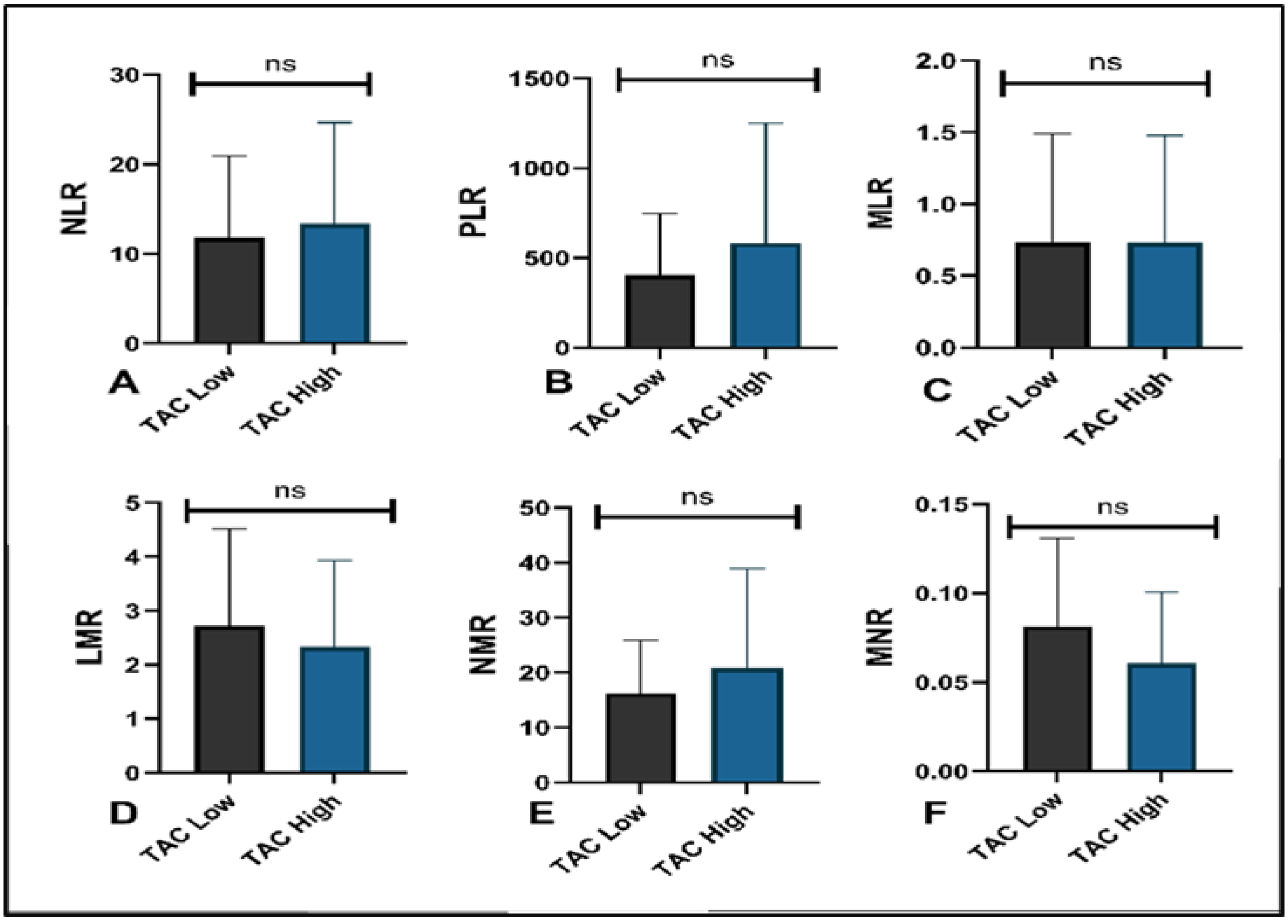

Figure 3: Effect of different tacrolimus levels on hematological markers after 3 months of kidney transplantation. ns: non-significant (p> 0.05).

