

## Incidence and Risk Factors for Diabetes, Hypertension and Hyperlipidemia after Liver Transplantation

Mohamed Saad Hashim<sup>1</sup>, Maha Alsabaawy<sup>1</sup>, Sameh Afify<sup>1</sup>, Gasser El-Azab<sup>1</sup>, Nabil Omar<sup>1</sup>

<sup>1</sup> National Liver Institute, Menoufia University, Shebin Elkom, Egypt.

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**Correspondence to:** Mohamed Saad Hashim, National Liver Institute, Menoufiya University, Shebin Elkom, Egypt.  
Email: [msaadhh@hotmail.com](mailto:msaadhh@hotmail.com)  
Telephone: +00201007556891

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### ABSTRACT

**INTRODUCTION:** Post-liver transplant recipients present a vast array of metabolic disturbances in the post-transplant period which impact on their morbidity and mortality. Therefore, predicting and preventing post-transplant metabolic complications would be a compelling objective for improving care of post-transplant recipients. The aim of this study was to identify the incidence and risk factors of metabolic complications after liver transplantation.

**PATIENTS AND METHODS:** Incidence and risk factors for new onset hypertension, diabetes mellitus and hyperlipidemia were assessed progressively in 100 post-liver transplant recipients at least one year after transplantation.

**RESULTS:** The incidence of hypertension was 38.6%; diabetes, 39.7% and hyperlipidemia, 19% at one year post-liver transplantation (LTX). Independent risk factors for new onset of hypertension were family history of hypertension (OR: 4.85; 95% CI: 3.04-7.74), and cyclosporine use (OR: 6.33; 95%CI: 2.36-16.96). Risk factor for new onset of diabetes were HCV infection (OR: 2.54; 95%CI: 0.84-7.72)

and cyclosporine use (12.63; 95%CI: 3.06-52.09). The incidence of hyperlipidemia after LTX was related to the use of cyclosporine (OR: 1.56; 95%CI: 1.04-1.98), or tacrolimus (OR: 1.34; 95%CI: 1.02-1.67).

**CONCLUSION:** LTX was associated with significantly increased rates of hypertension, diabetes and hyperlipidemia. The incidence of these disorders was related to immunosuppressive therapy.

**Key words:** Liver Transplantation; Immunosuppression; Calcineurin inhibitors; Metabolic syndrome; Hypertension; Diabetes mellitus; Hyperlipidemia

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### Abbreviations

AASLD: American Association for the Study of Liver Diseases; ADA: American Diabetes Association; BMI: Body Mass Index; CNI: Calcineurin inhibitors; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; DM: Diabetes mellitus; EASL: European Association for the Study of Liver Diseases, International normalized ratio; JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDLT: Living donor liver transplantation; LTX: Liver transplantation; MELD: Model for end-stage liver disease.

### INTRODUCTION

Liver transplantation (LTX) has become a widely accepted life-saving procedure for patients with end stage liver disease and selected patients with acute liver failure<sup>[1,2]</sup>.

Post liver transplant patients present a vast array of metabolic changes in the early and late phase which impact their morbidity and mortality. Diabetes mellitus, arterial hypertension and obesity are higher among transplant recipients than in the general population<sup>[3]</sup>.

Risk factors for post-transplant metabolic disorders may be related to the immunosuppressant regimen, higher blood fasting

glucose levels pre-transplant, greater BMI, previous alcohol abuse, and greater donor BMI. Furthermore, variables that have also been considered to be risk factors in the general population for development of these disorders were also found to be risk factors for transplant patients<sup>[4]</sup>. Because some of these variables are capable of modification, interventions should aim to prevent these complications in transplant patients by promoting life style changes and better managing immunosuppression, especially in groups with preexisting risk factors<sup>[5]</sup>.

The aim of this study was to identify the incidence and risk factors for the components of the metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia) after liver transplantation.

## PATIENTS AND METHODS

During the period from December 2014 to March 2017, 226 adult patients underwent living donor liver transplantation (LDLT) in the National Liver Institute, Menoufia University, Egypt. One Hundred consecutive patients who were not diabetic or hypertensive followed up for at least twelve months. Arterial hypertension, diabetes mellitus and hyperlipidemia incidence and risk factors were assessed at 12 months.

The study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of National Liver Institute (NLI), Menoufia University, Egypt. Written informed consents were obtained from both donors and recipients regarding surgery and research. Pre-specified data were collected regarding demographic, clinical, and laboratory data.

