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Case Report

New-Onset Diabetes Post Kidney Transplant

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Abstract:

BACKGROUND: New-onset diabetes after kidney transplantation (NODAT) is becoming more common and considered as significant clinical problem. It is one of the most frequent complications following kidney transplantation and has a negative impact on the survival and function of the graft.

AIM: To compare the accuracy of an oral glucose tolerance test to a fasting blood glucose test in the diagnosis of NODAT and to pinpoint common risk factors.

MATERIALS AND METHODS: Between December 2020 and March 2021, a descriptive cross-sectional hospital-based study was carried out in the Post Kidney Transplant Referred Clinic at both Ahmed Gassim Hospital and Ibn-Sina Hospital. This study included 60 people in total thanks to a practical sampling technique. Patients who had diabetes mellitus prior to or following a kidney transplant as well as those who were within the first three months after the transplant were excluded. Fisher exact tests and chi-square were used to collect and analyze biomedical data, and logistic regression models were then utilized to determine risk factors. RESULTS: Abnormal blood glucose levels were found in 21.6% of participants, IFG was found in 5% cases and IGT was detected in 10% of the participants. Concurrent IGT and IFG were found in 3.3%.Participants,with normal FBG, NODAT was detected in two cases by using the OGTT test.

Conclusion: Both IGT+IFG increase the risk of NODAT and as consequence cardiovascular mortality and morbidity which is the major cause of death. FBG failed to detect NODAT but, combination of FBG and OGTT improved the sensitivity of them in diagnosis of NODAT.

LIST OF ABBREVIATIONS: NODAT=New onset diabetes after transplant OGTT=Oral glucose tolerance test FBG=Fasting blood glucose IFG=Impaired Fasting Glucose IGT=Impaired Glucose Tolerance.

Keywords: Diabetes, kidney transplantation, Central Sudan.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material,which is available to autho-rized users.

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Background:

New-onset diabetes after transplantation NODAT is becoming more common and posing a significant clinical problem (Abecassis M, et al. 2008), negatively affecting graft function and survival (Kasiske BL, et al. 2003). It accounts for almost half of deaths (Kasiske BL, 2001) and considerably increases the cardio-vascular morbidity and mortality seen in transplant recipients (Markell M. 2004). The exact time after which the post kidney transplant recipients develop NODAT is ranging from 2 to 6 month after transplantation (Sahay M, et al 2013).

Hypertriglyceridemia, hypertension, low density lipoprotein (Kuypers DR, et al. 2008), hypomagnesaemia (Maskey R, 2015), and hyperglycemia are the independent predictors for NODAT (Osio FG, et al 2002). At one year, 70% of individuals with IFG prior to transplant had hyperglycemia (Hjelmesaeth J, et al. 2005). Patient age, ethnicity (Black and Hispanic populations), genetic background, and family history of diabetes are risk factors as well as cadaveric kidney donation and male gender (Krentz AJ and Wheeler DC, 2005). These characteristics can raise the risk of NODAT by up to seven times (Hjelmesaeth J, et al. 1997). The relative risk is 1.4 for patients with a BMI between 25 and 30 kg/m2 (overweight or obese class 1) and 1.7–1.8 for those with a BMI more than 30 kg/m2. Additionally, a risk factor that may be modified is the presence of microorganisms such the hepatitis C virus (Rodrigo E, et al., 2006) and cytomegalovirus infection (Perneger TV, et al. 1995).

Impaired glucose metabolism has also been linked to calcineurin inhibitors (CNI). According to clinical studies, tacrolimus carries a greater risk of IGT and NODAT than cyclosporine. According to the United States Renal Data System (USRDS), patients who got tacrolimus had a 53% higher chance of developing NODAT, and their likelihood of having the disease diagnosed in the second year was likewise higher (Rodrigo E, et al. 2006).

To the best of the researcher's knowledge, no published information about the use of OGTT as a diagnostic technique for early detection and diagnosis of NODAT in Sudan is currently available. Because it evaluates the sensitivity and predictability of the OGTT test for detection of pre diabetes and NODAT, evidence suggests that it is the optimal and best diagnostic test for NODAT (Sharif A, et al. 2006). This may offer significant scientific data that could guide clinical decisions and improve outcomes for patients after kidney transplants. It could also help with early detection and intervention, which would help prevent NODAT and the difficulties that follow (Shabir S, et al. 2013).

