Effect of Demographic and Clinical Factors on New- Onset Diabetes Mellitus after Liver Transplantation in Iranian Patients

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ABSTRACT

Backgrounds: New- onset diabetes after transplantation (NODAT) is a serious complication which runs the risk of infections, morbidity and mortality. Older age, male sex, immunosuppressive agents and hepatitis C are reported as risk factors. The focus of this research is evaluating some demographic and clinical factors in development of NODAT in hepatic transplanted patients. This study aims to help identifying high risk recipients in order to prevent NODAT and improve transplantation prognosis.

Methods: In this study 134 liver recipients without pre-transplantation diabetes were investigated; 70 euglycemic and 64 with NODAT within 2 years after transplantation. All the patients were on tacrolimus-based immunosuppressive regimen. The role of recipients' age, sex, body mass index (BMI), model for end- stage liver disease (MELD) score, blood group, diseases leading to transplantation, tacrolimus dose and serum level, mycophenolate mofetil (MMF) and prednisolone dose in the incidence of NODAT were assessed.

Results: The prevalence of NODAT in this study was 17.92%. The means of duration after transplantation that NODAT occurred, was 98.36 ± 21.62 days. The mean age of all patients was 37.83 ± 16.26 years and 60.4% were females. Two groups were similar in terms of pre- transplantation fasting blood sugar (FBS) (P=0.091). Age (P=0.001,OR=1.063,CI:1.025-1.102) and prednisolone dose (P<0.0001,OR=1.270,CI:1.163-1.388) were the only independent predictors of NODAT, while tacrolimus daily dose and plasma level, MMF daily dose, sex, BMI and underlying diseases were not risk factors for NODAT.

Conclusions: Recipients with older age and higher prednisolone dose are more prone to NODAT and need more accurate monitoring.

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Introduction

New-onset diabetes after transplantation (NODAT) is a

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prevalent and serious complication of liver transplantation. NODAT is defined as normal blood glucose before transplantation, interpreted as fasting blood sugar (FBS) <100 mg/dl without taking any anti-diabetic medications, and diabetic condition after that; FBS≥126 mg/dl in two separate episodes or experiencing symptoms such as polyuria or polydipsia, along with random plasma glucose concentration≥200 mg/dl or 2-hour glucose tolerance

Table 1. Diseases included in each group.

	Group			
	Cryptogenic origin(unknown)	**Viral hepatitis**	**Autoimmune hepatic and biliary disorders**	**Congenital hepatic and biliary disorders**
Diseases	• Cryptogenic cirrhosis • Non-alcoholic steatohepatitis	• Hepatitis B • Hepatitis C • Hepatitis B + Hepatitis C • Hepatitis C + Hepatocellular carcinoma	• Primary sclerosing cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis	• Wilson • Hypercholesterolemia • Tyrosinemia • Progressive familial intrahepatic cholestasis • Hemochromatosis • Biliary atresia • Caroli disease • Hyperoxaluria • Crigler najjar

test≥ 200 mg/dl or taking anti-diabetic medications after transplantation are standard criteria for diabetes diagnosis (1-3). NODAT pathophysiology is similar to type 2 diabetes; insulin resistance and low secretion (4, 5). Since there are some uncertainties about the criteria, ranging from 6 to 60 months, the prevalence reported in different studies, varies from 2% to 53% (6-8).

Some NODAT risk factors particularly after liver transplantation may include: Recipient's older age (2, 9), ethnicity (most black and Hispanic) (2, 10, 11), pre-transplant and early post-transplant hypomagnesemia (12, 13), male gender (14, 15), close relatives' history of diabetes (2, 15), immunosuppressive medications including tacrolimus and corticosteroids particularly bolus injection (13, 15, 16), positive hepatitis C serology (8, 13, 15), metabolic syndromes (hypertriglyceridemia, low HDL-C, hyperuricemia and hypertension) (2, 17), pre-transplant alcoholic cirrhosis (15, 18) and higher body mass index (BMI) (8, 15). In addition to demographic and environmental factors genetics can be effective in development of NODAT (3, 5, 19, 20).

