Prevalence and risk factors of new onset diabetes after liver transplantation (NODAT): A single Egyptian center experience.

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Abstract

Aim: To estimate the prevalence of New Onset Diabetes after Liver Transplantation (NODAT) and to investigate the possible risk factors. Methods: This retrospective study comprises 213 patients subjected to living donor liver transplantation (LDLT). Patients' data were collected from medical registry files for a period of two years after transplant. Results: Of the total 213 recipients, complete data for the whole study period were available for 164 recipients who were enrolled in this study. Fifty one 51 (31.1%) patients were already diabetic prior to transplantation. The prevalence of NODAT was 27.43% (31/113). Eight of NODAT cases (25.8%) were transient with recovery within 6-months period in 5/8 cases while the other 3 cases recovered in more than 6 months to a year. The only drug that showed statistically significant difference was tacrolimus (p=0.02). Interestingly, three pre-transplant diabetics (3/51, 5.9%) recovered after liver transplant with elimination of their anti-diabetic therapy. Conclusion: NODAT is a common medical complication that occurs in 27.4% of liver transplant recipients. The study suggests using one year cutoff rather than 6 months for defining transient NODAT. Post-transplant tacrolimus-based immunosuppression is a significant independent predictor of NODAT development.

Keywords: New onset diabetes, Liver transplantation, Chronic liver disease, Immunosuppression drugs, Tacrolimus

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Introduction

The high prevalence of chronic liver disease (CLD) in Egypt has led to increasing number of patients suffering from end-stage liver disease for which Liver transplantation (LT) is the most effective treatment [1]. This surgery carries a risk of many significant complications including new-onset diabetes mellitus after liver transplantation (NODAT) which has a great variation in its incidence across different studies that ranged from 2% to 53% [2-6]. This variation might be explained by many factors that include reporting bias, small sample sizes, and how NODAT was defined.

Many other factors were blamed to increase the risk for NODAT including family history of DM, patient's age, immunosuppressive regimen used, obesity, ethnicity, and etiology of CLD [7-11]. When NODAT develops, patients should be closely monitored to differentiate between transient and persistent NODAT albeit there is no agreement to date for the definition of transient NODAT [12-14]. To the best of our knowledge, no data describing NODAT following living donor liver transplantation (LDLT) in Egypt had been published. Therefore, this retrospective study was conducted to estimate the prevalence and possible risk factors of NODAT in our population.

Patients and Methods

Patients

This retrospective study comprises a total number of 213 patients subjected to LDLT at Mansoura Gastroenterology Surgical Center from May, 2004 to January, 2013. Patients' data were collected from the database system of the transplantation unit. Approval of ethical scientific committee in Faculty of Medicine, Mansura University was obtained. Of these 213 patients, 164 patients were enrolled while the remaining 49 patients (23%) were excluded either due to early mortality (16%) or due to lack of follow up (7%). Out of the enrolled 164 patients, 51(31.1%) were diabetic prior to LDLT while the remaining 113 patients (68.9%) were not. A flowchart for enrolled cases was illustrated in (Figure 1).

For all patients, the following data were reviewed and recorded at enrollment and for two years after LDLT:

A. **Thorough review of history taking** with special stress on; age, sex, detailed history of DM, family history of DM, and indication for liver transplantation.

B. **Thorough review of physical examination with special stress on** BMI, stigmata of CLD, and presence of diabetic complications.

