Academic Journal of Clinicians
Published by Academic Journals Publishing Group
ISSN: XXXX-XXXX

Risk Factors for New Onset Diabetes Millitus after Live Donor Kidney Transplantation in Erbil Transplant Center

Ali Abdulrahman Al-Tabbakh[1*], Safaa Ezzuldin Nooraldin [2], Majeed Hassan Mahmood[3]

1. M.B.Ch.B., trainee at Kurdistan Board-Nephrology-Erbil Teaching Hospital-Erbil city-Kurdistan region-Iraq.
2. MBChB, FICMS (Internal Medicine) FICMS (Nephrology) FRCP-Zheen International Hospital-Erbil.
3. MBChB, FICMS (Internal Medicine) FICMS (Nephrology)- Zheen International Hospital-Erbil.

Corresponding Author ,** contact email : **alialtabbakh@yahoo.com

Original Article

Summary

New-onset diabetes after kidney transplant (NODAT) is a serious metabolic complication that occurs frequently in recipients after renal transplantation. Analysis of NODAT causes and the associated aspects is crucial to understanding its origin. This study aimed to address the risk factors and associations that predispose to diabetes after kidney transplant with the relative increase in weight, BMI, viral infections and the effect of immunosuppressant therapy

Hence we conducted a cross-sectional study included 90 post-renal transplant patients Demographic and clinical parameters including age, gender, body mass index (BMI), glycated Hemoglobin (HbA1c) associated viral infections, preemptive kidney transplant or previously hemodialysis, primary causes of renal failure, and cyclosporin, prednisolone doses were analyzed. All patients were on cyclosporine, mycophenolate mofetil and prednisone treatment. Patients with and without NODAT were compared. Findings revealed that the mean age of patients was 39.8 ± 1.5 (range: 18-.0) years , they were 2. females and 63 males. Donor type was live-related 16 (1..8%) and live-unrelated about .4 (82.2%). In addition, 2. patients (30%) have O+ blood group. The remaining .0% of the patients have other blood group. The second and third highest percentages of blood groups are 26 (28.9%) and 24 (26..%) for B+ and A+ respectively. Thirteen patients (i.e. 14.4%) were not on dialyses (preemptive kidney transplant) while .. recipients (presenting 85.6% of all the recipients) were on hemodialysis. About 58 patients (46.4%) did not develop diabetes after 90 days of transplant (post-transplant) while 32 patients (35.6%) were diagnosed with diabetes after 90 days post kidney transplant. In respect to our inclusion criteria for this study, 19 patients (21.1%) were CMV positive by real time PCR prior transplantation time, 9 patients (10%) were diagnosed with HCV and 2 patients (2.2%) have HBV. In conclusion, number of predictors either negatively or positively affect the outcome such as glycated hemoglobin. These are found to influence the elective tendencies of individuals undergoing renal transplant to develop diabetes mellitus type-2. Patients who are HCV and CMV positive are predicted to develop DM. Similarly, patients with blood group O+, with prior history of hemodialysis and a relatively high BMI pre-transplant, are more prone to have a higher level of HbAC1 following a successful transplant. This augments the probability of manifesting with DM type-2.

Keywords: *Kidney transplant, NODAT, body-mass index, viral infection, risk factors*

1. INTRODUCTION

Renal transplantation is the best-known treatment procedure for patients diagnosed with end-stage renal disease (ESRD) due to foreseen advantages. Despite so, new-onset diabetes after transplantation (NODAT) is a common and serious complication that is estimated to occur in 10–53% of recipients who are not diagnosed as being diabetic prior to the transplantation (1, 2). NODAT is also associated with increased risk of the renal allograft, development of infections, and cardiovascular morbidity (3, 4). Despite these effects, it is not until 2003 the World Health Organization (WHO) (following the American Diabetes Association (ADA)) established the first international consensus guidelines (5, 6) Thus, the NODAT refers strictly to patients not diagnosed with pre-transplant diabetes mellitus and acute infections, nor on a stable maintenance immunosuppressive regimen (.). For epidemiological and clinical inentions, it is critical to differentiate NODAT from other forms of post-transplant hyperglycemia such as stress-induced hyperglycemia or transient post-transplant hyperglycemia. The International Congress Guidelines (ICG) stated that diagnosis of NODAT should fulfill the following conditions:

a. fasting glucose ≥ 126 mg/dL (. mmol/L) in more than one occasion.

b. random glucose ≥ 200 mg/dL (11.1 mmol/L) with symptoms.

c. two-hour glucose after a .5-g oral glucose tolerance test (OGTT) ≥ 200 mg/dL (11.1 mmol/L).

d. hemoglobin A1C (HbA1c) ≥ 6.5%.

we choose the HbA1C percentage for the availability of data in our patients records,Regarding the American Diabetes Association (ADA) criteria , when a patient has a different test with a conflict results,the test result above the diagnostic cut-off point better to be repeated with evidence that possibility of interposing HbA1C assay. For example, if a patient affiliates the HbA1C needed for diabetes criterion but not the one related to fasting plasma glucose, that person should even so be considered to have diabetes.

The risk factors related to the NODAT can generally by classified into modifiable and nonmodifiable factors (8). The former factors include types of immunosuppressive mdications and regimens such as corticosteroids and tacrolimus/cyclosporine-containing regimens and high body mass index (BMI) (8, 9). The latter are associated with the recipient such as age, DM family history, ethnicity, presense of other diseases such as hepatitis C

virus (HCV) and cytomegalovirus (CMV) (9, 11).