Since cardiovascular disease is the primary factor in around half of transplant recipient fatalities, both frank NODAT and IGT raise the risk of cardiovascular mortality and morbidity. Furthermore, NODAT may impact graft function and potentially result in graft failure if not properly treated and controlled, in addition to increasing morbidity and mortality as a result of diabetes. Due to its simplicity and availability, FBG is frequently used in our clinical setting in Sudan to diagnose NODAT; however, it is less sensitive and specific than OGTT.

Materials and methods:

Between December 2020 and March 2021, two of Khartoum's leading renal transplant centers—Ahmed Gassim Hospital and Ibn-Sina Hospital—conducted a descriptive cross-sectional hospital-based study in the Post Kidney Transplant Referred Clinic. This study included 60 people in total thanks to a practical sampling technique. Patients who had diabetes mellitus prior to or following a kidney transplant as well as those who were within the first three months after the transplant were excluded. The data collection sheet was made with the patient's sociodemographic

characteristics, medical history, blood pressure, body mass index (BMI), oral glucose tolerance test results, and lipid profile in mind. Fisher exact and Chi-square tests were used to examine associations for categorical data before logistic regression models were applied to determine risk variables. Statistical significance was defined as a P-value of 0.05 or lower. The Sudan Medical Specialization Board-Education Development Center provided ethical clearance and approval for the study.

Results:

This study included 60 patients who had undergone kidney transplantation. Participants' average age was 42 years (SD 12.88). 83% of participants were men.

Table 1: The socio-demographic characteristics of the study participants

Variable	Characteristic	Frequency (n=60)
Gender	Male	50 (83.3%)
	Female	10(16.7%)
Educational level	None	6(10%)
	Primary school	14(23.3%)
	Secondary school	17(28.3%)
	University and above	23(38.3%)
Employment	Employed	26(43.3%)
	Unemployed	34(56.7%)

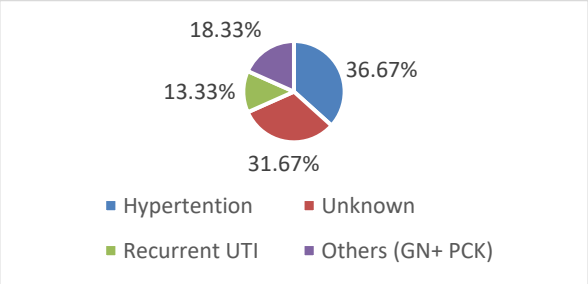

Figure 1: **The common causes of renal failure among participants**

According to figure 1, the most frequent causes of renal failure were hypertension (36.6%), unknown etiology (31.67%), glomerular nephritis (9%), and polycystic kidney disease (9%).

Table 2 showed that hemodialysis was a common form of treatment for the patients. One of them had both peritoneal and hemo dialysis. One of the participants had a kidney transplant as a preventative measure. Participants reported a family history of diabetes more often than hypertension 20% (12) and 38.3% (23) respectively. The duration of transplantation in months in this studied group ranged from 0-108 months and a median 36 and inter quartile range of 54.

Table 2: Medical history of the participants

Variable		Median	IQR(Inter quartile range)
Duration of Dialysis before transplantation\months		12	18
Duration of Transplantation in months		36	54
		Frequency	**Percent**
Type of dialysis before transplantation	HD	58	96.67
	HD+PD	1	1.67
	None	1	1.67
Family history of diabetes	Yes	12	20.0
	No	48	80.0
Family history of hypertension	Yes	23	38.3
	No	37	61.7

HD= Hemodialysis; PD=Peritoneal dialysis

Steroids and calcinurin inhibitors are taken by all individuals. Tacrolimus is used by 90% of them, as seen in table 3.

Table 3: Immunosuppressant agents used by study participants

Variable	Characteristics	Frequency	Percent
CNI	Tacrolimius	54	90.0
	Cyclosporine	6	10.0
Antimetabolite	MMF	31	51.7
	Azathioprine	19	31.7
	MPA	10	16.6
Steroid	Prednisolone	60	100

CNI=Calcineurin inhibitor drugs; MMF= Mycophenolatemofetil; MPA= Mycophenolic acid

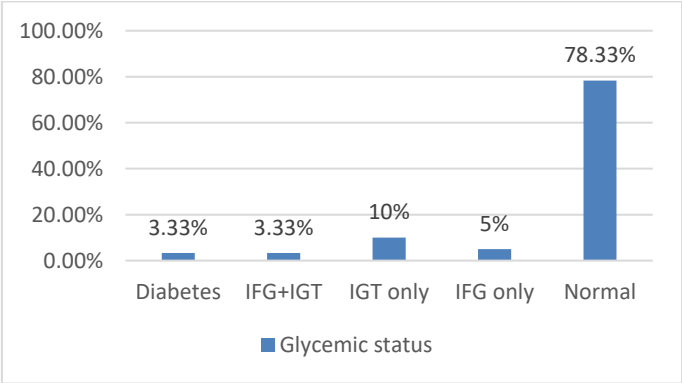

Figure 2: Glycemic status of study participant's

Blood glucose levels were found to be abnormal in 13 (21.6%) of the subjects. The OGTT test identified two subjects (3.3%) as having NODAT, although the FBG by itself missed their glycemic abnormalities. Six individuals (10%) had IGT successfully detected by OGTT, as explained.

