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*Original Article*

# Effect of Tacrolimus Treatment on Blood Glucose level among Renal Transplanted Sudanese patients

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***ABSTRACT:***

**Background:** Tacrolimus is immunosuppressive drug prevents graft rejection in renal transplanted patients. Recent researches suggested that tacrolimus might have side effect on renal function, lipid profile, and blood glucose level. **Objective:** To assess the effect of tacrolimus treatment on blood glucose levels in renal transplanted Sudanese patients. **Materials and Method**: Case control hospital base study was performed in Khartoum state at Sudanese Association specialized Hospital (Renal Transplant Center), during the period from Augusts to November 2018. 50 blood samples were collected from renal transplanted patients treated with tacrolimus. In addition to other 50 sample from healthy individual sex and age matched as control. Trough level of tacrolimus was measured by Cobas 411, fasting blood glucose measured by Cobas Integra 400 plus, and HbA1c was measured by mispa i2. **Results:** The levels of FBG and $HbA_1C$ were significantly increased in the test group when compared with control group (141.48±57.73 mg/dl versus 88.53±8.041 mg/dl, p = 0.000 and 7.47±1.61% versus 4.39±0.57%, p = 0.000) respectively. Across gender the study observed that FBG level is significantly increased in female patients when compared to male patients in the study group (165.00±73.97mg/dl versus 128.25±42.02 mg/dl, p = 0.029). In contrast HbA1c level was insignificantly increased in female patients when compared to male patients in the study group (7.84±1.89% versus 7.26±1.43 %, p = 0.227). Also the study demonstrated significant positive correlation of both FBG and HA1C levels with tacrolimus dose (R=0.413, P=0.003 and R=0.284, P=0.046) respectively in the study group. Furthermore there is positive correlation between tacrolimus concentration and FBG (R=0.307,P=0.030),and duration of treatment with both FBG and HA1c levels in the study group (R=0.455 P=0.001 and R=0.40, P 0.004) respectively. Also the study deduced positive correlation of CD Ratio with both FBG and HA1C levels in the study group (R=0.536, P=0.000, R=0.450, p = 0.001). **Conclusion:** the study bared that Calcineurin inhibitor tacrolimus is risk factor for hyperglycemia in renal-transplanted Sudanese patients.

**Key words:** Tacrolimus, immunosuppressive drug, Blood Glucose, Glycosylated hemoglobin (HbA1C), Renal Transplantation, Sudanese.

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## INTRODUCTION:

Kidney transplantation is the treatment of choice for patient with end-stage renal disease (ESRD), improvement in immunosuppression management has dramatically improved the outcome of kidney transplant recipients.[1] Tacrolimus (FK506) is the backbone of most immunosuppressive regimens 1.[2] Tacrolimus binds to immunophilin FK506 binding protein (FKBP12), forming a complex which inhibits Calcineurin- induced dephosphorylation of the transcription factor, nuclear factor of activated T cells (NFAT).[3] This causes suppression of interleukin-2 (IL-2) transcription and inhibition of T-cell-mediated action. Tacrolimus have narrow therapeutic index, in order to maintain a balance between under immunosuppression and subsequent rejection risk with over immunosuppression and risk of toxicities[4] Various pharmacokinetic profile of tacrolimus exists, many factors affect the pharmacokinetics of tacrolimus, including the gender of patient, liver impairment, and genetic variances in cytochrome p 450 (CYP) enzyme and/or P-glycoprotein expression. Tacrolimus is metabolized by the CYP3A4 isoenzyme, the most abundant of the CYP enzyme.[5] It is also a substrate of P-glycoprotein (PGP) transport system. CYP3A4/PGP inhibitors may increase tacrolimus concentration, resulting in potential toxic concentration and serious adverse effect such as hyperglycemia, neuro-nephrotoxicity, whereas inducers may decrease tacrolimus concentration resulting in suboptimal immunosuppression and elevated risk for rejection.[6,7,8] Certain agent act as inhibitors of CYP3A resulting in a decrease in metabolism and an increase bioavailability of tacrolimus.[9] Several herbal supplements interact with tacrolimus, and it recommended that transplant recipients avoid them.[10] When enzyme inducing agent is used, the onset and length of induction can vary from days to weeks as these factors depend on the half-life of both the medication and CYP enzyme being induced.[11,12]