The Glucocorticoid-associated hyperglycemia often occurs in coincidence with obesity and usually due to acquired insulin resistance (12). Multiple mechanisms are probably involved in the origin of glucocorticoid-induced insulin resistance. The exertion of Glucocorticoids and their effect on metabolism may interfere with many different tissues in the body. In the presence of glucocorticoids, there is an increase in adiposity, as well as an increase in lipolysis, leading to elevated levels of free fatty acids in the blood circulation and an increase in insulin resistance. Suppressed insulin secretion and β-cells apoptosis may be accompanied with insulin resistance to glucocorticoid-associated hyperglycemia (13). Diabetes develops after some weeks or months of oral glucocorticoids therapy. cyclosporine and tacrolimus exert their diabetogenic properties, which can be worsened by the concomitant use of glucocorticoids in a high-dose. CNIs can induce glucose intolerance by different mechanisms, including a decrease in insulin secretion (14), an increase in insulin resistance and toxicity on β-cells (15). The effects of tacrolimus are more profound and intense than cyclosporine . It should be noted that the tacrolimus specific binding protein (FKBP-12) is located in β-cells. Thus, tacrolimus can potentiate glucolipotoxicity in β-cells, possibly by sharing common pathways of β-cell dysfunction. In contrast, the (cyclophilin) which regards as a binding protein for cyclosporine is mostly be located in the heart, liver, and kidney (16).

2. PATIENTS and METHODS

This study was conducted over a time span of one year in Zheen Private Hospital in Erbil following the standard protocol of the thics and Scientific Committee of the Council of Kurdistan Board for Medical Specialties (KBMS) and according to the declaration of Helsinki by the World Medical Association, the EU protocol on protection of animals used for scientific purposes (EU Directive 210/63/EU), and the ethical principles of Framingham consensus of 199.. This is a cross-sectional study which aims to compare cases versus non-cases of diabetes Mellitus type-2 following renal transplant. Data analytics and statistical analyses, including Frequentist statistics and non-Bayesian statistical models, were conducted using SPSS version 24 from IBM with the Analysis ToolPak plugin. A questionnaire was prepared to evaluate the positive and negative association of the patient inclusion criteria, which we expect to have in any aspect of our study. The questionnaire

presents data of a single-centre within 1 year for 90 patients from 0 to 90 days post-transplant period. The samples investigated are to ethnicity restricted.. All the patients (2. female (30%) and 63 male (.0%) in the range 18– .0 years) were on standard treatment, with prednisone, mycophenolate mofetil, and cyclosporine that compromise the standard immunosuppressant regimen. All the inclusion criteria were obtained as follows: Body Mass Index (BMI) was calculated as the ratio of body weight in kg to the square value of height. Obesity is associated to BMI value equal or greater than30. The HbA1c values are expressed, in the present study, in a percentage format. Other parameters included age, sex, blood group, viral infections (HCV, HBV, CMV) and immunosuppressive drugs. Patients under the age 18 years old, with diabetes prior to transplantation, were excluded. The importance of this study is to identify the risk factors responsible for the new-onset diabetes mellitus after live donor kidney transplantation. This will help decreasing modifiable risk factors among transplant recipients with obesity, hepatitis C virus, CMV virus infection and those affected with immunosuppressant medication. To decrease the incidence of graft loss and better patient survival on early detection post kidney transplant.

3. RESULTS

A total of 90 patients were involved in this study, of them 2.(30%) females and 63(.0%) males live-related donor were16 (1..8%) and about .4 (82.2%) live-unrelated. 2. patients (30%) have O+ blood group. blood group B+ 26 (28.9%) and A+ 24 (26..%). 13 patients (14.4%) not on dialyses (preemptive kidney transplant) and .. (85.6%) recipients on hemodialysis. 32 patients (35.6%) diagnosed with diabetes post kidney transplant, (Table1). The mean body mass index (BMI) pre-transplant (time of transplantation) was 23.8± 0.59 kg/m² while post transplant BMI was 25.54±0.48 kg/m². The mean glycated haemoglobin (HbA1c) was (5.12% ± 0.038%) pre-transplantation with a mean value of 5..4%± 0.08% after 90 days post-transplant. The mean cyclosporine used at transplantation time was 503.5±10.6 in the range 296-800 mg. This increases in the post- transplantation from 184-to-420 mg with a mean value of 2.4.4 ± 5.1 mg The mean prednisolone dose was 44.3±0.9 and 9.6±0.13) at pre- transplantation and post transplantation, respectively. All patients received anti-thymocyte globulin (ATG) as induction therapy , (Table 2).

The mean age of patients developing diabetes post transplant was 44..± 2.5 years. As

regarding the mean BMI pre-transplant was 22.8±0.62 kg/m² for non diabetes and 25..± 0.9 kg/m² for diabetes. The BMI post at 90 days post transplant was 24.4 ± 0.55 kg/m² for non-diabetes and 2..48±0.8 kg/m² for the diabetes. According to the American Diabetic Association criteria for diagnosis of diabetes, the mean HbA1c for pre- transplantation patients was 5.35±0.04% for non diabetes and 5.2.±0.0.% for the diabetes patients at 95% confidence interval.

The mean HbA1c for patients 90 days post transplantation was 5.21±0.05% for non-diabetes and 6..±0.09% for diabetes at 95% confidence interval. The mean cyclosporine at the time of transplantation was 489.16±12.4 mg for patient not developing diabetes and a mean value of 529.62±19.1 mg for patient who become diabets at 95% confidence interval. The mean cyclosporine dose was 262.26±5.6 mg at day 90 post-transplant with no diabetes. For those with diabetes the mean cyclosporine was 296.4±9.0 at 95% confidence interval. The average mean for prednisolone pre-transplant was 43.19±1.13 mg for non-diabetes and 46.41±1.6 mg for diabetes at 95% confidence interval. After 90 days post kidney transplant the mean prednisolone was 9..4±0.14 mg for patient with no diabetes and 9.53 ±0.26 mg for non-diabetes at 95% confidence interval. The mean number of age for patients with blood group O, after 90 days post transplant, was 38.3.±2.4 years for non-diabetes and 40.52±1.9 years for diabetes at 95% confidence interval, (Table 3).