Diagnosis of DM was based on the 2013 American Diabetes Association (ADA) criteria<sup>[6]</sup> (fasting glucose levels above 126 mg/dL, or post-prandial glucose > 200 mg/dL that were recorded at least twice or HbA1c > 6.5). Diagnosis of hypertension was based upon the seventh report of the Joint National Committee (JNC 7)<sup>[7]</sup> (arterial systolic blood pressure > 140 mmHg and/or arterial diastolic blood pressure > 90 mmHg, which were registered at least twice). Hyperlipidemia was considered if fasting cholesterol  $\geq$  200mg/dL and/or fasting triglycerides  $\geq$  150mg/dL.

Statistical analysis was performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL). Numeric variables were presented as mean and standard deviation. Categorical variables were presented as percentages. Risk factors for the incidence of diabetes, hypertension and hyperlipidemia were determined using multiple linear regression analysis after performing a univariate analysis (Chi-Square or Fisher test; T Student test or Mann-Whitney). Variables that had *p* values < 0.05 in the univariate analysis were included in the logistic regression analysis, which was performed in a stepwise, backwards method. *P* values < 0.05 were considered statistically significant.

## RESULTS

One hundred patients were included in the study; their mean age was  $52 \pm 7.7$  years. They consisted of 91 males (91%) and 9 females (9%) (Table 1).

HCV-related cirrhosis was the most common indication for transplantation (79%). HCC accounted for 28% of cases combined with other causes of cirrhosis.

The general characteristics of the patients are depicted in table 1.

The incidence of hypertension was 38.6%, diabetes mellitus 39.7% and that of hyperlipidemia was 19% at one-year post-liver transplantation.

Risk factors for the incidence of hypertension were family history

of hypertension and cyclosporine, Tacrolimus and pulse steroid use. By multivariate analysis only family history of hypertension (OR: 4.85; 95% CI: 3.04-7.74), and cyclosporine use (OR: 6.33; 95%CI: 2.36-16.96) were the independent predictors.

Risk factors for incidence of diabetes were obesity, HCV infection and cyclosporine use. By multivariate analysis only HCV infection (OR: 2.54; CI: 0.84-7.72) and cyclosporine use (12.63; 95%CI: 3.06-52.09) were the independent predictors.

The incidence of hyperlipidemia after LTX was related to the use of cyclosporine, tacrolimus, mTOR and hypertension. On multivariate analysis; cyclosporine (OR: 1.56; 95%CI: 1.04-1.98), or tacrolimus (OR: 1.34; 95%CI: 1.02-1.67) were the independent predictors (Tables 2 and 3).

All variables are expressed as Mean  $\pm$  Standard deviation except for categorical variables expressed as no (percentage).

## DISCUSSION

As longer survival rates have been achieved with Liver transplantation, the incidence of metabolic derangements such as hyperglycemia, hypertension, dyslipidemia and obesity, has also increased. They are associated with higher costs of care and increased risks of graft failure, infection, CVD, and death<sup>[8,9]</sup>. Hence, the primary aim of this study was to investigate the incidence of the components of the metabolic syndrome, as well as the associated pre-operative and post-operative risk factors. A total of 100 patients who underwent LDLT in NLI were prospectively recruited and followed for at least one year after transplant.

In the current study the incidence of hypertension was 38.6 % at one year after LTX.

An increased incidence of hypertension has been described in many studies. The incidence of post-transplant hypertension ranged in different studies from 19% to 77% at 1-year post-transplant<sup>[10-18]</sup>.

The use of immunosuppressive agents specially cyclosporine was

**Table 1** Baseline characteristics of the included recipients Pre-LTX.

Variable	Value	
Age (Years)	52 $\pm$ 7.7	
Sex (males)	91 (91%)	
MELD	18.4 $\pm$ 5.4	
FPG (mg/dL)	110.6 $\pm$ 28.3	
2h PG (mg/dL)	174.6 $\pm$ 53.7	
HbA1c %	5.5 $\pm$ 1.5	
Total cholesterol (mg/dL)	107.8 $\pm$ 55.1	
Triglycerides (mg/dL)	84.1 $\pm$ 66.4	
BMI (kg/m <sup>2</sup> )	27.2 $\pm$ 4.4	
Hypertension	12 (12%)	
DM	37 (37%)	
Family history of hypertension	20 (20%)	
Family history of DM	18 (18%)	
Family history of Hyperlipidemia	9 (9%)	
Indication	HCV	79 (79%)
	HBV	5 (5%)
	autoimmune	4 (4%)
	cryptogenic	12 (12%)
	HCC	28 (28%)
Donor age (Years)	29.1 $\pm$ 5.7	
Donor sex (males)	-84.84%	
Donor BMI	27.5 $\pm$ 1.5	