C. **Reporting of available laboratory investigations with special stress on** ABO and Rh Blood groups for donor and recipient, complete blood count (CBC), prothrombin Time (PT), International Standardized Ratio (INR), serum fasting (FBG) and post prandial (PPG) blood glucose (mg/dl), albumin (gm/dL), AST (IU/L), ALT

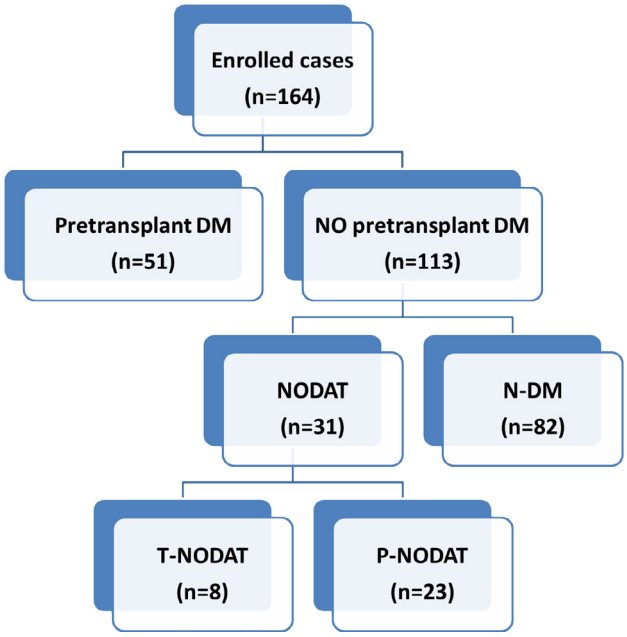

***Figure 1**: Flowchart of enrolled cases in the study.*

(IU/L), total bilirubin (mg/dL), GGT (IU/L), alkaline phosphatase (ALP) (KAU), serum creatinine (mg/dl), Alpha-fetoprotein, Anti-nuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), viral serological markers (HBsAg, Anti-HBc, and HCV Antibody) as well as quantification of serum HCV-RNA and HBV DNA.

D. The date of onset of NODAT was assumed to be the date of earliest report of diabetes mellitus after liver transplantation [15]. Diagnosis of NODAT was based on the American Diabetes Association (ADA) definition of diabetes mellitus (FBG level of ≥126 mg/dl on two consecutive occasions, and/or PPG level of ≥200 mg/dl in the OGTT) [16]. Results of blood glucose levels were reported throughout the first two years after liver transplantation to detect the optimum time for diagnosis of transient NODAT.

E. Reporting available radiological studies including abdominal ultrasonography (US), tri-phasic computerized tomography (CT) of abdomen, and magnetic resonance imaging (MRI) of abdomen.

F. All patients were assessed by **Child Turcott Pugh (C.T.P) score** [17] and **Model for End stage liver disease (MELD) score** [2,18].

G. Detailed drug history with special stress on immunosuppressive, and anti-hyperglycemic agents.

Statistical analysis

Collected Data were entered and analyzed using an SPSS software version 17. Qualitative data were expressed as numbers and percentages and were compared using Chi-square (or Fisher's exact) test. Quantitative data were initially tested for normality using Shapiro-Wilk and considered as normally distributed if $p>0.05$. Quantitative data were expressed as mean ± SD if normally distributed or median if not and were compared using independent samples t-test for two groups or one way ANOVA test for more than two groups if normally distributed or using the alternative nonparametric tests (Mann-Whitney U and Kruskal-Wallis tests respectively) if not. Univariate logistic regression models were used to predict the associations between outcomes and different variables. Multivariate analysis was done for the associations between outcomes and significant variables on univariate analysis. Statistical significance was defined as p value ≤ 0.05.

Results

Based on the flowchart (Figure 1), our enrolled cases (n=164) were classified into 3 groups:

1. **N-DM** (n=82): Those who were not diabetic prior to LDLT and remained so during the whole two-year period of follow up after surgery.
2. **Pre-transplant DM** (n=51): Those who were diabetic prior to LDLT. This group was further subdivided into:

a. **Recovered pre-transplant DM** (n=3).

b. **Persistent pre-transplant DM** (n=48).

3. **NODAT** (n=31): Those who were not diabetic prior to LDLT but developed DM after surgery. This group was further subdivided into:

a. **Transient NODAT [T-NODAT]** (n=8): Those who recovered during the study period.

b. **Persistent NODAT [P-NODAT]** (n=23): Those who didn't recover during the study period.