The mean BMI at time of transplantation with blood group O+ was 24.56±1.1 and 23.5±0.6 for other blood groups at 95% confidence interval. The mean BMI with hihest for blood group O+ equal to 26.3±0.9 kg/m² and 25.2±0.56 kg/m² for other blood groups at 95% confidence interval. The mean HbA1c with blood group O+ pre-transplant was 5.08±0.08% and 5.13±0.04% with other blood groups at 95% confidence interval. A higher results obtained for the mean HbA1c with blood group O+ after 90 days of transplant was 5.98±0.6% and 5.64±0.10% for other blood groups at 95% confidence interval. For cyclosporine at the time of transplantation the mean value was 49..92±18.3 mg for blood group O+ and 505.95±13.1 mg for other blood groups at 95% confidence interval. The mean cyclosporine dose after 90 days post-transplant for blood group O+ was 2.9.61±10.2 mg and 2.2.18±5.9 mg for other blood groups at 95% confidence interval. We found that a weak relationship in the mean of prednisolone dose with blood group O+ pre-transplant was 43.33±1.8 mg and 44..6±1.1 mg for other blood groups with p-value =0.81. at 95%

confidence interval. The mean for prednisolone with blood group O+ at 90 days was 9.44±0.6 mg and 9..±1.35 mg for other blood groups,p-value=0.81. at 95 % confidence interval, (Table 4)

The mean age for primary kidney disease with hypertension was 52.6±1.9 years with a strong significant p-value of <0.001 and For CKD, this value was 36.2±1.94 years and for others it was 33.41 ±3.25 years at 95 % confidence interval. The mean BMI for primary kidney disease in the pre and post transplantation periods was 22.69±0.6 kg/m2 and other blood groups was 22.6.±1.5 kg/m2 sharing no significsnce unlike for HTN 2..26±0.99 kg/m2 with p-value of <0.001, at 95 % confidence interval. As thr same results obtained for the mean BMI with primary kidney disease and CKD of 90 days post-transplant was 24.55±0.55 kg/m2, 28.11±0.94 kg/m2 for HTN, and 24.98 kg/m2 for others at 95 % confidence interval. The mean for HbA1c for primary kidney disease with CKD at the time of transplant was 5.09±0.05%. This value was found equal to 5.19±0.08 %for HTN and 5.10±0.08% for other groups at 95 % confidence interval. The mean HbA1c for primary kidney disease with CKD at 90 days was 5.80±0.12% and 5..4±0.1. for HTN group and 5.5.±0.1.% for other groups at 95% confidence interval. The mean for cyclosporine dose for a patient with primary kidney disease complaining from CKD at the time of transplant was 482.60±12.8 mg and 581.95 ±19.9 mg for HTN group and 459.05±20.3 mg for other groups at 95% confidence interval. The mean for cyclosporine for CKD group as a cause of primary kidney disease at 90 days was 264.81±5.. mg and 306.38±9.5 mg and 259.38±13.9 mg for other blood group at 95% confidence interval. The mean prednisolone dose for CKD patient at time of transplantation was 42.8±1.3 mg and 48..±1.4 mg for HTN group and 42.94±2.1 mg for others at 95% confidence interval. The mean prednisolone dose at 90 days for CKD patient as a cause for primary kidney disease and HTN was 9.6 ±0.19 mg and 9.41±0.4 mg for others, (Table 5).

Pearson's bivariate correlation analysis revealed a strong positive correlation between age, BMI pre-Trnasplantation and BMI post-Trnasplantation (P<0.001). A weak correlation between HbA1c and BMI pre-transpant (P=0.003). A strong correlation between cyclosporine dose at the time of transplantation and BMI with significant value of 0.001 or less. In addition, prednisolone and pre-transplant BMI show significant correlation (P=0.001). a poor correlation was noticed between post-Trnasplantation prednisolone and

BMI at 90 days (Pearson's correlation coeffecient=0.025, P.value=0.81.). Pearson's Chi-square of independence and Fisher's yield conclusive results concerning the categorical variables' independence or association. Using SPSS, we ran automatic linear modelling as a function of regression analysis to explore the existence of potential significant predictors concerning the two variables diabetes and blood group O+ regarding the dosing of cyclosporine at the time of transplantation and after 90 days (Pearson's correlation coefficient = 0.854, p-value = 0.001 and 0.695, p-value = 0.001). Based on independent sample t-testing for unpaired test for diabetes versus non-diabetes post renal transplant, we found all not significant except for 90 days post transplant regarding BMI t=3.032, p-value = 0.004, mean difference 3.00.11 at 95% confidence interval of 1.02 - 4.99. For HbA1c, t = 14.29, p-value = 0.001, mean difference = 1.485 at 95% confidence interval 1.2..-1.96. For cyclosporine t = 3.95, p-value = 0.002, mean difference 34.15 at 95% confidence interval 12..3-55.5.. Based on independent sample t-testing for unpaired test for blood group O+ versus other groups we found it insignificant at 95% confidence interval. In opposition a significant test result was obtained at 90% confidence interval t = 1..25, p-value = 0.091, mean difference 0.34. According to chi square test there is a strong significant association between HCV and patients developed diabetes (fisher's exact test p-value < 0.001, Cramer's V = 0.3.1, odd ratio for HCV N/Y = 19. The incidence of HCV in patients developing NODAT is shown in (Figure 1).

In addition, a significant association was observed between CMV and post-transplant diabetes at 90% confidence interval Pearson chi square value = 3.065, p-value=0.80, Cramer's V = 0.185, odd ratio for CMV N/Y = 2.4.5. In opposite, no association was observed between gender, type of donor, blood group, primary kidney disease, hemodialysis of HBV and diabetes post transplant at 90 days period. The incidence of CMV patients developing NODAT is shown in (Figure 2).