Table 4: Cross tabulation between Oral glucose tolerance test and Fasting blood glucose

Variable		Fasting blood glucose			Total
	Characteristics	**Normal**	**Impaired fasting Glucose**	**Diabetes**	
OGTT	**Normal**	47	3	0	50
	Impaired Glucose tolerance	6	2	0	8
	Diabetes	2	0	0	2
Total		55	5	0	60

At a p-value of 0.05, the cross-tabulation between socio-demographic variables and glycemic status revealed that none of the socio-demographic factors had significantly affected the participants' glycemic status.

Table 5: Cross-tabulation between socio-demographic variables and glycemic status

Variable	Characteristics	Glycemic Status		P. Value
		Abnormal	**Normal**	
Age	40 and below	4 (15.4%)	22 (84.6%)	0.30
	above 40	9(26.5%)	25(73.5%)	
Gender	Male	10(20.0%)	40(80.0%)	0.68
	Female	3(30.0%)	7(70.0%)	
Education level	below secondary school	5(25.0%)	15(75.0%)	0.74
	Secondary school	8(20.0%)	32 (80.0%)	
Employment status	Employed	5(19.2%)	21(80.8%)	0.69
	Unemployed	8(23.5%)	26(76.5%)	

Referring to table 6, it appears that none of the medical history variables had a statistically significant impact.

Table 6: Cross-tabulation between medical history and glycemic status

Variable	Characteristics	Glycemic Status		p-value
		Abnormal	Normal	
Duration of dialysis	1year or less	7(53.8%)	30(63.8%)	0.54
	more than 1year	6(46.2%)	17(36.2%)	
Duration of transplantation	3 years and below	8(61.5%)	23(48.9%)	0.42
	above 3years	5(38.5%)	24(51.1%)	
Family history of diabetes	Yes	2(15.4%)	10(21.3%)	1.00
	No	11(84.6%)	37(78.7%)	

While 69.2% (9/13) of individuals with poor glycemic control had a BMI of 25 and above (overweight and obese 1), 68.1% (32/47) of those with normal glycemic levels had a BMI below 25, with a p-value of 0.015. 61.7% (29/47) of those with normal blood pressure also had normal glucose levels. The prevalence of hypertension was 69.2% (9/13) among those with high blood glucose levels (p=0.047). All participants had triglyceride and cholesterol levels within the normal range, therefore it was impossible to compare their benefits of having normal or non-normal blood glucose, as indicated in Table 7.

Table 7: Cross-tabulation between cardiovascular profile and glycemic status

Variables		Glycemic Status		p-value
		Abnormal	Normal	
BMI	**Below 25**	4(30.8%)	32(68.1%)	0.015
	25 and above	9(69.2%)	15(31.9%)	
Hypertension	**No**	4(30.8%)	29(61.7%)	0.047
	Yes	9(69.2%)	18(38.3%)	
Cholesterol level	**<200mg/dl**	13(100.0%)	47(100.0%)	-
LDL level	**<130mg/dl**	12(92.3%)	43(91.5%)	1
	>=130mg/dl	1(7.7%)	4(8.5%)	
Triglycerides levels	**<150mg/dl**	13(100.0%)	47(100.0%)	-
HDL level	**Low**	6(46.2%)	29(61.7%)	0.31
	High	7(53.8%)	18(38.3%)	

When fitted into a binomial regression model the only factor that had a statistically significant effect was BMI where participants with <25 were 4 times more likely to have normal blood glucose levels compared to individuals with BMI >=25. (OR=4.050, P=0.044) as demonstrated in Table 8.

