

## New Onset Diabetes Mellitus after Living Donor Renal Transplantation: A Unique Pattern in the Egyptian Population

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### Abstract

**Objectives:** Our aim was to identify the diabetic risk profile of new onset diabetes after live donor renal transplantation (NODAT) and its impact on patient and graft survival in Egyptian population.

**Patient and methods:** A retrospective review of 2019 renal allograft recipients has been performed. Risk factors, medical complications, patient and graft survival were analyzed.

**Results:** After a mean follow up period of  $8.8 \pm 5.8$  years, 450 (22.2%) recipients developed NODAT. A 455 post transplantation time matched control recipients without DM was selected. Time table revealed that 50% of NODAT cases discovered during the first 6 months post transplantation. The NODAT recipients were significantly older and obese with higher body mass index. Family history of DM was significantly positive among the NODAT group. Cox's multivariate regression analysis revealed that the older age, positive family history of DM, high BMI, HCV infection and hypercholesterolemia were of significant risk factor. Medical complications were significant in the NODAT group. Patient survival was significantly lower in the NODAT group on the other hand the graft survival was comparable.

**Conclusion:** NODAT does not statistically affect the graft survival. But, NODAT is a major problem endangers the patient life and must be minded to consider such patient as especially at higher risk for diabetic complications.

**Keywords:** Diabetes mellitus; Graft survival; Cox's multivariate regression analysis; Renal allograft

### Introduction

Kidney transplantation is the most cost effective treatment option for patients with ESRD yielding the best quality of life among different renal replacement modalities available to such individuals. Even this treatment option for kidney failure has some complications, one of them being New Onset Diabetes After Transplantation (NODAT). The development of NODAT is not restricted to the kidney allograft recipients but can occur in practically all solid organs transplantation including those patients that have received lungs, liver and heart allograft [1-3]. Guidelines for NODAT were published in 2003 [4]. NODAT is present when persistent hyperglycemia occurs in the period after transplantation in an individual who was previously a non-diabetic. Diabetes mellitus in transplant recipients greatly increases the already elevated risk profile of cardiovascular disease, graft loss and death. The criteria for the diagnosis of diabetes mellitus in the post-transplant period are the same as those set out by the American Diabetes Association (ADA) for the definition of diabetes mellitus in clinical practice [5]. NODAT in effect encumbers the patient with both the usual complications of diabetes such as retinopathy, neuropathy and nephropathy in addition to those complications that are unique to the allograft recipient. Diabetes mellitus is more common in transplant recipients than in the general population with some estimating that there is a nine-fold increase in the risk of diabetes in solid organ recipients than their age-matched controls. Up to 40% of patients with NODAT will require insulin therapy. The majority of patients however, have features of type-2 DM and do not require insulin [6]. There are disparities in the reported frequencies of NODAT that could be related to geographic, ethnic or socioeconomic peculiarities of the study population. Moreover, the design of the study from which the frequency of occurrence of NODAT was reported is to be considered while comparing prevalence rates. Studies that reported retros-

pective analysis of a data base often state the cumulative frequencies while some others have tended to differentiate the prevalence rates on temporal basis thus separating early, late and transient NODAT patient-groups. For example Hur et al. reported an overall incidence of NODAT of 39% at one year and 35.1% at seven years for NODAT but went on to differentiate between persistent NODAT (23.4%) who had hyperglycemia within the first year of transplantation that continued to the seventh year post-transplant [7]. The development of NODAT does not increase risk of death-censored graft loss [8].

### Patient and Methods

Between March 1976, and November 2010, a total of 2019 patients received live-donor renal allograft at our center. Among these recipients, 450 (22.2%) recipients developed NODAT, (diabetic group). NODAT was diagnosed when fasting blood sugar  $\geq 126$  mg/dl, random blood sugar or 2 HPP  $\geq 200$  mg/dl. The NODAT group was retrospectively analyzed and compared with a control group of (455) non diabetic kidney transplant recipients selected from the transplant registry field by date of operation to be matched with the NODAT group regarding the transplantation timing (same week of operation).