According to the paired sample t-test, we found a significant difference for individuals before and after kidney transplant regarding the glycated haemoglobin (HbA1c) with a mean value of 0.625, t = -0..5, p-value < 0.001, and a BMI mean value of -1.68, t = -6.8, p-value < 0.001. Based on independent sample t-testing, there was a significant difference between patients with HCV and CMV as compared with those lacking the virus in relation to the HbA1c post-transplant with t = 4.63, p-value = 0.001, mean difference = 1.2. and

with t = 2.68, p-value = 0.011, mean difference = 0.52. No significant difference in relation to HBV was observed. According to multiple linear regression and predictors importance analysis, we assumed that glycated haemoglobin post-Trnasplantation is the dependent variable while all the HCV, HbA1c, BMI post-Trnasplantation, CMV, Hemodialysis, blood group, Pred.-post-Trnasplantation, BMI Pre-Trnasplantation variables are predictor independent ones. The significance of risk factors in NODAT patients is shown in (Figure 3).

It was found that the predictor importance for HCV (0.25, p < 0.001), HbA1c pre-Trnasplantation (0.15, p-value = 0.005), BMI post-Trnasplantation (0.15, p-value = 0.005), CMV (0.15, p-value = 0.006), HD (0.10, p-value = 0.023), blood group (0.08, p-value = 0.046), pred.- post-Trnasplantation (0.06, p-value = 0.0..), BMI pre-Trnasplantation (0.06, p-value = 0.0.9). The risk factors associated with the HbA1c post-transplant and the predictors of harmful and protective effects are shown in (Figures 4 & 5).

Table 1. General characteristics of patient criteria with NODAT

Variable		No.	%	Number of recipients with NODAT
Gender	Male	63	.0.0	23
	Female	2.	30.0	9
Type of donor	LR	16	1..8	8
	LU	.4	82.2	24
Blood group	O+	2.	30.0	12
	Others	63	.0.0	20
Primary cause of kidney disease	CKD	50	55.5	20
	HTN	23	25.6	8
	Others	1.	18.9	4
Hemodialysis	Yes	..	85.6	30
	No	13	14.4	2
Virology	HBV	2	2.2	1
	HCV	9	10.0	8
	CMV	19	21.1	10

Table 2. Summary of recipients' criteria included in the study of NODAT

Variable	Pre-Transplantation		Post-Transplantation	
	Mean	SE	Mean	SE
Age (year)	39.8	1.5	-	-
BMI (kg/m²)	23.8	0.55	25.5	0.48
HbA1C (%)	5.1	0.038	5..	0.08
Cyclosporine A	503.5	10.68	2.4.4	5.13
Prednisolone	44.3	0.94	9.6	0.13

Table 3. The criteria mean values for the recipients with diabetes before and after kidney transplantation.

Variable*		Pre-transplant	Post-transplant
BMI	Diabetic	25.69 ± 0.98	2..48 ± 0.81
	Non-diabetic	22.83 ± 0.62	24.4. ± 0.55
HbA1C (%)	Diabetic	5.2. ± 0.0.	6..0 ± 0.09
	Non-diabetic	5.35 ± 0.04	5.21 ± 0.05
Cyclosporine (mg)	Diabetic	529.6 ± 19.1.	296.4 ± 9.06
	Non-diabetic	489.1 ± 12.48	262.2 ± 5.66
Prednisolone (mg)	Diabetic	46.4 ± 1.65	40.5 ± 1.93
	Non-diabetic	9.5 ± 0.26	9.. ± 0.14

**All values presented as mean ± Standard error*

Table 4. The association of blood group with mean values of BMI, HbA1C and medications among recipients with diabetes

Variable*		Blood group O	Other blood group	P. value
BMI (kg/m^2)	Pre-Transplantation	24.5 ± 1.14	23.5 ± 0.62	0.003 sig
	Post-Transplantation	26.3 ± 0.95	25.2 ± 0.56	
HbA1C (%)	Pre-Transplantation	5.08 ± 0.08	5.13 ± 0.04	0.001 sig
	Post-Transplantation	5.98 ± 0.59	5.64 ± 0.10	
Cyclosporine(mg)	Pre-Transplantation	49..9 ± 18.35	505.9 ± 13.16	0.002 sig
	Post-Transplantation	2.9.6 ± 10.28	272. ± 5.9	
Prednisolone(mg)	Pre-Transplantation	43.3 ± 1.8	44.. ± 1.1	0.81. ns
	Post-Transplantation	9.4 ± 0.59	9.. ± 1.35	

**All values presented as mean ± Standard error, sig: significant, ns: not significant*

Table 5. The association of primary kidney disease with criteria of patients

Variable*		Primary kidney disease			P. value
		HTN	CKD	Others	
Age (year)		52.6 ± 1.9	36.2 ± 1.9	33.4 ± 3.2	<0.001^S
BMI (kg/m^2)	Pre-Transplantation	2..2 ± 0.9	22.69 ± 0.6	22.6 ± 0.6	0.001^S
	Post-Transplantation	28.1 ± 0.9	24.5 ± 0.5	24.9 ± 1.3	
HbA1C (%)	Pre-Transplantation	5.. ± 0.1.	5.09 ± 0.04	5.10 ± 0.08	0.003^S
	Pre-Transplantation	5.. ± 0.1.	5.8 ± 0.12	5.5. ± 0.1	
Cyclosporine (mg)	Post-Transplantation	581.9 ± 19.9	482.6 ± 12.8	459.05 ± 20.3	0.001^S
	Pre-Transplantation	306.3 ± 9.5	264.8 ± 5..	259.3 ± 13.9	
Prednisolone (mg)	Post-Transplantation	48..0 ± 1.41	42.8 ± 1.3	42.9 ± 2.1	0.81.^{NS}
	Pre-Transplantation	NA	9.6 ± 0.1	9.4 ± 0.4	