The clinical and laboratory characteristics of the enrolled cases

Table 1 showed a statistically significant difference between the three groups for age (p=0.003), and pre-transplant FBG (p<0.0001). Post-hoc analysis of these data showed that age was significantly higher in pre-transplant DM group than N-DM group only (p<0.001) while FBG was significantly higher in pre-transplant DM group than the two other groups (p<0.0001). Also, hepatocellular carcinoma (HCC) showed significant difference between the three groups (p=0.043). It was diagnosed in 25/51 (49%) of pre-transplant DM patients and in 33/113 (29.2%) of those without pre-transplant DM. This difference was statistically significant (X^2=6.057, p=0.014), and the presence of pre-transplant DM increased the risk of HCC by two-fold (B=0.845, p=0.015, Odds=2.331). Among patients with no pre-transplant DM, HCC was diagnosed prior to LDLT in 9/31 (29.0%) of NODAT cases and in 24/82 (29.3%) of N-DM cases. This difference was not statistically significant (X^2=0.001, p=0.98).

Donor characteristics and development of NODAT

Table 2 showed that there was no significant differences in donor characteristics between NODAT and N-DM groups.

Hepatitis C virus (HCV) and development of NODAT

HCV was present in 71/82 (86.6%) of N-DM group versus 30/31 (96.8%) of NODAT group (X^2=2.460, p=0.117). HCV recurrence was diagnosed in 61/71 (85.9%) of N-DM group versus 28/30 (93.3%) of NODAT group (X^2= 1.108, p=0.292).

Table 1: *Clinical and biochemical baseline characteristics of 3 different groups.*

Parameter	NODAT (n=31)	N-DM (n=82)	Pre-transplant DM (n=51)	p value
Count (%)				
Gender: **Male** **Female**	 28 (90.32%) 3 (9.67%)	 72 (87.80%) 10 (12.19%)	 44 (86.27%) 7 (13.72%)	0.863
Pre-transplant HCV	30 (96.77%)	71 (86.58%)	48 (94.11%)	0.299
Pre-transplant HBV	1 (3.20%)	8 (9.75%)	4 (7.84%)	0.511
Pre-transplant HCC	9 (29.03%)	24 (29.26%)	25 (49.01%)	**0.043**
Pre-transplant hypertension	5 (16.19%)	3 (3.65%)	1 (1.90%)	0.844
Median				
Age (years)	50	47.5	52	0.003
BMI (kg/m^2)	30.49	30.07	28.01	0.367
FBG	96	93	136	**<0.0001**
ALT (IU/L)	46	33.50	40	0.519
AST (IU/L)	73.50	61.50	64	0.355
S. Albumin (gm/dL)	3.0	2.9	3.0	0.412
Alkaline phosphatase (KAU)	5	5	5	0.549
GGT(IU/L)	32	28	38	0.435
Bilirubin(mg/dl)	3.2	2.9	2.4	0.066
INR	1.6	1.5	1.5	0.453
S. creatinine (mg/dl)	0.80	0.80	0.80	0.606

Table 2: *Effect of donor characteristics on the development of NODAT in recipients.*

	NODAT (n=31)	N-DM (n=82)	P value
Median age	27	28	0.547
Sex **Male** **Female**	 28 (90.32%) 3 (9.67%)	 61 (74.39%) 21 (25.60%)	0.07
Donor BMI (kg/m^2)	26.77 ± 3.24	26.77 ± 3.24	0.614
Relation to donor **Unrelated** **First degree** **Second degree** **Third degree** **Fourth degree**	 11/38 9/34 2/15 5/15 4/11	 27/38 25/34 13/15 10/15 7/11	0.688
ABO similarity **Different** **Similar**	 9 (29.0%) 22 (71%)	 21 (25.6%) 61 (74.4%)	0.713
Rh similarity **Different** **Similar**	 2 (6.5%) 29 (93.5%)	 10 (12.2%) 72 (87.8%)	0.506

Immunosuppressive agents and NODAT

Table 3 showed that only use of tacrolimus was statistically significantly different (X^2= 5.355, p=0.021) between NODAT group (26/31, 83.9%) and N-DM group (50/82, 61%). Simple logistic regression revealed that use of tacrolimus increased the risk of NODAT by 3.3 times (B=1.202, Wald=4.990, p=0.025, Odds=3.328). Multivariable logistic regression analysis incorporating age, pre-transplant FBG, and tacrolimus use revealed that tacrolimus was the only independent risk factor for the development of NODAT.