NODAT may have a detrimental role in biliary duct tightness, cholangitis (6) post-transplantation infections, graft rejection and presumably loss (21). Thus, it's vital to identify the impact of risk factors with a purpose of enhancing graft survival and improving patients' life quality.

This research has been done in Organ Transplantation Research Center and Namazi hospital, affiliated to Shiraz University of Medical Sciences (SUMS), the first and the biggest center of organ transplantation in Iran and the third greatest one in the world after United States of America and Spain. There are 3310 successful liver transplantations conducted in Namazi hospital since 1993 (22). Therefore, identification the risk factors of a common complication of this transplantation, NODAT, can be so important and valuable. This study aims to recognize these risk factors

in order to help identifying high- risk liver recipients in terms of NODAT, thus more accurate monitoring will be done on their post- transplantation blood glucose.

Methods
Patient collection
Data were collected from 134 patients, whose transplantation had been carried out in 2007-2013. Patients were divided into two groups, 64 patients with NODAT and 70 non-NODAT. NODAT was diagnosed as outlined in introduction (1-3). Clinical and demographic data from patients' files were studied and analyzed. This study has been confirmed in the ethics committee of SUMS due to using the patient files (Code No.: 93-01-05-7201).

The inclusion criteria for subjects were that all the patients had undergone liver transplantation and hadn't had diabetes mellitus before it or hadn't used any anti-diabetic drugs. The NODAT group got diabetes mellitus after this surgery until 2 years after that the non-NODAT group still maintained non- diabetic after liver transplantation for up period in this study. Two groups were also compared in aspect of pre- transplantation FBS.

The exclusion criteria were having diabetes mellitus before surgery. Also, patients who had undergone combined transplantations or any other transplantation except liver, was excluded.

Underlying diseases of recipients, which had led to liver transplantation, are classified into four groups in aspect of origin: cryptogenic (unknown), viral, autoimmune and congenital (Table 1). Data gathering sheet was designed and demographic, clinical and laboratory information of the included patients were recorded. These data were recipients' age, sex, BMI, blood group, pre- transplantation FBS, diseases leading to transplantation, model for end-stage liver disease (MELD) score, prednisolone and Mycophenolate Mofetil (MMF) dose, tacrolimus dose and serum level.

Table 2. Demographic and clinical information of the patients with liver transplantation (N=134).

Demographic and clinical factors		Total patients N=134	Non-NODAT patients N=70	NODAT patients N=64	P value (NODAT vs. non-NODAT)
Age (years), mean± SD		37.83±16.26	31.86±16.41	44.37±13.42	P<0.0001
Sex Male, ,%,(N) Female, ,%,(N)		39.60% (n=53) 60.40% (n=81)	39.13% (n=28) 60.87% (n=42)	39.06% (n=25) 60.94% (n=39)	P=0.994
BMI (kg/m²), mean± SD		21.91±5.54	20.81±3.86	22.90±6.65	P=0.238
MELD score		21.17±6.34	20.36±5.77	22.06±6.90	P=0.162
Prednisolone dose (mg/day), mean± SD		8.79±7.19	4.61±5.74	13.36±5.71	P<0.0001
Tacrolimus plasma level (ng/ml), mean± SD		11.12±4.68	8. 21±3.06	14.04±4.23	P<0.0001
Tacrolimus dose (mg/day), mean± SD		3.41±1.54	3.23±1.22	3.60±1.81	P=0.043
Mycophenolate dose (g/day), mean± SD		1.68±0.63	1.54±0.69	1.83±0.53	P=0.001
Blood group	A,%,(N)	34.71% (n= 42)	35.3% (n= 24)	34.0% (n= 18)	P= 0.09
	B,%,(N)	28.1% (n= 34)	35.3% (n= 24)	18.9% (n= 10)	
	AB,%,(N)	8.26% (n= 10)	4.4% (n= 3)	13.2% (n= 7)	
	O,%,(N)	28.92% (n=35)	25% (n= 17)	34.0% (n= 18)	
Disease	Cryptogenic origin,%,(N)	23.25% (n=30)	21.7% (n=15)	25.0% (n=15)	P=0.436
	Viral hepatitis ,%,(N)	30.23% (n=39)	26.1% (n=18)	35.0% (n=21)	
	Autoimmune hepatic or biliary disorders ,%,(N)	27.91% (n=36)	29.0% (n=20)	26.7% (n=16)	
	Congenital hepatic or biliary disorders,%,(N)	18.60% (n=24)	23.2% (n=16)	13.3% (n=8)	