All variables are expressed as Mean  $\pm$  Standard deviation except for categorical variables expressed as no (percentage).

the most common risk factor for the development of hypertension<sup>[10]</sup>. Other Risk factors included pre-LT high systolic blood pressure<sup>[11]</sup>, abdominal obesity, family history of hypertension<sup>[10,12]</sup>, use of m-TOR inhibitors<sup>[11,12]</sup> and Pre-LT diabetes<sup>[11]</sup>. We found that the independent risk factors for new onset of hypertension were family history of hypertension (OR: 4.85; 95% CI: 3.04-7.74), and cyclosporine use (OR: 6.33; 95% CI: 2.36-16.96) which are in concordance with most of the previous studies.

Hypertension is the most common cardiovascular complication after liver transplantation. The development of arterial hypertension is considered to be the consequence of immunosuppressive treatment and complex pathophysiological processes affecting the hormonal system and vascular endothelium<sup>[14]</sup>. Systemic vasoconstriction induced by renin, aldosterone, and endothelin (ET)-1 together with arterial stiffness; were determined to be contributing factors. Plasma ET-1 levels were elevated in hypertensive patients but not in normotensive patients<sup>[14]</sup>.

CNIs are known to increase sympathetic tone resulting in vasoconstriction and cause sodium dependent volume expansion<sup>[15]</sup>. Hypertension was observed less often with tacrolimus than with cyclosporine<sup>[16,17]</sup>. Additionally, changing CNIs from cyclosporine to tacrolimus resulted in decreased rates of hypertension<sup>[18,19]</sup>. Hypertension is observed also with corticosteroid use<sup>[20]</sup>. Decreasing rates of hypertension were observed with steroid sparing immunosuppression regimens<sup>[21, 22, 23]</sup>.

In our prospective study, we demonstrated that the incidence of DM was 39.7 % at one year after LTX which is consistent with the literature. The incidence of de novo diabetes ranged in different studies from 13 to 58%<sup>[10,12,15,17,18]</sup>.

Risk factor for incidence of diabetes that reported were impaired fasting glucose pre-LTX, HCV infection, alcoholic cirrhosis as an indication of LTX, tacrolimus use, older age, greater donor BMI and greater BMI prior to liver disease<sup>[10,12,15,17,18]</sup>. We reported that the Risk factor for *de novo* diabetes were HCV infection (OR: 2.37; 95% CI: 0.79-7.07) and cyclosporine use (12.63; 95% CI: 3.06-52.09) which is consistent with many of the previous studies.

Our current study determined the incidence of dyslipidemia to be 19 %. The use of cyclosporine (OR: 1.56; 95%CI: 1.04-1.98), or tacrolimus (OR: 1.34; 95%CI: 1.02-1.67) were the independent risk factors for the development of dyslipidemia. We found also that the presence of hypertension and the use of m-TOR inhibitors are risk factors for dyslipidemia in spite of the borderline significance. The limited number of sirolimus use in our study (5 recipients) did not allow us to draw a view about its role on dyslipidemia. Prior studies reported incidence rates of 47-70%<sup>[12,24,25]</sup>.

Cyclosporine was associated with more hyperlipidemia<sup>[17,26]</sup>. Additionally, changing from cyclosporine to tacrolimus improved hyperlipidemia in many studies<sup>[16,18,19]</sup>.

Attention to dyslipidemia is warranted because interventions for dyslipidemia have an impact on reducing cardiac events. Numerous mechanisms exist for the occurrence of post-transplant dyslipidemia, including those mediated by immunosuppressive drug therapy<sup>[28]</sup>.