Catabolic activity of CYP enzyme can be decreased during infection resulting in elevated tacrolimus concentration.[13,14] No treatment recommendation exist for tacrolimus toxicity, as hemodialysis and plasma exchange are ineffective and other modalities such as gastric lavage and activated charcoal are only minimally effective and must be given early after administration.[15,16] In some report, CYP3A inducers phenytoin and phenobarbital have been used in acute over dose settings to increase clearance and facilitate lowering of tacrolimus concentration.[17] Recent researches observed that Tacrolimus treatment might induces hyperglycemia, nephrotoxicity and neurotoxicioty in renal transplanted patients. Hence this research is conducted to visualize the effect of Tacrolimus treatment on blood glucose level among renal transplanted Sudanese patients.

## MATERIALS AND METHODS:

A case control hospital base study was performed in Khartoum state in the period from August 2018 to January 2019 . 50 renal transplanted patients using Tacrolimus drug and without history of diabetes before transplantation attended to Associated Specialized Hospital (Renal Transplant Center)were carefully selected, with age range20 - 50 years . In addition to other 50 healthy individual with normal physical examination and laboratory finding, sex and age matched. as control group.

**Inclusion criteria:** Known Sudanese patients with renal transplanted without history of diabetes and treated with Tacrolimus as cases. In addition to healthy volunteer individual as control.

**Exclusion criteria:** Renal-transplanted patients not under tacrolimus treatment , patient have diabetic history before transplantation, patients taking drugs that affect the tacrolimus result**,** patient has other diseases directly affect hemostatic status, and Patient not under strict dietary control **.**

**Data collection and clinical examination:** Each site used a standardized questionnaire which collected the demographic and clinical information assessed in this study. Clinical examinations were performed by physician in the above mentioned hospital.

**Sample collection:** 2.5 ml of blood was collected in Fluoride oxalate container for blood glucose estimation and other 2.5 ml of blood collected in Ethylene diamine tetra acetic acid container for HbA1c measurement, from all participants using standard procedures..

**Biochemical analysis :** Blood glucose was measured by automated cobas integra plus 400 analyzer**, HbA1C level was** measured by mispa i2 , and Tacrolimus was estimated by cobas 411 in the laboratory of Sudanese kidney transplantation association hospital. Tacrolimus metabolic rate was determined by dividing Tacrolimus concentration in blood (C) by corresponding daily Tacrolimus dose [18]

**Ethical Approval:** This study was approved by ethical committees of the faculty of MLS and Al-Neelain University, and informed consent was obtained from all participators and Ahmed Gasim Hospital before samples collection.

**Quality control:** Sample representing the normal and pathological level of all measured parameters was used for assessment of the quality control. Result ±2SD of the target values of the control sera were accepted.

**Statistical analysis:** Data was analyzed by computer software by using SPSS program manual master sheet (SPSS version 21), the results expressed as frequency percentage, mean and stander division SD, the independent t-test was used to compare the mean level of all measured parameters in case and control. Correlation between variable was significant at $p \leq 0.05$.

## RESULTS:

The study enrolled 100 subjects, 50 subjects have renal transplanted and using immunosuppressant drug (tacrolimus) as test group with age range 20-50 years (32 male and 18 female figures 1). The duration of renal transplantation between 1 month to 5 years. In addition to 50 healthy volunteers sex and age matched as control group (figure 1).

