

***Study Of Diabetes and Hypertension in Liver
Transplant Recipients***

Thesis

Submitted for partial fulfillment of Master Degree

Of internal medicine

Presented by

Ahmed Mahmoud Osman Daoud

M.B.B.ch

Faculty of medicine, Cairo University

Supervised by

Prof. Dr.Nouman Algarem

Professor of Internal Medicine.

Faculty of medicine, Cairo University.

Prof. Dr.Amany Abd-Elmaqsood

Professor of Internal Medicine

Faculty of medicine, Cairo University.

Prof. Dr.Moustafa Alshazly

Professor of Surgery

Faculty of medicine, Cairo University.

2013

ACKNOWLEDGEMENT

*Before all and above all, thanks to **GOD** for every thing*

*I am greatly honored to express my sincere gratitude, deepest appreciation to **Prof. Dr. Nouman Algarem**, for his outstanding guidance and kind support throughout the work.*

*I would like to express my deepest gratitude and appreciation to **Prof. Dr. Amany Abd-Elmaqsood**, for her generous help, guidance and faithful support.*

*I would like to express my deepest gratitude and appreciation to **Prof. Dr. Moustafa Alshazly**, for his generous help, guidance and faithful support*

I would like to thank all my fellow assistant lecturers for the great help they offered throughout this work .

I would like to thank all patients who participated in this study and wish them a soon recovery.

I dedicate this work to my family who supported me all through this work.

*May **ALLAH** accept the work of all those and reward them for it.*

Ahmed Daoud

ABSTRACT

Background: A lot of complications occur after liver transplantation including diabetes and hypertension.

Aim: Evaluation of the overall prevalence of the diabetes and hypertension and identification of the predictors for posttransplant diabetes and hypertension.

Methods: Our study is retrospective. We collected the data of the patients from the database of the patients in the liver transplant unit.

Results: Incidence of new onset diabetes after transplant (NODAT) was 25% and incidence posttransplantation hypertension was 20%. No predictors were found for NODAT. Predictors of posttransplantation hypertension were BMI and using Cyclosporine.

Conclusion: DM and HTN are common after liver transplantation. Predictors of posttransplant hypertension are high BMI and using cyclosporine.

Keywords: Liver transplant – New onset diabetes after transplant (NODAT) – Posttransplant hypertension

INDEX

List of abbreviations	7-10
List of tables	11-12
List of diagrams	13
Chapter one : Indications for liver transplantation	14-28
Chapter two : Metabolic syndrome as a complication of liver transplantation	29- 37
Chapter three : New- onset diabetes after transplantation	38- 64
Chapter four : Cardiovascular disease and posttransplant hypertension	65-76
Patients and methods	77-81
Results	82-105
Discussion	106-125
Summary and conclusion	126-127
References	128-143
Arabic summary and conclusion	144

LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
ADA	American diabetes association
AHA	American heart association
Alb	Albumin
ALT	Alanine transaminase
Anti-CD25 mAb	Anti-CD 25 monoclonal antibody
ARB	Angiotensin receptor blocker
AST	Aspartate Transaminase
AZA	Azathioprine
Bil.D	Direct bilirubin
Bil.T	Total bilirubin
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CMV	Cytomegalovirus

CNI	Calcineurin inhibitor
CSA	Cyclosporine
CV	Cardiovascular
DPP-IV	Dipeptidyl peptidase 4
DM	Diabetes mellitus
FBS	Fasting blood sugar
eGFR	estimated Glomerular filtration rate
GLP-I	Glucagon like peptide-I
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
INR	International normalized ratio
FPG	Fasting plasma glucose
FRS	Framingham risk score
GGT	Gammaglutamyl transferase
HbA1C	Hemoglobin A1 C
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipoproteins
HLA	Human leukocyte antigens
HTN	Hypertension

HypoMg	Hypomagnesemia
IDDM	Insulin dependent diabetes mellitus
LT	Liver transplantation
MELD	Model of End-Stage Liver Disease
MMF	Mycophenolate mofetil
MS	Metabolic syndrome
mTOR	Mammalian target of rapamycin
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NODAT	New onset diabetes after transplant
NODM	New onset diabetes mellitus
OGTT	Oral glucose tolerance test
OLT	Orthotopic liver transplantation
OPTN	Organ Procurement Transplant Network
OR	Odds ratio
PC	Prothrombin concentration
PELD	Pediatric End-Stage Liver Disease
PG	Plasma glucose
PIZZ	Protease inhibitor ZZ
PLT	Platelets

PPAR	Peroxisome proliferator-activated receptors
Pre-Tx	Pretransplant
PROCAM	Prospective Cardiovascular Münster
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PTDM	Posttransplant diabetes mellitus
PTMS	Posttransplant metabolic syndrome
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
Sir	Sirolimus
SRTR	Scientific Registry of Transplant Recipient
SVR	Sustained virology response
SUs	Sulphonylureas
Tac	Tacrolimus
TLC	Total leucocytic count
TZDs	Thiazolidinedione derivatives
UNOS	United Network for Organ Sharing
USRDS	United states renal data system
WHO	World health organization
2 hr PP	2 hour postprandial