Anti-diabetic therapy of NODAT

Of the 31 NODAT patients, 19 cases were treated with oral hypoglycemic agents, 10 cases were treated with insulin therapy and only two cases were treated with oral hypoglycemic agents initially then shifted to insulin therapy. Insulin was used in cases with impaired graft function, presence of infection or rejection.

Table 3: *The effect of immunosuppressive drugs on NODAT.*

	NODAT (n=31)	N-DM (n=82)	p value
Drug	**No (%)**		
Tacrolimus	26 (83.9%)	50 (61%)	**0.021**
Cyclosporine A	7 (22.58%)	30 (36.58%)	0.157
Everolimus	7 (22.58%)	20 (24.39%)	0.840
Corticosteroids	13 (41.93%)	33 (40.42%)	0.870
MMF/ MPA	29 (93.54%)	70 (85.36%)	0.343
Methylprednisolone	6 (19.35%)	9 (10.79%)	0.241

T-NODAT (n=8) versus P-NODAT (n=23)

Figure 2 illustrated the times of onset and recovery of transient cases of NODAT. Most cases were diagnosed one month after surgery (5/8, 62.5%) while the other 3 cases were diagnosed after 2, 4, and 5 months. The minimum duration of T-NODAT reported in our cohort was 3 months, and the maximum was 11 months.

Table 4 showed that there was no statistically significant difference in clinic-laboratory data between P-NODAT and T-NODAT.

Discussion

Using the ADA definition of diabetes mellitus, the prevalence of NODAT in our study was 27.43% (31/113); these results are in accordance with other previously published data that ranged from 2 to 53% in solid organ transplantation, about 4 to 25% in renal transplantation, and 2.5 to 25% in liver transplantation [2-6].

Although some studies [19,20] introduced FBG as an independent risk factor for NODAT, our cohort had slightly higher FBG which was statistically insignificant in NODAT group. This lack of significance might be explained by the fact that all cirrhotic patients are at increased risk for fasting hypoglycemia that may blunt the rise in FBG as risk factor for later development of NODAT.

In a similar way, increased recipient' age was not associated with

Table 4: *Clinical and laboratory characteristics of the P-NODAT vs. T-NODAT.*

Parameter	Persistent NODAT (n=23)	Transient NODAT (n=8)	p value
	Mean ± SD, No (%)or median		
Age(years)	48.39 ± 6.807	50.63 ± 5.854	0.416
Sex*			0.550
Male	20 (71.42%)	8 (28.57%)	
Female	3 (100%)	0 (0%)	
BMI (Kg/m^2)*	31.221	28.405	0.259
ALT (IU/L)*	34.50	60.50	0.655
AST (IU/L)*	52.0	90.50	0.467
S. Albumin (gm./dL)	3.02 ± 0.605	2.81 ± 0.379	0.369
Alkaline phosphatase (KAU)	5.0	6.0	0.249
GGT(IU/L)	32.0	33.0	0.677
Bilirubin (mg/dl)	2.60	4.60	0.190
INR	1.60	1.55	0.786
S.creatinine (mg/dl)	0.80	0.75	0.221
Etiology of liver disease HCV HBV HCV+ HCC	 15 (65.21%) 1 (4.34%) 7 (30.43%)	 6 (75%) 0 (0%) 2 (25%)	0.782
Immunosuppression Tacrolimus Cyclosporine Everolimus Corticosteroids MMF/ MPA Methylprednisolone	 19 (67%) 3 (50%) 5 (71.42%) 8 (61.53%) 20 (71.42%) 4 (66.66%)	 6 (24%) 3 (50%) 2 (28.57) 5 (38.46%) 8 (28.57%) 2 (33.33%)	 0.589 0.300 1.00 0.242 1.00 0.645
Anti-diabetic medication Oral Insulin Oral then shift to insulin	 14 (60.9%) 7 (30.4%) 2 (8.7%)	 5 (62.5%) 3 (37.5%) 0 (0%)	 0.674