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A number of variables were studied in both groups. These variables includes recipient's age and sex, donor's age and sex, family history of DM, Body Mass Index (BMI), HLA matching, HCV antibody status at time of transplantation. Also the immunosuppressive agents, type of maintenance therapy, total dose of steroids in the first three months and the number of steroid pulses given. Serum creatinine was estimated at 3 month, 6 month and 12 month post-transplantation for both groups. Medical complications which developed post-transplant such as hypertension, hyperlipidemia, proteinuria, ischemic heart disease, neurological complications, retinopathy, and pancreatitis were carefully studied in both groups. Finally, both graft and patient survivals were analyzed.

### Statistical analysis

Qualitative data were displayed in cross tabulation and quantitative data were described in terms of arithmetic mean ± SD. Bivariate techniques were used for initial evaluation of contrasts. Thus, the chi-square and Fisher's exact tests were used for comparisons of frequencies of qualitative variables and the unpaired (t) test was used for comparisons of means two quantitative variables. A P value of less than 0.05 was considered significant. Means were compared by Student (t) test or the non-parametric test if the variable was not normally distributed. Cox's multivariate analysis was made for statistically significant data on univariate analysis. Patient and graft survivals were compared by means of Kaplan-Meier curve, using the log-rank test. All analyses were carried out using the computer package SPSS for windows, release 10 SPSS Inc Chicago, III, USA, 1993.

### Results

Among 2019 renal allograft recipients, 450 recipients (22.2%) developed NODAT. Characteristics of donors and recipients at the time of transplantation are shown in Table 1. The NODAT recipients were significantly obese body mass index (BMI)  $28.8 \pm 9.6$  Vs  $25.2 \pm 4.3$  in the control,  $P < 0.01$ ). Family history of DM was significantly positive among the NODAT group (216 Vs 64,  $P < 0.01$ ). There was 189 (42%) cases discovered in the first 3 months post transplantation, 37(8.3%) after 3 to 6 months, 47(10.4%) after 6 months up to one year, and 177 (39.3%) after 12 months from the transplantation (Figure 1). Hepatitis C virus infection (HCV) was significantly more prevalent among our diabetic recipients (134 vs 72  $P = .01$ ). Also total doses of steroids were significantly higher among the diabetic group in the univariate analysis only. Cox's multivariate regression analysis of the risk factors was carried out and revealed that the older age of recipients is the most important one followed by positive family history of diabetes mellitus, BMI above 25 and ultimately HCV (Table 2). Coronary heart disease was evaluated in both groups via clinical symptoms, electrocardiogram (ECG) and cardiac enzymes in some cases. The NODAT recipients suffered from significant ischemia, 125 versus the control recipients 47 of the controls ( $p < 0.01$ ). Hypercholesterolemia was significantly encountered among the NODAT recipients 100 versus 45 of the controls ( $P < 0.01$ ). Arterial blood pressure was evaluated in both groups pre and post transplantation, erect and supine. The NODAT group were more hypertensive post-transplant 304 (67.5%) versus 249 (54.6%) in control group ( $P < 0.01$ ). However pre transplant, hypertension was comparable among the two groups. Post-transplant complications named retinopathy; infection and pancreatitis also significantly dominate in the NODAT (Table 3). The difference in the serum creatinine initially tends to be better in the NODAT recipients but at last follow up it was in NODAT group versus the control recipients. Graft survival was comparable in the two groups ( $p = 0.738$ ) (Figure 2), Proteinuria was significantly higher among the NODAT

group even there were 6 patient had biopsies proven post-transplant diabetic nephropathy. Patient survival was significantly less in the diabetic group ( $P < 0.046$ ) (Figure 3).