a) New- Onset Diabetes After Transplantation
b) Standard Deviation
c) Body Mass Index
d) Model for End-Stage Liver Disease

Statistical analysis

This analysis was conducted using SPSS version 19.0. Quantitative and qualitative data are reported as mean± SD and percent (frequencies), respectively. Normality of distribution was studied utilizing Kolmogorov-Smirnov approach. Depending on equality or inequality of variances, Independent samples T test or Mann-Whitney was carried out. Sex was studied by crosstab test, tacrolimus and MMF dose were investigated by Mann-Whitney and age, tacrolimus serum level, Model for End-stage Liver Disease (MELD) score, pre-transplantation FBS, BMI and prednisolone dose were evaluated by independent sample test (T test). MELD, a criterion for assessment of chronic liver diseases' severity, is calculated by Equation 1(23).

Equation 1:

MELD = 3.78×ln [serum bilirubin (mg/dl)] + 11.2× ln [INR] + 9.57× ln [serum creatinine (mg/dl)] + 6.43

At last a logistic binary regression was done among statistically significant factors. Although tacrolimus serum level was one of the effectives in this study, it is eliminated from the modeling, as missing data were too much for this factor. P-value <0.05 was considered significant.

Results

There are 1487 patients who underwent liver transplantation between 2007 and 2013 in Namazi hospital. 17.92% (n=266) of all patients got NODAT.

Table3. Binary logistic regression among factors being accepted as effective parameters on NODAT (N=134).

Factors	B	P value	Odds ratio	95% CI for EXP (B)	
Age	0.061	0.001	1.063	1.025	1.102
Tacrolimus dose	0.006	0.975	1.006	0.715	1.414
Prednisolone dose	0.239	< 0.0001	1.270	1.163	1.388
Mycophenolate dose	-0.294	0.492	0.745	0.322	1.725

Among the total transplanted patients, only 134 were enrolled in this study according to the inclusion and exclusion criteria

Demographic and clinical information of the included patients were presented in Table 2. The means of duration after transplantation that NODAT occurred in the subjects of this study, was 98.36± 21.62 days meanwhile 79.24% of them showed this complication within 90 days after the surgery.

The means of pre- transplantation FBS was compared between the two groups. Means of this parameter in NODAT and non- NODAT group was 92.53± 16.32 mg/dl and 87.38± 15.61 mg/dl, respectively (P= 0.091).

A logistic regression which has been done between age, prednisolone, tacrolimus and MMF dose shows the relationship between effective factors (Table 3). Binary logistic regression found out age and prednisolone dose has a significant effect on NODAT.

Discussion

NODAT, a complication of liver, kidney or many other organs transplantation, may lead to graft rejection, post-transplant infections, cardiovascular events and eventually reduced survival (9).

The prevalence of NODAT in this survey was 17.92% which is consistent to other studies (2-53%) (6-8). In this study it was found out that 79.24% of the patients showed NODAT within 90 days after transplantation. A review on 27 published reports, including 3611 renal recipients in 19 researches, has reached the same result (24). Moreover, a research on Korean renal allograft recipients showed a considerably reduction in insulin level during the oral glucose tolerance test (OGTT) at months 1 and 3 after transplantation. Cho et al., the authors, noted that insulin secretion enhanced gradually, as tacrolimus dose was reduced (25). Thus the most critical period for the high-risk patients is the first 3 months. It's suggested to follow these ones up more accurately in this interval.