The levels of FBG and $HA_1C$ were significantly increased in the test group when compared with control group (141.48±57.73 mg/dl versus 88.53±8.041 mg/dl, p = 0.000). In addition, the mean ofHbA1c was significantly increased in patients (7.47±1.61% versus 4.39±0.57%, p = 0.000) respectively depicted in table 1.

Across gender FBG level is significantly increased in female patients when compared to male patients in the study group (165.00±73.97mg/dl versus 128.25±42.02 mg/dl, p = 0.029). In contrast HbA1c level was insignificantly increased in female patients when compared to male patients in the study group (7.84±1.89% versus 7.26±1.43 %, p = 0.227) shown in table 2.

As illustrated in table 3.Tacrolimus concentration and HA1C levels were positively correlated with tacrolimus dose (R=0.413, P=0.003 and R=0.284, P=0.046) respectively in the study group. As well as there was positive correlation between FBG and tacrolimus concentration (R=0.307, P=0.030), In addition, there was positive correlation between FBG and HA1c(R=0.676, P=0.000).

There was positive correlation between duration of treatment with both FBG and HA1c in the study group (R=0.455 P=0.001 and R=0.40, P 0.004) respectively depicted in figures 2, 3.

As shown in figures 4, 5, both FBG and HA1C levels were positively correlated with CD Ratio in the study group (R=0.536, P=0.000, R=0.450, p = 0.001)

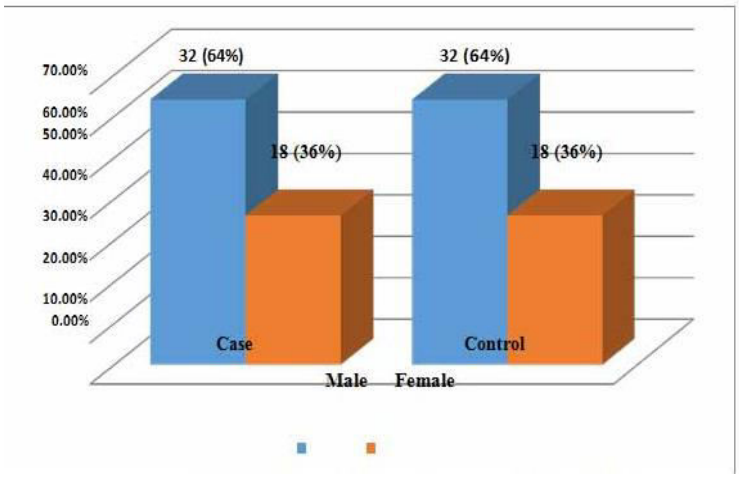


**Figure (1):** The percentage of male and female in the study group

**Table (1):** Mean comparison of study parameters in case versus control group

| Parameters | Case (Mean±SD) n=50 | Control (Mean±SD) n=50 | *P-value* |
|---|---|---|---|
| FBG mg/dl | 141.48±57.73 | 88.53±8.041 | 0.000 |
| HbA1c % | 7.47±1.61 | 4.39±0.57 | 0.000 |

**Table (2):** Shows mean comparison of study parameters across gender in the study group

| Parameters | (Male (Mean±SD | (Mean±SD)Female | *P-value* |
|---|---|---|---|
| FBG mg/dl | 42.02±128.25 | 73.97±165.00 | 029. |
| HbA1c % | 1.43±7.26 | 1.89±7.84 | 0.227 |