**All values presented as mean ± Standard error, sig: significant, ns: not significant, NA: not available*

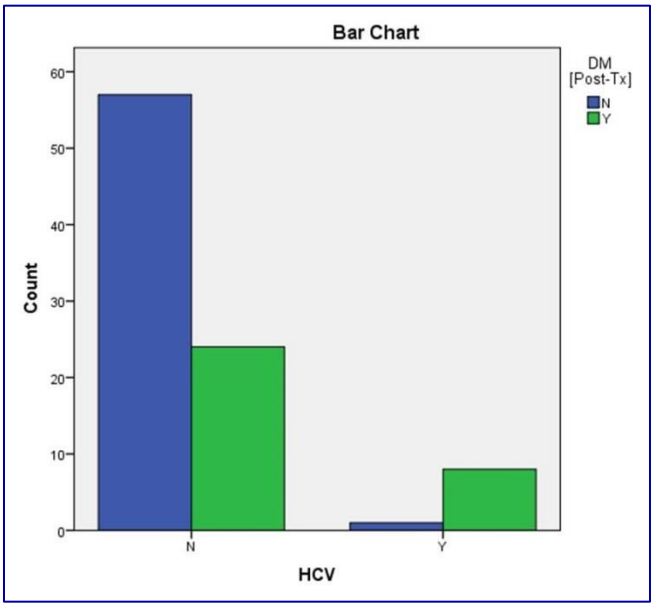

Figure 1. The incidence of HCV in patient developing NODAT

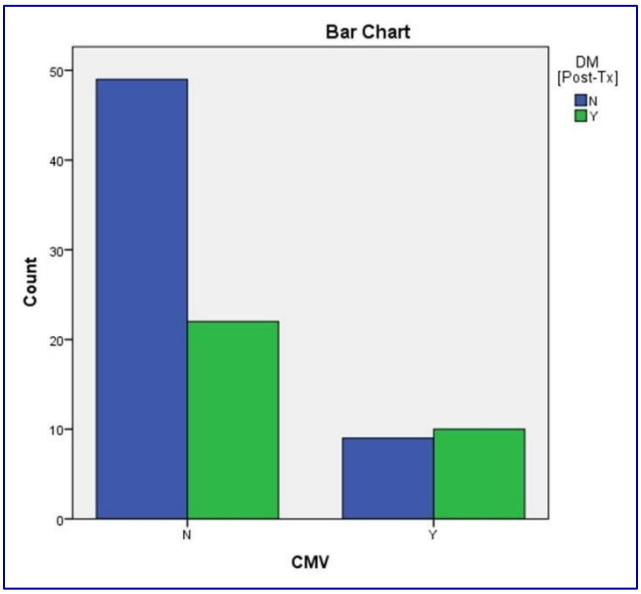

Figure 2. The incidence of CMV patients developing NODAT

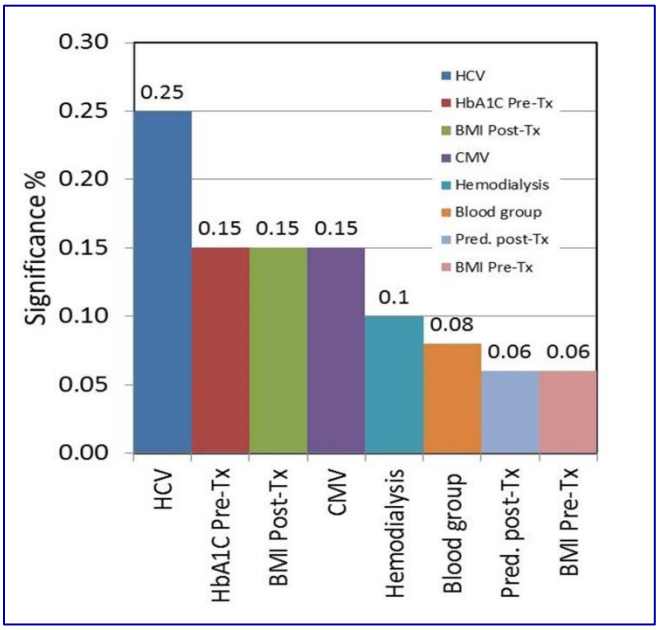

Figure 3. The significance of risk factors in NODAT patients

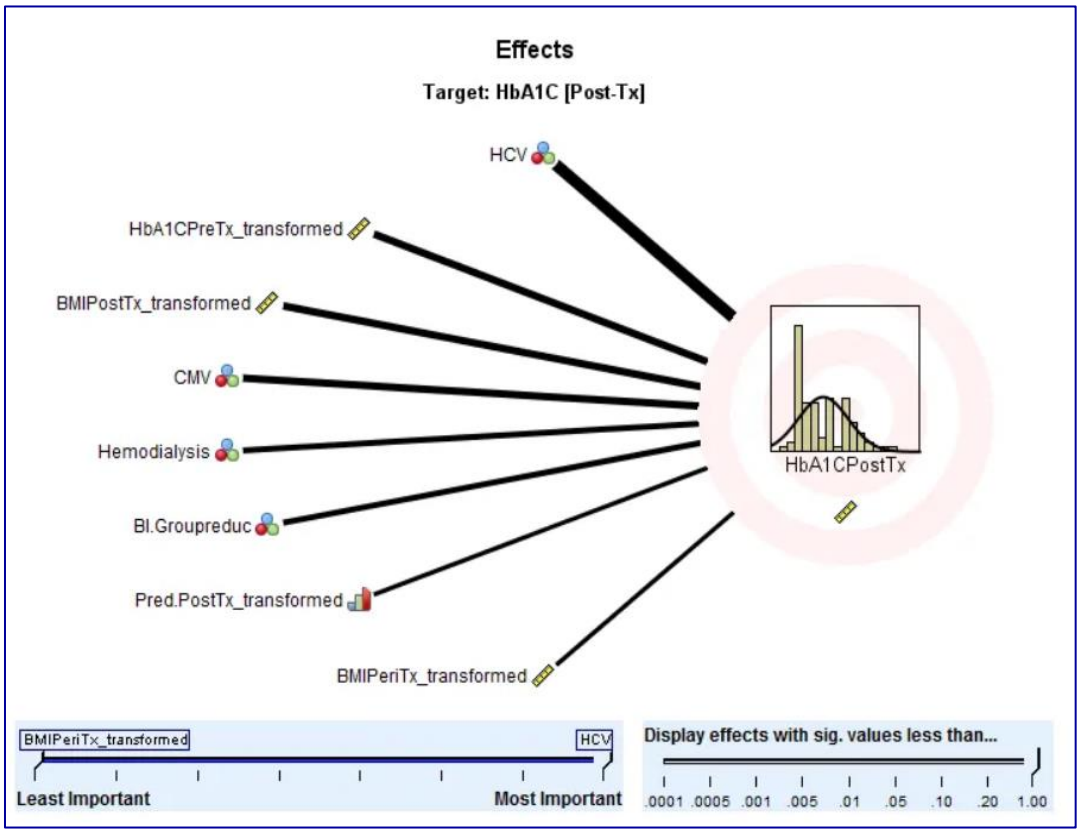

Figure 4. The risk factors associated with the HbA1c post-transplant.

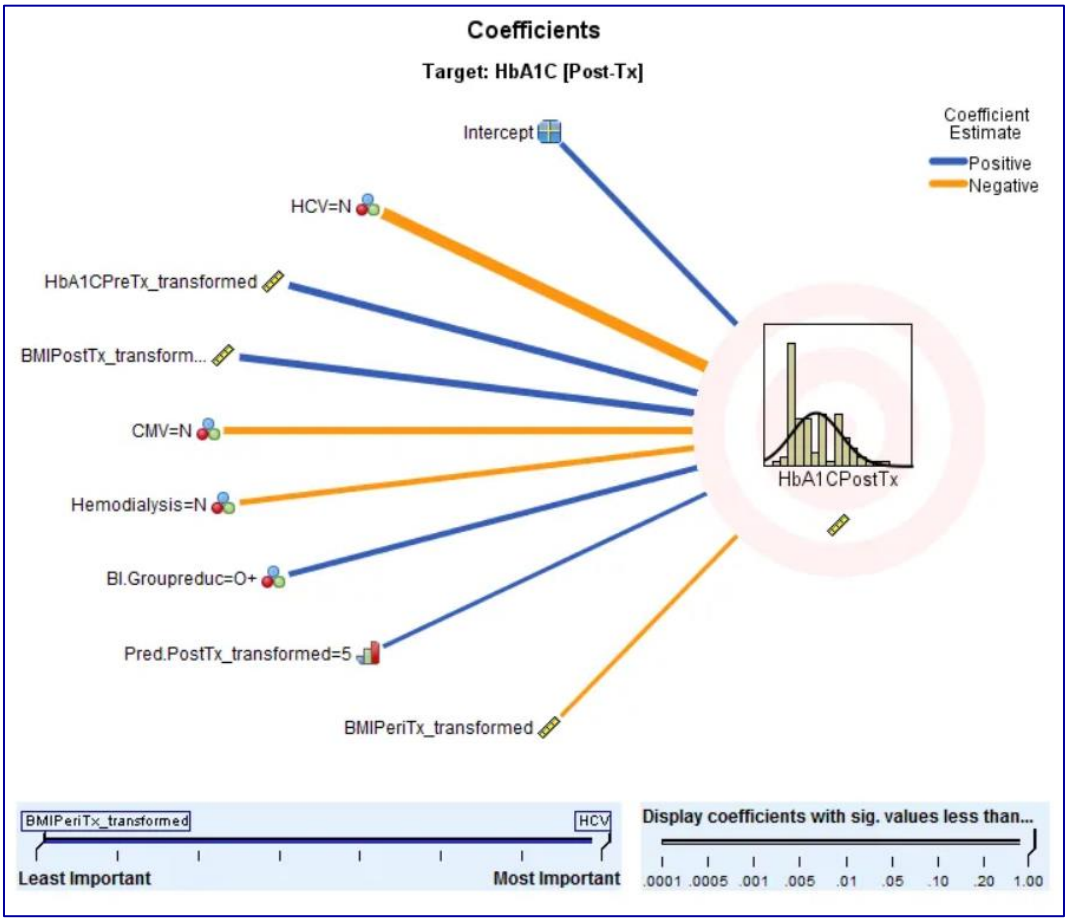

Figure 5. Predictors of harmful and protective effect in relation to HbA1c post-transplant.

4. DISCUSSION

Diabetes mellitus has been cited as one of the most frequent causes of CKD. About more than 30% of non-diabetic patients with renal transplantation experience NODAT which is also referred to as PTDM (1.-19). In the present study, our findings agree with these findings where diabetes mellitus (DM) developed after renal transplantation in 32 out of 90 patients such that a percentage of 35.6% is obtained. The true incremental incidence of diabetes occurs mainly during the first 6 months post transplantation when patients are treated with high doses of immunosuppressive medication. The NODAT incidence is six times higher among recipients during the first year of transplantation (20). Among the non-modifiable risk factors, age is considered the strongest risk factor for the development of PTDM (21). A study by Cosio et al., which included 20.8 allograft recipients, showed that individuals older than 45 were 2.9 times more likely to develop PTDM than those younger

at the time of transplantation (22). Age increased the risk for the development of diabetes 1.5-fold for every 10-year increase in age.