* Median (as it is non-Gaussian)

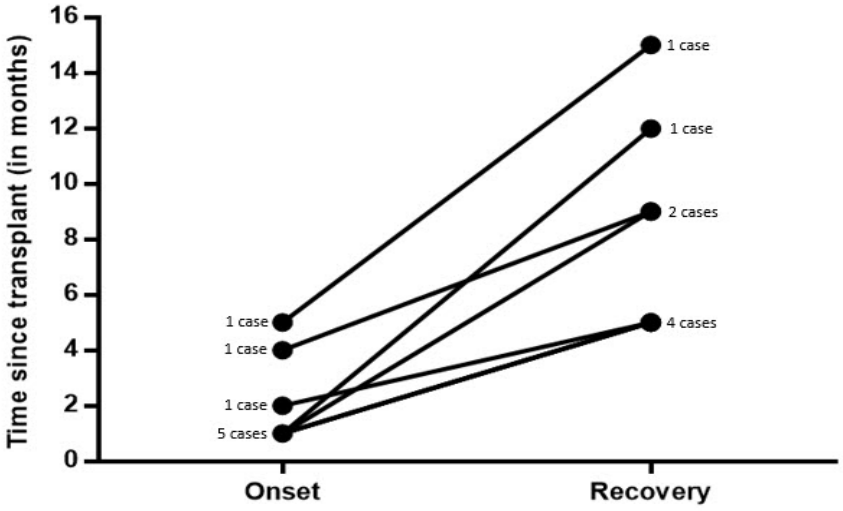

Figure 2*: Cases with transient NODAT.*

NODAT. This is contrary to Sumrani et al. [20]and Reisaeter et al. [21] who reported that age >40 years is considered an independent risk factor of developing NODAT. On the other hand, Lv et al. [19] reported a similar result to our study. This difference between studies might be explained by different sample sizes, selection bias, and presence of confounders as co-morbidities. Gender, as well was an independent risk factor for NODAT in this and other studies.

Moreover, a BMI >25 kg/m^2 was found to be associated with an high risk of NODAT in the study by Saliba et al. [22] and was later confirmed by Oufroukhi et al. [23]. However, our study didn't prove this association which was in agreement with the results of the study by Lv et al. [19]. This conflicting results between different studies might be explained by the lack of accuracy of BMI in diagnosing overweight and obesity in patients with advanced cirrhosis.

In our study, none of the components of CTP and MELD, had statistically significant difference between those who developed NODAT and those who remained non-diabetic (N-DM group). Similarly, differences between alkaline phosphatase, GGT, ALT, AST, etiology of liver disease and pre-transplant hypertension were all insignificant.

Although HCV recurrence was reported to be associated with the development of NODAT [24,25], this relationship was not confirmed in our study when comparing NODAT and N-DM groups for HCV etiology at enrollment for LDLT and HCV recurrence after surgery. Therefore, we suggest another study that compare the effect of newer direct acting anti-viral drugs and achievement of sustained virological response (SVR) before transplantation on the later development of NODAT after surgery.

Cosio et al. [25] reported that the stress of surgery and use of immune-suppressive medications can cause hyperglycemia in the recipients. This hyperglycemic state will not persistent in all cases, instead the term transient NODAT is used to define the state of hyperglycemia that started and ended within the first year of transplantation [26-28]. However, Honda et al. [13] defined transient NODAT as termination of treatment of hyperglycemia within six months after the diagnosis. We aimed at studying this time frame in our cohort and according to our results, T-NODAT was diagnosed 1-5 months after surgery, and recovered in 3-11 months after diagnosis. Therefore, we adopt a new definition for T-NODAT as a state of hyperglycemia that developed within 6 months after transplantation and recovered in less than 1 year duration that needs a large-scale study to confirm this new definition.