### Discussion

The prevalence of diabetes mellitus is rapidly increasing worldwide, as a consequence of western life style and Diabetes currently affects

Variable	Diabetic group N=450	Control group N=456	P value
Follow up period (years)	$8.8 \pm 5.8$ (7.8)	$7.7 \pm 6.0$ (6.3)	
Recipients			
Age (years)	$35.2 \pm 9.9$	$28 \pm 9.6$	$< 0.01$
Sex (M/F)	351/99	340/116	0.140
Body mass index (BMI)	$28.8 \pm 4.6$	$25.2 \pm 4.3$	$< 0.01$
Donors			
Age (years)	$34.4 \pm 9.2$	$35.5 \pm 10.2$	0.115
Sex (M/F)	309/141	314/142	0.456
Consanguinity			
Related/unrelated	346/104	377/79	0.15
HLA-DR			
One match	391(86.8%)	406(89.03%)	
Two match	49(10.8%)	44(9.64%)	
Not determined	10(2.22%)	6(1.31%)	0.471
Family history of DM	216(86.4%)	64(25%)	$< 0.01$
Number of transplant received			
First	430(95.5%)	437(95.8%)	0.486
Second	20(4.5%)	19(4.2%)	
Total dose of steroids	$6.35 \pm 3.1$ gms	$5.8 \pm 3.4$ gms	0.047

Table 1: Patient characteristics.

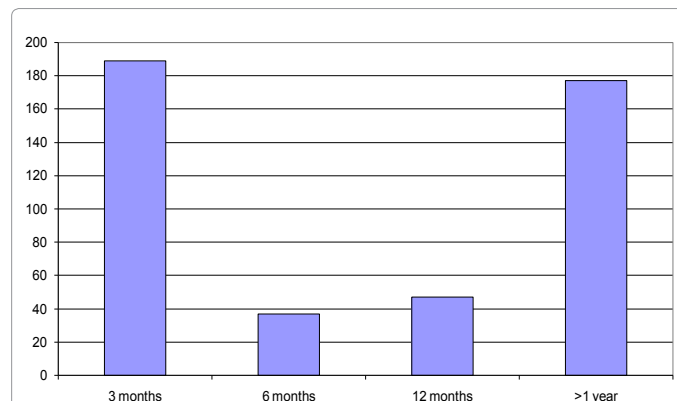


Figure 1: Onset of DM post-transplantation: There were 224 cases discovered in the first 6 months post transplantation, 48 after 6 months up to one year and 178 after 12 months from the transplantation.

Characteristic	Regression Estimate (B)	S.E.	Relative Risk Exp. (B)	P-Value
Age < 40 years	1.46	0.36	4.31	$< 0.01$
Age > 40 years				
Negative family history	-1.63	0.31	0.2	$< 0.01$
Positive family history				
BMI ≤ 25	1.66	0.27	5.24	$< 0.01$
BMI > 25				
Hypercholesterolemia	-0.75	0.35	0.47	0.03
HCV	0.81	0.27	2.24	$< 0.01$

Table 2: Multivariate analysis of risk factors.

Variable	Diabetic group N=450	Control group N=456	P value
Post-transplant Hypertension	304(67.5%)	249(54.6%)	<0.01
Hypercholesterolemia	100(22.2%)	45(9.8%)	<0.01
Ischemic heart disease	125(27.7%)	47(10.3%)	<0.01
Proteinuria	275(61.1%)	198(43.4%)	<0.01
<b>Neurological complication :</b>			
Cerebral strokes:	9(2%)	4(0.87%)	<0.01
Peripheral neuropathy:			
Sensory	30(6.66%)	1(0.21%)	<0.01
Motor	7(1.5%)	4(0.87%)	<0.01
Autonomic	9(2%)	20(4.3%)	<0.01
Combined	109(24.2%)	11(2.4%)	<0.01
Retinopathy	37(8.22%)	0	<0.01
Malignancy	8(1.9%)	15(3.28%)	0.344
Pancreatitis	5(1.1%)	0	<0.01
Bacterial infections:	55(12.22%)	37(8.11%)	0.027
Viral infection:(HCV)	134(29.77%)	72(15.7%)	<0.01

Table 3: Medical complications.