Table 8: Cardiovascular profile predictors of glycemic status

Glycemic status		B	p-value	Exp(B)
Normal	**Non-hypertensive**	1.067[a]	0.124	2.907
	hypertensive	0[b]		-
	BMI <25	1.399[a]	0.044	4.050
	BMI >=25	0[b]		-

a. The reference category is: abnormal glycemic level; b. This parameter is set to zero because it is redundant

Discussion:

Between December 2020 and March 2021, 60 post-renal transplant patients were included in this hospital-based trial who were being monitored at the Ahmed Gasim and Ibn-Sina hospitals. Similar research was done in Sudan in 2017 by Ahmed et al, who looked at 59 transplant patients' NODAT prevalence and risk variables (Ahmed I, et al. 2018). In accordance with Sharif et al. (2006) and Sahay et al. (2013), the age of the patients in the current study, with a mean age of 4212.88 years, indicated a non-significant increased prevalence of elevated blood glucose.

Males made up 83.3% (50) of the respondents in a recent study, which contrasted with Sahay et al, 2013 findings that found no gender difference. This result was consistent with prior investigations showing that males were more likely than females to have kidney transplantation. According to Ahmed et al. (2018) and in contrast to Sharif et al. (2006), who found that the proportion of NODAT patients with a positive family history for diabetes was nearly twice as high as that of healthy patients, no association between family history of diabetes and NODAT was discovered in the current study. Along with the patient's family history, the use of immunosuppressive drugs may cause the development of NODAT (Ahmed I, et al. 2018).

According to Hjelmesaeth J, et al. 2004 who suggested a link between higher BMI growing and the increase risk of post-transplant diabetes, BMI exhibited statistical significance by p=0.015.

Two tests the FBG and OGTT were employed as a glycemic control for subjects after two hours. Using OGTT, the data identified two cases of diabetes (3.3%), although the elevated FBG was not reported. In the current investigation, all diabetes cases exhibited normal FBGs (<110mg/dl). This is greatly less than what was found in the DECODE-study group's meta-analysis of epidemiological data from 29.108 participants in 20 European studies of the general population, which found that 31% of those with two-hour postprandial glucose 200 mg/dl or more (diabetes) had fasting glucose less than 110 mg/dl and more than 50% had a fasting glucose less than 126 mg/dl (European Diabetes Epidemiology Group, 1999). In a different study by Sharif et al., 122 patient received oral glucose tolerance testing (OGTT) to determine their risk of developing new-onset diabetes after organ transplantation. Of those with frank diabetes in the OGTT, 25% had normal fasting blood sugar (<110 mg/dl), and 50% had fasting blood sugar of less than 126 mg/dl (Sharif A, et al. 2006). The sample size might be to blame for the discrepancy between the current study and the previous two investigations.

Pre-diabetic conditions include impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). IGT was defined as having normal fasting plasma glucose (< 6.1 mmol/l) and abnormal 2-hr post-challenge plasma glucose and IFG was defined as having abnormal fasting plasma and normal 2-hr post-challenge plasma glucose (< 7.8 mmol/l)(Lin JD, et al. 2007). 75% of the participants (6/8) in the current study had normal FBG (100 mg/dl), and 13%(8) were diagnosed as IGT and IGT+IFG. The findings indicated elevated levels of IGT, either alone or in combination with IFG, pointing to a higher correlation between IGT and cardiovascular disease than IFG (Unwin N, et al. 2002).

IFG was found in 5% (3/60) of participants, while IFG with IGT was found in 8.3% (5/60), and 47 cases (78.3%) have normal glycemic levels in both tests. In a comparable to UK study, 18% of the tests were IFG and 49% were normal (Sharif A, et al. 2006). This variation in results could be due to the difference in ethnicity

Conclusion:

Both IGT+IFG increase the risk of NODAT and as consequence cardiovascular mortality and morbidity which is the major cause of death. FBG failed to detect NODAT but, combination of FBG and OGTT improved the sensitivity of them in diagnosis of NODAT.

Recommendation:

- Estimation of plasma IGF, IFG to NODAT is recommended beside measuring of BMI.
- Further investigation into the risk factors including immunosuppressant’s drugs with larger sample size.

- Involvement of endocrinologist in the post kidney transplant referred clinic.

Limitation:

Due of the COVID-19 pandemic, a few cases of transplantation within the first year of transplantation were included.