Our results were consistent with the previously published data regarding the diabetogenic effect of tacrolimus and its role in the development of NODAT and against the conclusion coined by Mirabella et al. [29] that tacrolimus has no role in occurrence of NODAT [30-34]. Therefore, tacrolimus remained, according to previous and our own results, an independent risk factor for NODAT. Contrary to tacrolimus, using everolimus was not associated with the development of NODAT [34] and there is a trend to incorporate everolimus in the immunosuppressive regimen in liver transplant recipients in our institute to minimize the adverse effects including nephrotoxicity. Also, although some studies suggested that administration of post-transplantation high dose corticosteroids as a risk factor for NODAT [9], this was not proved in our cohort which might be attributed to the use of smaller doses for a short period. Similarly, MMF/MPA was not associated with the occurrence of NODAT.

In our study, presence of pre-transplant DM increased the risk of HCC by two-folds than those who were not diabetic. This goes with the pooled risk estimate of 17 case-control studies with OR of 2.40 [34]. For those who were not diabetic at time of surgery. The presence of pre-transplant HCC had no statistically significant difference between those who developed NODAT and those who remained non-diabetic. This goes also with the results of Ling et al. study [34] from China where the presence of HCC increased the risk of NODAT by 1.2 on univariate analysis but not on multivariate analysis. Therefore, type 2 DM would be a risk factor for HCC while HCC per se would not be a risk factor for NODAT.

To date, our governmental policy allowed living donor transplantation from only patients' relatives. Analysis of blood group matching and degree of consanguinity between the recipient and donor showed no effect on the development of NODAT.

The main stay of treatment of NODAT in our cohort followed the well-established treatment policy of type 2 DM worldwide relying upon oral agents with the use of insulin being limited to those who have severe hyperglycemia from the start or those who developed post-operative complications especially infections as well as those who were not controlled on oral agents. This confirms that treatment of NODAT would not be different from that of type 2 diabetes.

Interestingly, successful LT led to complete recovery of diabetes in three patients with pre-transplant DM (5.9%). One explanation for this finding would be the elimination of the diabetogenic effect of liver cirrhosis (hepatogenous diabetes) after LDLT. More explanations await further studies.

Our study has several strengths, including the specific Egyptian population and being census study involving all transplant surgeries performed over a decade, but also some limitations. Firstly, the study was conducted in a single center for a limited time period resulting in a small sample size. Secondly, the study population was predominantly hepatitis C-based. Thirdly, some important data such as serum magnesium and blood levels of calcineurin inhibitor were not routinely recorded in hospital database and thus were missing. Finally, this is an observational study in nature and the basis of every important finding still needs to be further explained.

Conclusion

NODAT is a common medical complication occurring in the recipients of LDLT in Gastroenterology Surgical Center, Mansoura University. So screening of NODAT is mandatory. It might be either persistent or transient resolving within one year. Patients with NODAT should be strictly followed up to differentiate transient form persistent NODAT. Post-transplant immunosuppression using tacrolimus plays a cardinal role in the occurrence of NODAT and other drugs as everolimus, cyclosporine A and MMF/ MPA were not found to be independent risk factors for NODAT. On the other hand, those with pre-transplant diabetes might recover after transplantation.

Author Contributions

Bahgat MH, contributed to selection of topic of the research, its deign, analysis and interpretation of the data, drafted the article and revised it. Wahab MA, contributed to surgical intervention procedures. Zayed RA, El-Etreby SA, Saad RA, Elmorsy FM, and contributed to collection of data from medical database of Gastroenterology Surgery & liver transplantation unit, wrote the manuscript and analysis of the data. Bahgat MH, contributed to statistical analysis of all data.

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Conflict of Interest

All authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

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