**Table (3)**: Correlation between study parameters and study variables in the study group

| Parameters | Statisitics | Age | Dose | tac.conce | FBG | HbA1c |
|---|---|---|---|---|---|---|
| Age | *R-value* | | 0.092 | 0.130 | -0.208 | -0.199 |
| | *P-value* | | 0.524 | 0.369 | 0.147 | 0.166 |
| Dose | *R-value* | 0.092 | | 0.413** | 0.206 | 0.284* |
| | *P-value* | 0.524 | | 0.003 | 0.152 | 0.046 |
| tac.conce | *R-value* | 0.130 | 0.413** | | 0.307* | 0.103 |
| | *P-value* | 0.369 | 0.003 | | 0.030 | 0.475 |
| FBG mg/dl | *R-value* | -0.208- | -0.206- | 0.307* | | 0.676** |
| | *P-value* | 0.147 | 0.152 | 0.030 | | 0.000 |
| HbA1c % | *R-value* | -0.199 | -0.284* | 0.103 | 0.676** | |
| | *P-value* | 0.166 | 0.046 | 0.475 | 0.000 | |

Correlation is significant at P ≤ 0.001
Correlation is significant at P ≤ 0.01
Correlation is significant at P ≤ 0.05

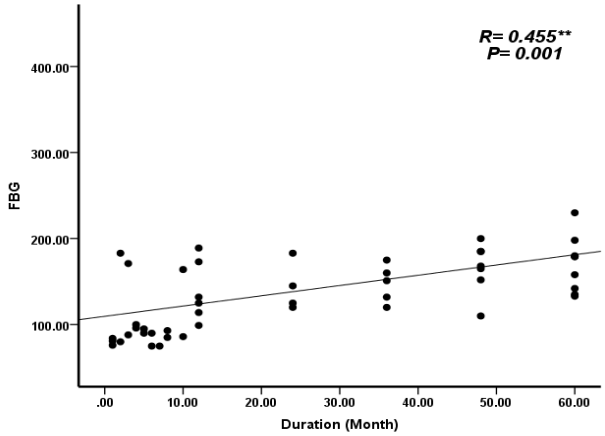


**Figure (2):** correlation between FBG level and duration (month) in the study group

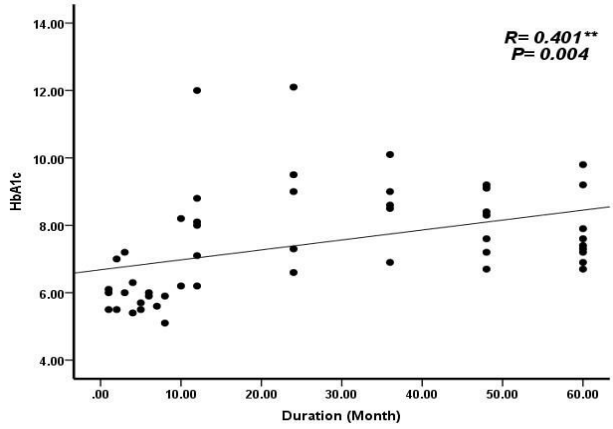


**Figure (3):** correlation between HA1c level and duration (month) in the study group

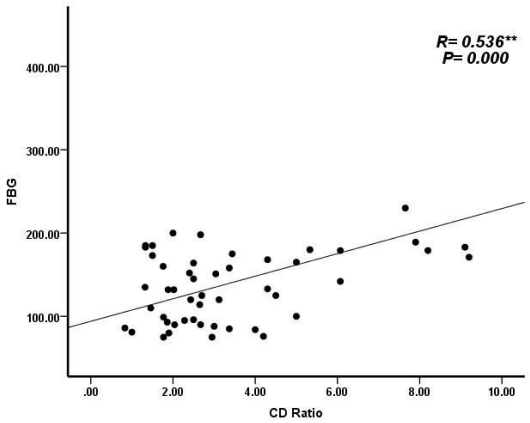


**Figure (4):** correlation between FBG level and CD (Ratio) in the study group

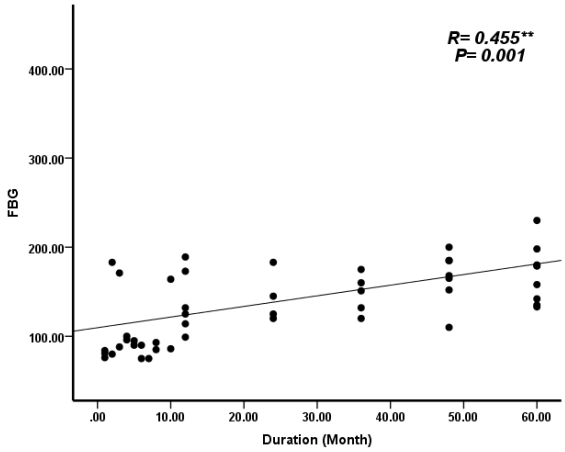


**Figure (5) correlation between HA1c and CD (Ratio)** in the study group

## DISCUSSION:

Tacrolimus is a Calcineurin inhibitor that has been used as an immunosuppressant for the prevention of rejection in renal transplant patients since early 1980s (Maurizio et al 2010).[19] Recent researches showed that the use of Tacrolimus to prevent graft rejection was associated with reduction in acute rejection, graft loss and incidence of hypertension, post-transplant diabetes mellitus and neurotoxicity.[4,20]

In the current study, there is significant difference in mean serum glucose and HbA1c level between the study group and control group. Serum glucose and $HbA_1c$ level are significantly increased in the test group when compared with their control group. Accordance to Fei et al.(2015 )[21] who reported TAC induced insulin resistance and strengthened intestinal glucose absorption by increasing the activity and expression of the glucose transporter, Shoichi et al.(2010)[22] illustrated that careful monitoring and management based on the result of the pre-transplantation OGTT appear to prevent the deterioration of impaired glucose tolerance in renal transplant recipients receiving FK-based therapy, even when a pre-operative OGTT shows impaired glycemic control.[22]