References:

1. Abecassis M, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ, Hays R, Howard A, Jones E, Leichtman AB, Merion RM, Metzger RA, Pradel F, Schweitzer EJ, Velez RL, Gaston RS. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. Clin J Am SocNephrol. 2008 Mar;3(2):471-80. doi: 10.2215/CJN.05021107. Epub 2008 Feb 6. PMID: 18256371; PMCID: PMC2390948.
2. Ahmed I, Musa E, Shaikh Q, Elsharif M. Kidney Transplantation in Sudan. Transplantation. 2018; 102(10):1583-1585.
3. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet. 1999 Aug 21;354(9179):617-21. PMID: 10466661.
4. Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrom J, Leives-tad T, Egeland T, Fauchald P: Glucose intolerance afterrenal transplantation depends upon prednisolone doseand recipient age.Transplantation64: 979 –983, 1997
5. Hjelmesaeth J, Muller F, Jenssen T, Rollag H, Sagedar S, Hartmann A. Is there a link between cytomegalovirus infection and new-onset posttransplant diabetes mellitus? Potential mechanisms of virus induced β-cell damage. Nephrol Dial Transplant. 2005; 20(11): 2311–2315
6. Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. The DECODE-study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe. Diabetologia. 1999 Jun;42(6):647-54. doi: 10.1007/s001250051211. PMID: 10382583.
7. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant2003; 3(2): 178 .
8. Kasiske BL. Epidemiology of cardiovascular disease after renal trans-plantation.Transplantation2001; 72(6 Suppl): S5.
9. Krentz AJ, Wheeler DC. New-onset diabetes after transplantation: a threat to graft and patient survival.Lancet2005; 365(9460): 640.
10. Kuypers DR, Claes K, Bammens B, et al. Early clinical assessment of glucose metabolism in renal allograft recipients: diagnosis and prediction of post-transplant diabetes mellitus. Nephrol Dial Transplant. 2008; 23(6):2033–2042.
11. Markell M. New-onset diabetes mellitus in transplant patients: patho-genesis, complications, and management. Am J Kidney Dis2004; 43(6):953.
12. Maskey R (2015). New-Onset Diabetes after Transplant (NODAT). J Diabetes Res Ther 1(1): doihttp://dx.doi.org/10.16966/2380-5544.105
13. Osio FG, Pesavento TE, Kim S, et al. Patient survival after renal trans-plantation: IV. Impact of post-transplant diabetes. Kidney Int2002; 62(4): 1440.
14. Perneger TV, Whelton PK, Klag MJ. Race and end-stage renal disease. Socioeconomic status and access to health care as mediating factors. Arch Intern Med 1995; 155:1201–1208.
15. Rodrigo E, Fernández-Fresnedo G, Valero R, Ruiz J, Piñera C, Palomar R et al. New-Onset Diabetes after Kidney Transplantation: Risk Factors: Table 1. Journal of the American Society of Nephrology. 2006;17(12 suppl 3):S291-S295.
16. Sahay M, Sahay RK, Narayan G; Anuradha. New-onset diabetes after transplantation--role of oral glucose tolerance test for diagnosis and study of risk factors. Saudi J Kidney Dis Transpl. 2013 Sep; 24(5):897-902. doi: 10.4103/1319-2442.118068. PMID: 24029252.
17. Sahay M, Sahay RK, Narayan G; Anuradha. New-onset diabetes after transplantation--role of oral glucose tolerance test for diagnosis and study of risk factors. Saudi J Kidney Dis Transpl. 2013 Sep; 24(5):897-902. doi: 10.4103/1319-2442.118068. PMID: 24029252.

18. Shabir S, Jham S, Harper L, Ball S, Borrows R, Sharif A. Validity of glycated hemoglobin to diagnose new onset diabetes after transplantation. Transpl Int. 2013 Mar; 26(3):315-21. doi: 10.1111/tri.12042. Epub 2013 Jan 2. PMID: 23279163.

19. Sharif A, Moore R, Baboolal K. The Use of Oral Glucose Tolerance Tests to Risk Stratify for New-Onset Diabetes After Transplantation: An Underdiagnosed Phenomenon. Transplantation. 2006; 82(12):1667-1672.

20. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose toleranceand impaired fasting glycaemia: the current status on definition andintervention.Diabet Med 2002; 19(9): 708.

21. Ussif AM, Åsberg A, Halden TAS, Nordheim E, Hartmann A, Jenssen T. Validation of diagnostic utility of fasting plasma glucose and HbA1c in stable renal transplant recipients one year after transplantation. BMC Nephrol. 2019 Jan 10;20(1):12.

22. Lin JD, Wan HL, Li JC, Wu CZ, Kuo SW, Hsieh CH, Lian WC, Lee CH, Kao MT, Pei D. Impaired glucose tolerance and impaired fasting glucose share similar underlying pathophysiologies. Tohoku J Exp Med. 2007 Aug;212(4):349-57. doi: 10.1620/tjem.212.349. PMID: 17660700.