There are many studies which have investigated the risk factors for NODAT (2, 13, 14). Age, sex, BMI, MELD, prednisolone and tacrolimus dose, tacrolimus plasma level and MMF dose are factors which have been evaluated in this research.

In this study age is known as a risk factor for NODAT. Many others obtained the same result that the older is a patient, the higher risk is for this complication (2, 6, 26). The means of age in NODAT and non-NODAT group at the time of transplantation is 44.37± 13.42 and 31.86± 16.41 years, respectively (P< 0.0001) The binary logistic regression showed each one year increase in age may cause 1.063 times more risk for NODAT (P= 0.001, CI 95%: 1.025- 1.102). Multivariate ordinal logistic regression in Danish renal recipients showed that pre- transplant insulin sensitivity index and age were the only predictive factors of NODAT.(27) In Korean kidney recipients age at transplantation was revealed to be the only predictor for this complication in multiple logistic regression analysis (25). Although Saliba, conducting a research on 211 liver recipients from 10 transplantation centers in France, could not introduce recipients' age as an effective factor for NODAT and just showed an association between this complication and donors' age (P<0.0001) (8). In a study which has been done on Iranian liver recipients, their higher age was introduced as the only independent parameter which affects NODAT prevalence, using multivariate regression model (5). Another survey among these population, revealed both recipients and donors' older age may induce NODAT (20).

There was not a significant difference in frequency of NODAT in male and female in our research. It supports the result of some previous studies, conducted on Iranian hepatic transplanted patients (5, 20); although it's against some others, expressing male gender as a notable risk factor (14, 15, 17). A study has expressed a noteworthy point, implying men are prone to NOADT, just if come with some cardiovascular risk factors. This study doesn't know sex as an independent risk (8).

BMI effect is contradictory in different studies. Whilst it was known as one of the strongest risk factors in some studies (8, 28), some others fell through detecting a significant relationship (14, 29-32), as same as ours. Even in two previous researches on the population who had undergone liver transplantation in Iran, higher BMI was implied significantly more in NODAT group (5, 20). However some emphasize waist to hip ratio may be more than or as important as BMI.(17, 28) Generally higher BMI is a warning for diabetes mellitus and its complications, even moderately enhanced one (33, 34). In our study, NODAT group had greater means of BMI (22.90±6.65 kg/m²) compared to non- NODAT (20.81±3.86 kg/m²) but the

difference was not significant (P=0.238). An investigation pointed out maximum BMI≥ 25kg/m² lifetime and even more, BMI≥ 30kg/m² is a threat in terms of NODAT(8). Meanwhile, the both groups of our study, the means of BMI is less than 25kg/m².

Furthermore, there was not any significant relation between NODAT and recipients' blood group (P= 0.09). A previous study had reported similar result too in liver transplantation in Iranian population (20).

In this survey, any association could not be found between NODAT and distribution of diseases leading to liver transplantation (P=0.436). This was against many previous studies which had identified hepatitis C as an important risk factor (2, 8, 17).

On the other hand, no relation was detected between the recipients' MELD and their suffering from NODAT in the present research (p=0.162). This tallies what had been concluded in many other previous researches (5, 7, 28, 32).

Prednisolone is a common immunosuppressive agent and hyperglycemia is a frequent adverse effect of it. The averages of prednisolone dose administered in NODAT and non- NODAT group were 13.36± 5.71 and 4.61± 5.74 mg/day in respect and showed a significant difference (P< 0.0001). In most studies, as same as ours, it has been proved that higher doses, run the risk for NODAT (15, 17, 35, 36) .But there are some others which fell through to find any relationship (37-39). Binary logistic regression in this survey shows 1mg/day rise in prednisolone dose may increase 1.27 times the risk of NODAT (CI 95%=0.643-0.824). The risk of this complication in Norwegian population, who had undergone renal transplantation, was calculated 5% for each 0.01 mg/kg/day addition in prednisolone dose. Furthermore a significant relationship was shown between 2- hour blood glucose and prednisolone dose in univariate and multivariate linear regression in these patients, and between impaired glucose tolerance and prednisolone dose in multivariate model (40). Besides a significant relationship was observed between decreasing prednisolone daily dose to 5mg and less serum glucose in renal transplantation in Norwegian patients (P= 0.001) (41).