As far as the non-modifiable risk factors are concerned, obesity was found associated with the development of PTDM in many cases (23). Analysis of the USRDS database revealed that the relative risk (RR) of obesity amounts to 1..3 with p-value < 0.0001. Although some studies failed in demonstrating an association between PTDM and obesity, the associated peripheric insulin resistance state is a known risk factor for type 2 diabetes. Shah et al. found that the risk of PTDM increased as BMI increased. As compared with patients having BMI < 0.001, patients with a BMI ≥30 kg/m2 shoed RR value of 1.64 and p-vlaue < 0.001. In the present study, obesity was determined as risk factors of PTDM (24). Several published reports demonstrated a higher incidence of NODAT following the introduction of calcineurin inhibitors in renal transplantation (25). In the present study we didn't establish a comparison between tacrolimus and cyclosporine. Patients on tacrolim were excluded in this work. Studies showed no difference between the two CNI in developing NODAT (26). Previous studies suggested that asymptomatic CMV infection and CMV disease are independently associated with the development of NODAT (see for example (2.)). Other studies reported that CMV was not a risk factor for NODAT (28).

In the present study, we found that 50% of the recipients with CMV infection developed NODAT. HCV infection is associated with insulin resistance and a higher incidence of diabetes mellitus. We found that chronic HCV infection represented a risk factor for NODAT. A significant p-value less than 0.001 is obtained here. A meta-analysis confirmed an independent relationship between HCV infection and NODAT with an approximately four times greater risk of NODAT in HCV-infected recipients (29, 30). In HCV-infected recipients, NODAT manifests usually in the first months after transplantation when higher doses of immunosuppressants are administered (31). Assessment of pre-transplant HbA1c levels may be a valuable tool for an early diagnosis of NODAT in kidney transplant recipients. In the presnt study , patients with NODAT showed higher pre-transplant BMI and HbA1c than those without NODAT. In a study of 1499 non-diabetic primary kidney transplant recipents, interpretation of the data from the United States Renal Data System (USRDS) from 2005 to 2011 was considered. The HbA1c levels ≥ 6.5% were excluded for pre-transplant recipents. A relation between the pre-transplantation HbA1c level and PTDM

was recognized while 395 recipients (presenting 26.4% of the total recipents) developed PTDM over a median follow-up time of 1.8 years (32).

In a study of 400 reciepents were followed up to 4 years after renal transplantation with a cyclosporine and prednisolone based regemin showed that increasing HbA1C levels and increasing the risk of developing pre-diabetes with low dose prednisolone(33) , in our patient we found a weak relation ship between HbA1C and prednisolone after 90 days of trandsplantation with (p-value 0.81.) and only small numerical difference observed that need more period of time to find significance result. In the prospective study by Boots et al., glucose metabolism improved after corticosteroid withdrawal of 10 mg of prednisolone by decreasing insulin resistance. Further dosage reduction under 5 mg/d has not been related to a clear improvement in glucose metabolism (34). As a result of the current lower dosages, several previous studies did not find any effect of cumulative corticosteroid dosages on developing NODAT.

This study comes with several strengths as we assumed a relationship between patient developing higher HbA1C levels and in association with blood group O+ with a significant p-value=0.001, with a high predictive rate of prediabetic incidence within 90 days post kidney transplantation that has not seen in previous studies. Similar finding with high BMI level and a higher doses of cyclosporine has been noticed in the results for recipients after kidney transplantation with blood group O+ in comparison with others.

5. CONCLUSIONS

In conclusion, NODAT is a common and serious issue after kidney transplant with more than one third of individuals developing it within 3 months post transplantation, so potential measures to minimize diabetes risk after kidney transplantation, that involve the choice of optimization the dose of immunosuppressant (CNIs) medication in the first year post transplantation period, identification of patients conditions with high BMI and prediabetic states , infections as with HCV , CMV should be considered to prevent NODAT. These reversible factors could exacerbate diabetes post transplant that necessitate monitoring of patient circumstances and establish early management to limit further complications. Further studies exploring the impact of ethnicity and genetics on the incidence of NODAT,

and new clinical trials considering specific medical treatment for NODAT in kidney transplant patients are also needed.

Ethical Clearance: Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical principles for medical research involving human subjects. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

Funding: None, self-funded by the authors

References

1. *Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D. et al. International Expert Panel. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation. 2003 2.;.5(10 Suppl):SS3-24.,*
2. *Boyce EG, Lawson LA. Preprofessional curriculum in preparation for doctor of pharmacy educational programs. American Journal of Pharmaceutical Education 2009; .3(8): 155.*
3. *Ye X, Kuo HT, Sampaio MS, Jiang Y, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. Clinical transplantation. 2011 Nov;25(6):885-91.*
4. *Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. Diabetes care. 2002 Mar 1;25(3):583-92.*
5. *Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(.): 539–553,*
6. *Araszkiewicz A, Bandurska-Stankiewicz E, Budzyński A, et al. 2019 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clinical Diabetology. 2019; 8(1): 1–95,*
7. *A. Sharif, M. Hecking, A. P. J. de Vries, E. Porrini, M. Hornum, S. Rasoul-Rockenschaub, G. et al. Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions. American Journal of Transplantation,2014; 14(9), 1992–2000.*

8. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. American Journal of Transplantation. 2003 Feb;3(2):1.8-85.
9. Hjelmesæth J, Müller F, Jenssen T, Rollag H, Sagedal S, Hartmann A. Is there a link between cytomegalovirus infection and new-onset posttransplantation diabetes mellitus? Potential mechanisms of virus induced β-cell damage. Nephrology Dialysis Transplantation. 2005 Nov 1;20(11):2311-5.
10. Kuo HT, Sampaio MS, Ye X, Reddy P, Martin P, Bunnapradist S. Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. Transplantation. 2010 May 15;89(9):1134-40.
11. Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature. Reviews in Endocrine and Metabolic Disorders. 2018 Dec;19.....405-20.
12. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. Endocrinology and Metabolism Clinics. 2014 Mar 1;43(1):.5-102.
13. Ullrich S, Berchtold S, Ranta F, Seebohm G, Henke G, Lupescu A, Mack AF, Chao CM, Su J, Nitschke R, Alexander D. Serum-and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. Diabetes. 2005 Apr 1;54.....1090-9.
14. Øzbay LA, Smidt K, Mortensen DM, Carstens J, Jørgensen KA, Rungby J. Cyclosporin and tacrolimus impair insulin secretion and transcriptional regulation in INS-1E beta-cells. British journal of pharmacology. 2011 Jan;162(1):136-46.
15. Relimpio F. " The Relative Contributions of Insulin Resistance and Beta-Cell Dysfunction to the Pathophysiology of Type 2 Diabetes", by Kahn SE. Diabetologia. 2003 Dec;46(12):1.0..
16. Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. American Journal of Transplantation. 200. Jun;.(6):1506-14. Vincenti F,

Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. American Journal of Transplantation. 200. Jun;.(6):1506-14.

1.. Evans PD, Taal MW. Epidemiology and causes of chronic kidney disease. Medicine. 2015 Aug 1;43(8):450-3.

18. Chaoyang Lv, Yao Zhang, Xianying Chen, Xiaowu Huang, Mengjuan Xue, Qiman Sun,et al. , New-onset diabetes after liver transplantation and its impact on complications and patient survival. Journal of Diabetes, 2015; .(6), 881–890.

19. Yu H, Kim H, Baek CH, Baek SD, Jeung S, Han DJ, Park SK. Risk factors for new-onset diabetes mellitus after living donor kidney transplantation in Korea-a retrospective single center study. BMC nephrology. 2016 Dec;1.(1):1-4.

20. Woodward RS, Schnitzler MA, Baty J, Lowell JA, Lopez-Rocafort L, Haider S, Woodworth TG, Brennan DC. Incidence and cost of new onset diabetes mellitus among US wait-listed and transplanted renal allograft recipients. American Journal of Transplantation. 2003 May;3(5):590-8.

21. Palepu S, Prasad GR. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. World journal of diabetes. 2015 Apr 15;6(3):445.

22. Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM.. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney International, 2001; 59(2):.32-..

23. V. Bonato, R. Barni, D. Cataldo, A. Collini, G. Ruggieri, C. De Bartolomeis, F. Dotta, M. Carmellini,. Analysis of Posttransplant Diabetes Mellitus Prevalence in a Population of Kidney Transplant Recipients. Transplantation Proceedings, 2008; 40(6), 1888–1890.

24. Shah, T., Kasravi, A., Huang, E., Hayashi, R., Young, B., Cho, Y. W., Bunnapradist, S. Risk Factors for Development of New-Onset Diabetes Mellitus After Kidney Transplantation. Transplantation, 2006; 82(12), 16.3–16.6.

25. Cole EH, Prasad GR, Cardella CJ, Kim JS, Tinckam KJ, Cattran DC, Schiff JR, Landsberg DN, Zaltzman JS, Gill JS. A pilot study of reduced dose cyclosporine and corticosteroids to reduce new onset diabetes mellitus and acute rejection in kidney transplant recipients. Transplantation research. 2013 Dec;2(1):1-..

26. Zolota A, Miserlis G, Solonaki F, Tranda A, Antoniadis N, Imvrios G, Fouzas I. New-onset diabetes after transplantation: comparison between a cyclosporine-based and a Tacrolimus-based immunosuppressive regimen. In Transplantation proceedings 2018; 50, (10): 3386-3391)..

27. Hjelmesaeth J, Sagedal S, Hartmann A, Rollag H, Egeland T, Hagen M, Nordal KP, Jenssen T. Asymptomatic cytomegalovirus infection is associated with increased risk of new-onset diabetes mellitus and impaired insulin release after renal transplantation. Diabetologia. 2004 Sep;4.(9):1550-6.

28. Sinangil A, Celik V, Barlas S, Koc Y, Basturk T, Sakaci T, Akin EB, Ecder T. The incidence of new onset diabetes after transplantation and related factors: single center experience. nefrologia. 201. Mar 1;3.(2):181-8.

29. Abbott KC, Lentine KL, Bucci JR, Agodoa LY, Koff JM, Holtzmuller KC, Schnitzler MA. Impact of diabetes and hepatitis after kidney transplantation on patients who are affected by hepatitis C virus. Journal of the American Society of Nephrology. 2004 Dec 1;15(12):3166-.4.

30. Baid S, Tolkoff-Rubin N, Farrell ML, Delmonico FL, Williams WW. Tacrolimus-associated posttransplant diabetes mellitus in renal transplant recipients: role of hepatitis C infection. InTransplantation proceedings 2002 (Vol. 34, No. 5, pp. 1..1-1..3).

31. Cruzado JM, Bestard O, Grinyó JM. Impact of extrahepatic complications (diabetes and glomerulonephritis) associated with hepatitis C virus infection after renal transplantation. Hepatitis C in Renal Disease, Hemodialysis and Transplantation. 2012;1.6:108-16.

32. Chen H, Busse LW. Novel therapies for acute kidney injury. Kidney international reports. 201. Sep 1;2(5):.85-99.

33. Tillmann FP, Schmitz M, Rump LC, Quack I. Impact of low-dose steroids on HbA1c levels and development of pre-diabetes and NODAT in non-diabetic renal transplant recipients on long-term follow-up. International urology and nephrology. 2018 Apr;50.....1-...

34. Boots JM, Van Duijnhoven EM, Christiaans MH, Wolffenbuttel BH, van Hooff JP. Glucose metabolism in renal transplant recipients on tacrolimus: the effect of steroid withdrawal and tacrolimus trough level reduction. Journal of the American Society of Nephrology. 2002 Jan 1;13(1):221-..