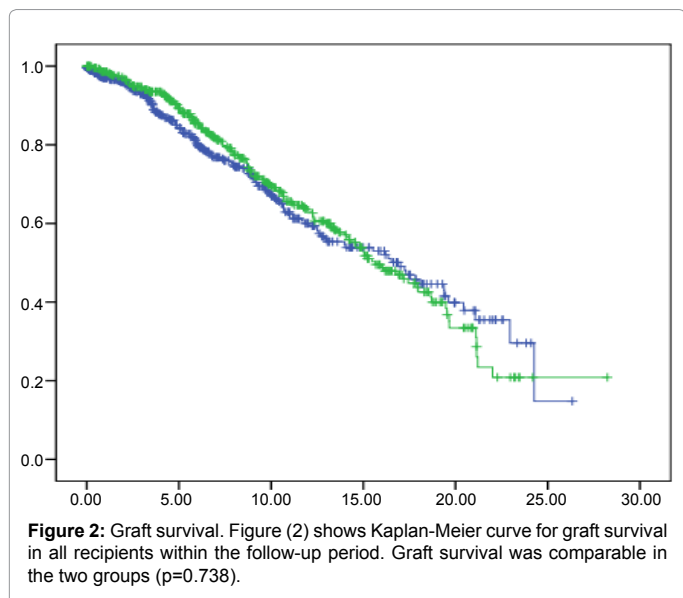


Figure 2: Graft survival. Figure (2) shows Kaplan-Meier curve for graft survival in all recipients within the follow-up period. Graft survival was comparable in the two groups (p=0.738).

over 346 million people worldwide. Transplantation may accelerate the development of type 2 diabetes in individuals at risk (WHO, august, 2011). In our study, the incidence of NODAT was 22.2 % which compares closely to that reported being 16-24% [9]. This discrepancy may be attributed to; variable number of patients, racial, different protocols of immunosuppressive agents employed in the management of these patients and different follow up periods. The onset of NODAT among our recipients was predominantly in the first six months post transplantation (50.3%) and this in accordance with that reported previously [10,11]. These findings may be explained by stress, surgery, relatively larger doses of corticosteroids in the early post transplantation period.

The mean age of NODAT group was significantly higher than the control group (35.2 ± 9.9 vS 28 ± 9.6 years, P=0.001). Moreover 28% of NODAT recipients were above the age of 40 years versus 10% in the controls (P=0.0001). These results agree with that reported [12] and disagree with that previously reported, who find the incidence of NODAT dominate among the age above 45 years [13]. This difference can be attributed to Egyptian selection of younger age recipients that

is expected to resume professional activities after being transplanted. In an attempt to find out the possible factors which may play a role in the development of NODAT several variables were studied. We found that the prevalence of positive family history of DM is significantly higher among the NODAT recipients (216 vs 64 of controls P=0.001) this accords with that cited in literatures [14-16]. Also, we found a significant correlation between NODAT and obesity evaluated by BMI (28.8 ± 9.6 vs 25.2 ± 4.3, of controls P=0.001). Our results are similar to that reported [15,17,18]. However, Sumrani et al., and Montori et al., [8] found no correlation between NODAT and obesity in transplant recipients. These findings could be explained by racial difference and different life styles of the studied Egyptian patients.