Furthermore, a study revealed that fasting blood sugar in patients with kidney transplantation on tacrolimus was significantly higher than in healthy individuals [24]. This variability may stem from individual risk factors for developing type 2 diabetes after exposure to immunosuppressive agents. Such factors include being over 45 years of age at the time of transplantation, having overweight or obesity, and presenting with hypertriglyceridemia, a recognized indicator of insulin resistance [20]. Differences in tacrolimus dosage may also play a role. A previous study reported dose-dependent glucose malabsorption in the jejunum following tacrolimus administration [25]. Moreover, maintaining tacrolimus trough concentrations below 15 ng/mL has been associated with a lower incidence of nephrotoxicity, neurotoxicity, PTDM, and other adverse effects linked to elevated drug levels. [26]. Additionally, in a study done by Alghanem *et al*., they observed that PTDM is more prevalent among patients aged 40-59 years and those ≥ 60 years compared with those aged 18-39 years [27]. Our findings displayed that fasting blood glucose levels were significantly reduced in the female gender; however, another study observed that fasting blood sugar was significantly higher in female patients when compared to male patients [24]. Despite the nephrotoxicity of tacrolimus [28-30], the current study revealed that the level of serum creatinine and blood urea was significantly reduced after 3 months of taking tacrolimus, which resembles other findings of studies [23,27]. Additionally, a study done by Jurewicz observed that glomerular filtration rate improved significantly after 3 months in patients that received tacrolimus [31]. In addition, the current results showed that serum creatinine and blood urea levels were significantly reduced in female patients compared to male patients. Several factors may contribute to sex related differences in allograft function, including anatomical, hormonal, and sociocultural influences. While sex hormones primarily act on reproductive organs, emerging evidence suggests they exert effects on nearly all organ systems. The kidneys, for instance, show sex-based variation in both structure and function—differences have been reported in kidney mass, vasopressin excretion, responsiveness to the antidiuretic effects of vasopressin and desmopressin, susceptibility to renal and oxidative injury, and the prevalence of conditions such as renal carcinoma, urolithiasis, and gout. Notably, estrogens have been shown to protect against renal ischemia–reperfusion injury via activation of the PI3K/Akt/eNOS pathway through estrogen receptors [32]. Tacrolimus demonstrates both inter- and intra-patient pharmacokinetic variability, largely influenced by differences in cytochrome P450 3A5 (CYP3A5) isoenzyme expression and P-glycoprotein (P-gp) activity [33]. Recent research has highlighted the impact of CYP3A5 genetic polymorphisms on tacrolimus disposition following kidney transplantation, and patients with CYP3A5*1/*1* or *CYP3A5*1/*3* genotypes tend to have lower tacrolimus trough concentrations compared with those carrying the *CYP3A5*3/*3 variant [34]. Our findings showed that the concentration of tacrolimus was significantly reduced after 3 months of using tacrolimus. The increased systemic clearance of certain CYP3A4 substrates (and possibly P-gp substrates) observed in women compared with men is partly explained by their higher hepatic CYP3A4 expression. For several CYP3A substrates, total clearance (when adjusted for body weight) tends to be slightly to moderately faster in women than in men. In contrast, our results indicated that tacrolimus trough levels had a highly significant reduction in male patients compared to female patients three months post-transplant. Circulating white blood cells (WBCs) and composite inflammatory indices derived from WBC and platelet counts provide simple, low-cost measures of systemic inflammation. Commonly used indices include the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) [35]. Among these, NLR and LMR have emerged as novel inflammatory biomarkers, with reported associations to overall mortality, disease severity, and potentially adverse clinical outcomes [36]. Neutrophils and lymphocytes play well-established roles in immune regulation, and systemic inflammation is often accompanied by increased lymphocyte apoptosis, heightened infection risk, and unfavorable cardiovascular events [37-39]. Elevated MLR and NLR values may indicate an imbalance between active (or subclinical) inflammatory processes and diminished immune defenses against pathogens [40]. Inflammation parameters, such as NLR, MLR, and PLR, are significantly elevated in patients with stage 5 of CKD compared to other stages [35]. Furthermore, elevation of NLR [17,41] and PLR [17] levels was accompanied by acute cellular rejection in patients submitted to kidney transplantation. There was not a significant difference in the level of the following hematological parameters, which include RBC, Hb, platelets, WBC, NLR, PLR, MLR, LMR, NMR, and MNR, in both genders after three months following administration of tacrolimus. A study displayed there was no significant difference between genders except for hemoglobin, which is significantly higher in males than females [33]. Furthermore, a study done by Cvetkovic *et al.* displayed that Hb was significantly higher in males compared to females [42]. We found no significant relationship between tacrolimus level and NLR, PLR, MLR, LMR, NMR, and MNR. However, a study done by Urbanowicz noted a significant association between tacrolimus level (> 15 ng/ml) and NLR in patients with heart transplantation [43]. In this study, we observed there was no significant association between blood glucose levels and low and high tacrolimus serum levels. Conversely, a study showed that the TAC trough concentration/daily dose ratio was significantly related to the development of PTDM [27]. The current study demonstrated no significant correlation between serum creatinine and blood urea and tacrolimus serum levels, which is in line with findings of other studies [44,45]. Currently, a study revealed no significant relation between serum tacrolimus levels, Hb, RBC, WBC, MPV, and platelets. This result is consistent with another study that found no significant association between drug level, WBC, and platelet except Hb [45]. Although a study done by Urbanowicz *et al*. showed the high level of MPV was correlated to high tacrolimus serum levels in patients with heart transplantation [43]. Mean platelet volume (MPV) is an additional marker that reflects the activation of inflammatory responses across various clinical conditions [43].

Study limitations

This single-center pilot study involved a small sample size and short follow-up, limiting statistical power and long-term assessment of tacrolimus effects. Potential confounders, including concomitant medications, lifestyle factors, and comorbidities, were not fully controlled. Hematological indices were based on single-point measurements, and grouping by a single trough level threshold may not reflect intra-patient variability, limiting generalizability.

Conclusion

In the early post-transplant period, tacrolimus therapy may be associated with reductions in fasting blood glucose, serum creatinine, and BUN, particularly among female recipients, without significantly influencing hematological inflammatory indices. The observed differences in drug level changes between sexes highlight the potential role of pharmacokinetic variability in tacrolimus metabolism. While the absence of significant correlations between tacrolimus levels and inflammatory markers may indicate a limited early impact on systemic inflammation, the small sample size limits generalizability. Future research with larger cohorts and extended follow-up is essential to validate these results, clarify sex-related pharmacological differences, and optimize individualized tacrolimus dosing strategies to balance efficacy and safety in kidney transplant recipients.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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