Our study data illustrated that the HbA1c & Fasting blood glucose is significantly increased in-patient who use Tacrolimus during renal transplantation ($p \leq 0.05$).).Which agree with Teh et al (2011)[23] who performed systematic review of the adverse effects of tacrolimus in organ transplant patients**,** and concluded that the uses of tacrolimus caused an increase in the incidence of post-transplant diabetes mellitus and neurotoxicity in renal transplanted patients.[23]

In the present study Tacrolimus concentration and HbA1C levels were positively correlated with tacrolimus dose, As well as FBG and HbA1c level were positive correlated with duration of treatment and CD Ratio in the study group. There are many studies focusing on changes in β-cell regeneration, insulin secretion, and insulin resistance after TAC administration.[24,25] Although glucose absorption in the intestines plays a crucial role in glucose homeostasis, it is unknown if intestinal glucose absorption is involved in the diabetogenic effect of TAC. According to a previous study[26,27], glucose malabsorption in the jejunum after TAC treatment was observed and the effect was dose-dependent. Therefore, intestinal glucose absorption may contributes in the diabetogenic TAC process Zhiwei et al., (2015).[28]

**CONCLUSION:** The study illustrated that renal-transplanted patients using immunosuppressant drug (Tacrolimus) may exposed to hyperglycemia especially for long-term

**Consent:** As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

**Ethical approval:** As per international standard or university standard written approval of ethics committee has been collected and preserved by the authors.

**Authors contribution Hiba Yasseir Mustafa Kamil:** The study was conducted in collaboration between authors HYMK and AMA. Author HYMK designed the study, performed the statistical analysis. Wrote the protocol and wrote the first draft of the manuscript. Author AMA managed the analysis of the study and the literature searches. All authors read and approved the final manuscript.

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## ABBREVIATION:

| | |
|---|---|
| ESRF | end-stage renal disease |
| FK506 | Tacrolimus |
| NFAT | nuclear factor of activated T cells |
| IL-2 | interleukin-2 |
| CYP | cytochrome p450 |
| PGP | P-glycoprotein |
| BUN | blood urea nitrogen |
| PTLD | post-transplant lymphoproliferative disorder |
| SGLT1 | Sodium-glucose transport proteins |

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