Hepatitis C virus infection was significantly more prevalent among our NODAT recipients (134 vs 72, P=0.01) (Table 3), this is in accordance with that reported [9], whom found unadjusted cumulative incidences of 15.6%, 25.6% and 35.4% at 3, 12, and 36 months respectively for diabetes after kidney transplantation for patients who were HCV positive at transplantation compared with 8.8%, 15.4%, and 23.4% for HCV negative patients, (p<0.0001). Moreover, Gentil et al. reported that NODAT was predominant among HCV positive recipients (28% vs 6.2%, p=0.001) [17]. The relatively high incidence of NODAT among HCV positive patients may be explained by a direct or immune-mediated effect on B cells of pancreatic islets [19]. Over the last three decades, different immunosuppressive protocols were adopted in our center since we started renal transplantation at 1976. We found a significant correlation between NODAT and total dose of steroids in the first 3 months (6.35 ± 3.1 gms vs 5.8 ± 3.4 gms; P=0.047) and, total doses of pulses of steroids needed to manage rejection (562.5 gms vs 570 gms; P=0.03) since rejection episodes (51.3% vs 43.7%; P=0.01). Our results agree with that reported [20-22]. The macro vascular complications of diabetes pose a major threat to patient survival. The risk of stroke in patients with diabetes is 2-4 folds greater than in the general population. Also patients with DM have a greater mortality risk than the general population largely due to increased mortality rates from CVD and cerebrovascular disease secondary to accelerated atherosclerotic process [23,24]. Cardiovascular disease is the commonest cause of death after kidney transplantation, and diabetes is one of the major risk factors for its development [25,26]. In our study we found a significant correlation between NODAT and coronary heart disease, (125 vs 47 of controls; P=0.01). These results are in accordance to that reported in the literatures [27]. Moreover, we found that the incidence

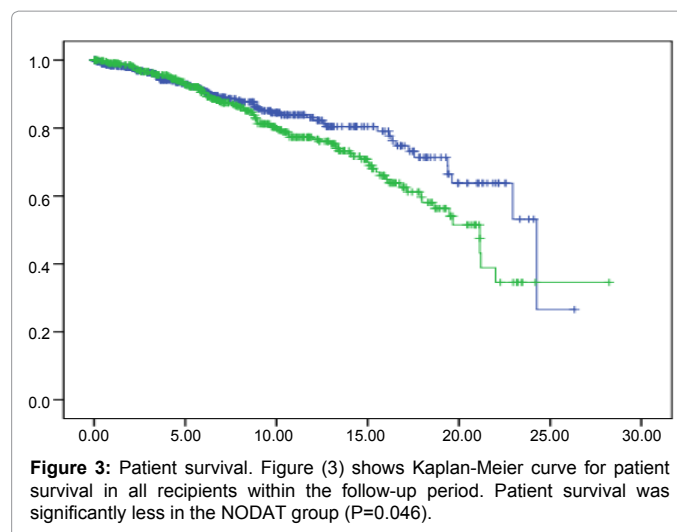


Figure 3: Patient survival. Figure (3) shows Kaplan-Meier curve for patient survival in all recipients within the follow-up period. Patient survival was significantly less in the NODAT group (P=0.046).