Table number	Title	Page
1	Biochemical and Clinical Indications for Liver Transplantation in Chronic Liver Disease	16
2	Medical conditions for which liver transplantation is indicated	17
3	King's College Criteria for Liver Transplantation in Fulminant Hepatic Failure	25
4	Prevalence of PTMS	33
5	WHO and updated ADA criteria for the diagnosis of Diabetes mellitus	40
6	Drug induced NODAT: Potential pathogenic mechanism(s)	49
7	Non-insulin drug therapy for NODAT	63
8	Management of NODAT	64
9	Child Turcotte-Pugh scoring system	78
10	Descriptive statistics of patients regarding Age, BMI, FBS and BP	84
11	Summary Descriptive statistics table	85
12	Causes of transplantation	86
13	New onset Diabetes after transplant	87
14	Data about the patients who developed NODAT	88
15	Number of cases that developed NODAT according to gender	92
16	Relation between pulse steroids and NODAT	92
17	Immunosuppressants and development of NODAT	93
18	Tacrolimus vs Cyclosporine and NODAT	95
19	Relation between cause of transplantation and NODAT	96
20	Child classification and NODAT	96

21	Data about the patients who developed posttransplantation hypertension (8 patients)	98
22	Relation between gender and posttransplant hypertension	101
23	Impact of pulse steroids on development of posttransplant hypertension	101
24	Immunosuppressants and development of posttransplant hypertension	102
25	Tacrolimus vs cyclosporine and posttransplant hypertension	104
26	Correlation between cause of liver cirrhosis and development of hypertension	104
27	Relation between Child class and posttransplantation HTN	105

LIST OF FIGURES AND DIAGRAMS

Figure number	Title	Page
1	Risk Factors for NODAT	42
2	Suggested pretransplant baseline evaluation of potential transplant candidates	57
3	Recommendations for the posttransplant surveillance of cardiovascular risk factors and the treatment of arterial HTN in liver transplant recipients	72
4	Cumulative rate of cardiovascular events in liver transplant recipients	74
5	Percentage of males and females in the study	83
6	ROC curve of Age & NODAT	89
7	ROC curve of BMI & NODAT	90
8	ROC curve of FBS before transplant & NODAT	91
9	Immunosuppressants and development of NODAT	94
10	ROC curve of BMI & hypertension after transplantation	99
11	ROC curve of age & hypertension after transplantation	100
12	Immunosuppressants and development of posttransplant hypertension	103

Indications for Liver Transplantation

Introduction:

Patients should be considered for liver transplantation if they have evidence of fulminant hepatic failure, a life-threatening systemic complication of liver disease, or a liver-based metabolic defect or, more commonly, cirrhosis with complications such as hepatic encephalopathy, ascites, hepatocellular carcinoma, hepatorenal syndrome, or bleeding caused by portal hypertension. While the complications of cirrhosis can often be managed relatively effectively, they indicate a change in the natural history of the disease that should lead to consideration of liver transplantation (*Leary et al, 2008*).

Indications of liver transplantation:

In the following tables, we will mention the indications of liver transplantation.

Table (1) : Biochemical and Clinical Indications for Liver Transplantation in Chronic Liver Disease

(Goldman's Cecil Medicine, 24th edition)

CHOLESTATIC LIVER DISEASE
Bilirubin >10 mg/dL Intractable pruritus Progressive cholestatic bone disease Recurrent bacterial cholangitis
HEPATOCELLULAR LIVER DISEASE
Serum albumin <3 g/dL Prothrombin time >3 seconds above control
BOTH CHOLESTATIC AND HEPATOCELLULAR LIVER DISEASES
Recurrent or severe hepatic encephalopathy Refractory ascites Spontaneous bacterial peritonitis Recurrent portal hypertensive bleeding Severe chronic fatigue and weakness Progressive malnutrition Development of hepatorenal syndrome Detection of small hepatocellular carcinoma

Table (2) : Medical conditions for which liver transplantation is indicated (*Goldman's Cecil Medicine, 24th edition*)

Viral	Hepatitis C
	Hepatitis B
Autoimmune liver disease	—
Alcohol-related liver disease	—
Inherited/metabolic liver diseases	Hereditary hemochromatosis
	α -1-Antitrypsin deficiency
	Wilson disease
	Nonalcoholic fatty liver disease
	Tyrosinemia
	Type IV glycogen storage disease
	Neonatal hemochromatosis
	Amyloidosis
	Hyperoxaluria
	Urea cycle defects
	Amino acid defects
Cholestatic liver disease	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Biliary atresia
	Alagille syndrome
	Progressive familial intrahepatic cholestasis
	Cystic fibrosis
	Bile duct loss
Malignancy	Hepatocellular carcinoma
	Cholangiocarcinoma
	Fibrolamellar carcinoma
	Epithelioid hemangioendothelioma
	Hepatoblastoma
	Metastatic neuroendocrine tumor
Polycystic liver disease	—
Vascular disorder	Budd-Chiari syndrome
Fulminant hepatic failure	—
Retransplantation	—