Immunosuppressive medication induces insulin resistance resulting in hyperinsulinemia leading to increased hepatic uptake of free fatty acids (FFA). Consequently, hepatic synthesis of VLDL and LDL is increased. Insulin resistance also leads to a reduction in lipoprotein lipase, which leads to reduced triglyceride clearance. Finally, the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is increased<sup>[28]</sup>. Cyclosporine interferes with the binding of LDL cholesterol to its receptors resulting in decline in LDL clearance. Cyclosporine also interferes with bile acid synthesis further reducing

**Table 2** Predictors of Post LTX hypertension, DM and hyperlipidemia by univariate analysis.

Variable		Hypertension (No, 34)	No Hypertension (No, 54)	P Value
Age		50.4 ± 7.5	52 ± 7.8	0.35
Sex	M	31 (91.2%)	50 (92.5%)	< 0.001
	F	3 (8.8%)	4 (7.5%)	
Family history		20 (58.8%)	0 (0%)	< 0.001
Overweight & obese		17 (50%)	29(53.7%)	0.58
smoking		3 (8.82%)	7(20.58%)	0.13
HCV infection		27 (79.4%)	40 (74.07%)	0.88
Tacrolimus		15 (44.1%)	45 (83.3%)	< 0.001
Cyclosporine		19 (55.8%)	9 (16.6%)	< 0.001
m-TOR		8 (23.5%)	1 (1.85%)	0.29
Pulse steroids		16 (47.05%)	12 (22.2%)	0.02
Diabetes		21 (61.7%)	32 (59.2%)	0.12
Variable		DM (No, 25)	Non-diabetic (No, 38)	P Value
Age		51.2 ± 6.8	50.4 ± 8.9	0.17
Sex	M	23 (92%)	35 (92.2%)	1
	F	2 (8%)	3 (7.8%)	
Family history		13 (52%)	3 (7.8%)	0.65
Overweight & obese		18 (72%)	17 (44.7%)	0.026
Smoking		2 (8%)	2 (8%)	0.07
HCV infection		21 (84%)	28 (73.6%)	0.01
Tacrolimus		17 (68%)	23 (60.5%)	0.613
Cyclosporine		8 (32%)	15 (39.4%)	0.02
m-TOR		4 (16%)	6 (15.7%)	1
Pulse steroids		15 (60%)	8 (21%)	0.003
Hypertension		15 (60%)	8 (21%)	0.203
variable		Hyperlipidemia (No, 19)	No Hyperlipidemia (No,81)	P Value
Age		49.8 ± 9.6	52.4 ± 7.3	0.37
Sex	M	13 (68.4%)	78 (96.3%)	0.62
	F	2 (10.5%)	7 (8.6%)	
Family history		6 (31.5%)	24 (29.6%)	0.37
Overweight & obese		9 (47.4%)	48 (59.3%)	0.29
Smoking		4 (21%)	8 (9.8%)	0.17
HCV infection		13 (68.4%)	65 (80.2%)	0.55
Tacrolimus		11 (57.9%)	57 (70.3%)	0.021
Cyclosporine		8 (42.1%)	28 (34.5%)	0.001
m-TOR		6 (31.5%)	7 (8.6%)	0.004
Pulse steroids		9 (47.4%)	25 (30.8%)	0.17
Hypertension		16 (84.2%)	34 (41.9%)	0.005
DM		15 (78.9%)	49 (60.4%)	0.043

**Table 3** Predictors of Post LTX hypertension, DM and hyperlipidemia by multivariate analysis.

Hypertension	P Value	OR	95% CI
Cyclosporine	0.005	6.33	2.36-16.96
FH	0.025	4.85	3.04-7.74
DM	P Value	OR	95% CI
Cyclosporine	0.005	12.63	3.06-52.09
HCV infection	0.036	2.37	0.79-7.07
Hyperlipidemia	P Value	OR	95% CI
Cyclosporine	0.026	1.56	1.04-1.98
Tacrolimus	0.015	1.34	1.02-1.67

the clearance of cholesterol<sup>[29]</sup>. Cyclosporine, by virtue of being highly lipophilic, is transported within the core of LDL cholesterol particles which may change the molecular configuration of LDL and alter the normal feedback regulation of cholesterol synthesis<sup>[22]</sup>. The effects of tacrolimus on lipid metabolism are generally similar to those of cyclosporine<sup>[28]</sup>.

In conclusion; our study suggests that liver transplant patients have a high incidence of hypertension, diabetes and dyslipidemia. Immunosuppressant agents appear to play an important role in the development of these metabolic disorders. Further studies are still needed to better understand these metabolic disorders after liver transplantation, especially their pathophysiology, treatment and prevention.

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