of the mortality with functioning graft secondary to cardiovascular cause is more among NODAT (23.5 vs 15.8% in controls;  $P=0.05$ ). These results agree with that reported [28]. This could be explained by the prevalence of post transplantation hypertension (304 vs 249;  $P=0.02$ ), hypercholesterolemia among the diabetics recipients (100 vs 45;  $P=0.001$ ), the older age of NODAT recipients ( $35.2 \pm 9.9$  vs  $28 \pm 9.6$  years;  $P=0.001$ ) and the obesity among the NODAT group ( $28.8 \pm 9.6$  vs  $25.2 \pm 4.3$ , of controls;  $P=0.001$ ). In our study, acute diabetic complications that require hospitalization (diabetic ketoacidosis and non ketotic hyperglycemic hyperosmolar states) occurred in 5.1% of our recipients, this result is higher than that reported [29] being 2.3%. This discrepancy may be attributed to shorter duration of follow up period in their study and the relatively poor compliance of our NODAT recipients. Retinopathy is a point of concern, since only 8.2% of our NODAT recipients suffered diabetic retinopathy. This was less than that reported [30] (8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years) and could be explained by the relatively shorter follow up period ( $7 \pm 5$  years) in our study. Proteinuria was significantly prevalent among the NODAT (275 vs 198;  $P=0.001$ ), also the degree of proteinuria tends to be more severe in the diabetics. Among the NODAT proteinuric recipients, 6 patients showed diabetic nephropathy proved by histo-pathological examination. Neuropathy, either peripheral and/or autonomic was prevalent among our NODAT group (109 vs 11;  $P=0.001$ ). Similar figures were reported (41.9%) [31]. However, Lower incidence was reported (30%) [32], which could be explained by different follow up periods, pre-transplant uremic period, and variable recipient's ages in the different studies. Moreover, cerebral strokes showed significant correlation to NODAT (9 vs 4  $p=0.01$ ), these results are in accordance to that reported [33]. The incidence of infection necessitating hospitalization was found to be significantly higher among our NODAT recipients (55 vs 37  $P=0.03$ ). These results agree with that reported [12] being 54% vs 17% in the control group. These results may be due to the use of different immunosuppressive protocols, different follow up period and relatively poor compliance of our diabetic recipients. We found a significant correlation between NODAT and malignancy being (15 vs 8;  $P=0.34$ ). Similar data were reported in the literature [34]. In the contrary, Danpanich and Kasiske [35] reported that recipients with type 1 diabetes (pre-transplantation) associated with lower incidence of malignancy. This could be explained by higher prevalence of HCV among our NODAT recipients (3 cases had hepatocellular carcinomas;  $P=0.01$ ). Also we found 5 cases of pancreatitis among our NODAT recipients (1.1%). Similar data, being (1.2%-6.8%) reviewed [36]. The numbers of potential risk factors in addition to those of the general population are perpetuated by number of other factors, uremia, and disorder of lipid metabolism, polycystic kidney, immunosuppressive drugs, and cytomegalovirus infection [36]. In our study, graft survival was comparable in both groups until 15 years post-transplantation. Then graft survival was markedly declined in the NODAT recipients (43.5% vs 53.6%;  $P=0.013$ ). These results came parallel to that reported in the literature being (48% vs 70%;  $P<0.001$ ) at 12 years. In contrast, our results disagree with that reported [37] considering graft survival after 3 and 4 years incurs significant difference being (71% vs 86% and 54% vs 82%;  $P<0.001$ ) respectively due to high incidence of acute rejection and uncontrolled hypertension among the diabetic recipients. These differences could be attributed to the fact that diabetic nephropathy needs several years to develop and may not account for the early graft failure. Also, the attempts to decrease the dose of immunosuppressive drugs to control diabetes and its complications may be account for increased long-term graft failure due to chronic allograft nephropathy [38]. On analyzing the patient survival in our study, we didn't find a significant difference in the first

8 years post-transplantation. Thereafter, a significant decline in patient survival among NODAT was prominent (79.9 vs 86.1%;  $p=0.001$ ) and continue to decline down to 15 years post transplantation (60.6% vs 77.8%;  $P<0.001$ ). Moreover, graft survival after 20 years showed (24% vs 70.3%;  $P<0.001$ ) of the control recipients. These results are similar to that reported in the literature [39]. Finally, a strong argument in favor of a deleterious effect of diabetes on post-transplantation outcome is the fact that the long-term survival of patients with diabetes who undergo simultaneous pancreas-kidney transplantation has been improved (8-year survival rates of 72% for pancreas-kidney recipients vs 55% for cadaveric kidney recipients) [40]. The deleterious effect of NODAT on the patient survival could be attributed to predominance of CVD, cerebrovascular disease, infections and malignancy among the diabetic recipients. At last, the management of NODAT is not different from that of patients with DM, comprising of diet regimen to initiate therapy and, if not sufficient to achieve glycemic control, addition of oral hypoglycemic and ultimately if insufficient insulin therapy is commenced. The same recommendations were reported in several literatures, as uncontrolled DM may affect the patient as well as graft survival [41,42].

## Conclusion

NODAT has a unique pattern among Egyptian populations regarding risk factors especially older age, positive family history, obesity and HCV infection. NODAT has no statistical significant affection on graft survival. Meanwhile, NODAT is a major problem endangers the patient life and must be minded to consider such patient as especially at higher risk for diabetic complications.

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