Tacrolimus dose was 3.23±1.22 mg/day in non-NODAT patients and 3.60±1.81 mg/day in NODAT ones in our study Binary logistic regression model showed that its dose was not a predictor for NODAT. Most of the other studies evaluated tacrolimus dose or serum level as a calcineurin inhibitor, proved a profound relationship (15, 16, 42-47). It has been expressed that tacrolimus dose is an effective factor on NODAT in African- Americans. So there's a possibility that race would be a stronger risk factor than tacrolimus dose (2, 10, 11, 17, 21). Previous researches which have been done on Iranian patients who received liver graft, could not find any association between tacrolimus dose or serum level and NODAT

(5, 20). Some other researches have failed to show any relationship between its dose and the complication (39). The mechanism suggested for its diabetogenicity is binding to FK506-binding protein 12 (FKBP12), inhibiting calcineurin and in this way, blocking insulin gene's transcription (25, 48, 49). On the other hand, it's notable that mostly tacrolimus serum level is too important rather than dose, as the results in this study and some others confirm it (42, 50) . In this investigation, the mean tacrolimus blood level was 14.04±4.23 ng/ml in NODAT and 8.21±3.06 ng/ml in non- NODAT group. There was a significant difference between these two (P< 0.0001). This parameter has not been entered regression model since its missed data were relatively much. There were some studies which showed no association between trough level of tacrolimus and NODAT (5, 20, 37). Two of these were carried out in Iranian liver transplant patients. Tacrolimus blood concentration is an important factor for preventing graft rejection. Tacrolimus blood level has been recommended in Chinese liver-transplanted patients to be maintained at 10-12ng/ml within 3 months post-transplantation, 8-10ng/ml in 3-6 months, 6-8ng/ml within 6-12 months and 4-6ng/ml as the maintaining concentration after the first year in order to prevent graft rejection (51). On the other hand, American kidney recipients had a lower risk of NODAT by achieving lower tacrolimus trough level (8-16ng/ml) along with using MMF and rapid tapering down the prednisolone (52). Furthermore, using multivariate regression, Ling et al., in 2013 showed that in Chinese liver recipients with blood tacrolimus level less than 10ng/ml, the threat of NODAT was reduced (19). Thus it's suggested that its level get adjusted to an amount which meet the need of both rejection and NODAT prevention.

In our study MMF daily dose was 1.54±0.69 g in non-NODAT and 1.83±0.53 g in NODAT group in average (P=0.001). Despite this, logistic regression showed an insignificant relationship (P= 0.492). In an editorial it has been mentioned that using this drug may reduce the risk of diabetes after kidney transplantation (26), though there is another one which confirms our study's result (53). There were two other studies done among Iranian liver recipients, both of which could not find any association between MMF daily dose and NODAT (5, 20). In general, there was no observed diabetogenic effect for MMF (54) and immunosuppressive combinations including MMF, had less risk of hyperglycemia compared to more potent agents, such as cyclosporine (52). Contrarily, hyperglycemia is named as one of MMF's frequent complications (44% to 47%) (55).

The differences between the results of this research and previous ones may be related to differences in the population of the center of study, sample size, guidelines for transplantation in each center and monitoring of the patients after that.

There were some limitations in this research, including limited data or unavailability of some patients' documents and small sample size. Furthermore, the donors' information were not available.

In conclusion, logistic regression just reported age and prednisolone dose as independent predictors of NODAT. Thus recognition high risk patients and applying preventive proceedings for them is recommended strongly.

Acknowledgement

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