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RESEARCH ARTICLE

Prevalence Of Metabolic Syndrome After Orthotopic Living-Donor Liver Transplantation

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Abstract

Liver transplantation (LT) is a life - saving procedure for patients with advanced liver diseases. Post-transplantation metabolic syndrome (PTMS)**,** a consequence of LT, was associated with major vascular events; rapid progression of graft fibrosis and graft loss. The aim of this study was to assess the prevalence of metabolic syndrome (MS) following living-donor liver transplantation (LDLT) and the possible risk factors predisposing to it. **Patients & Methods:** A retrospective -prospective study was conducted on 85 Egyptian patients who underwent LDLT in the liver transplantation unit of the Military International Medical Center (IMC) - Cairo and completed one year of regular follow up. **Results:** Eighty five percent of our patients were males & mean age was 52 years. Pre-transplantation prevalence of MS, impaired fasting plasma glucose (FPG), DM, hypertension (HTN), Hypertriglyceridemia, Low serum High density lipoprotein (HDL) and Obesity was 14.1% , 12 % , 31 % , 11% , 2 % , 89 % and 22 % respectively**.** Post-transplantation prevalence of MS, impaired fasting plasma glucose (FPG), DM, hypertension (HTN), Hypertriglyceridemia, Low serum High density lipoprotein (HDL) and Obesity was 48% , 14 % , 77 % , 59% , 51% , 32 % and 35 % respectively. **Conclusion:** PTMS is an early and prevalent phenomenon after LDLT and its possible risk factors are pre-transplantation diabetes, pre- transplantation family history of diabetes and post - transplantation Obesity & Cyclosporine use.

INTRODUCTION

Liver transplantation is a life - saving procedure for patients with advanced chronic liver disease, hepatocellular carcinoma and acute liver failure. The outcomes after LT are excellent, with 1- and 5-year survival rates of 85–90% and 70–80% respectively. This led to increasing numbers of transplant recipients who have long-term metabolic & cardiovascular consequences of LT. **[1]**

The presence of MS after transplantation was associated with increased rates of major vascular events, more rapid progression of hepatitis C- induced graft fibrosis, graft loss and patients death**. [2, 3]**

There are many definitions for MS in the literature. The most widely used is the criteria defined by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) adapted in 2001 by National Heart, Lung and Blood Institute/American Heart Association (NHLBI/AHA), and its modification in 2004 & 2009. **[4]**

NCEP/ATP III defined MS as presence of at least 3 parameters of the following: **[5]**

- Impaired fasting glucose (≥ 100 mg/dl) or drug treatment for DM.
- Abdominal obesity (waist circumference ≥102 cm in men, ≥ 88 cm in women)
- Hypertriglyceridemia (≥150mg/dl or drug therapy for high triglycerides)
- Low levels of HDL (< 40 mg/dl in men, < 50 mg/dl in women or drug treatment for low HDL)

- Elevated blood pressure (≥ 130/85 mmHg or drug treatment for hypertension).

The aim of the work:

This study was carried out to assess the prevalence of MS following LDLT and the possible risk factors predisposing to it.

Patients and methods

This retrospective-prospective study has been carried out in the Liver Transplantation Unit, Gastroenterology & Hepatology Department, Military International Medical Center (IMC), Cairo in collaboration with the Internal Medicine Department, Faculty of Medicine, Zagazig University, during the period from Mars 2013 to Mars 2015.

This study was conducted on a cohort of (85 patients) who underwent LDLT in IMC, Cairo. Those patients were in 2 categories:

- 65 patients : who underwent LDLT before the period of the study & continued to have regular follow up visits for at least one year post-LT. Their physical & laboratory data were collected from their paper, elctronic files and by telephone contact when necessary.
- 20 patients: who underwent LDLT during the period of the study. Their physical & laboratory data were followed up for one year after transplantation in ICU, ward & out-patient clinic of liver translantation unit of IMC.

Exclusion criteria :

1- Age of the patient less than 18 years.
2- Patients refused to enter the study .
3- Patients died during the period of the study

Methods :

This study had been approved by the internal review board (IRB) and the ethical committee of Zagazig Faculty of Medicine and also approved by the IMC executive & scientific board.

The selected patients were evaluated for MS pre-LT & re-evaluated every month post-LT for 12 months except during 1st month post-transplantation when patients were evaluated weekly. Post-transplantation follow-up lipid profile was ordered every 3 months. All subjects of the study were subjected to the following :-

A-Thorough history taking : with special emphasis on:

- Demographic data e.g.: age, gender, smoking status, alcohol intake and underlying aetiology of liver disease.
- Patient & family history of DM & hypertension.
- History of medications before & after LDLT (immunosuppressive, antihypertensive, hypoglycemic, and lipid-lowering drugs).

B- Physical Examination: with special emphasis on:

1.Blood pressure measurement : was done according to the 2013 Egyptian guidelines for hypertension. **[6]**

2.Body mass index measurement :

Body mass index (BMI) was used in our study instead of waist circumference as an indicator of obesity. Body weight and height were measured using a scale and a stadiometer. BMI was calculated [patient's weight (in kg) / (patient's height in meters)²].The patient was considered to be obese if his/her BMI was (≥ 30) kg/m² & non-obese if BMI (< 30 kg/m²). if the patient had ascites , the estimated dry weight was used for calculation of BMI either by askig the patients about their pre-ascitic weight or according to the following table : **[7, 8]**

(Table 1): Measurement of dry body weight in ascitic patients:

Degree	Ascites	L.L edema
Mild	2.2 kg	1 kg
Moderate	6 kg	5 kg
Severe	14 kg	10 kg

C- Investigations :

A venous blood sample by venipuncture was taken from the patient in ICU, ward & then later with each out-patient clinic scheduled visit according to the clinical sheet protocol for measurement of :

1. Fasting plasma glucose level .
2. Fasting lipid profile especially serum HDL & serum triglycerides levels .

Statistical analysis:

Data were subjected to statistical analysis using the Statistical Package for the Social Science **(SPSS)** software program version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results:

In table (3), highly significant changes in all parameters of PTMS compared to pre-transplantation parameters were observed, indicating that PTMS was an early & prevalent phenomenon after LDLT.

Table (4) showed highly significant increased prevalence of MS, DM, HTN and Hypertriglyceridemia after LT than before LT.

Table (5) showed that Pre-transplantation MS persists post-transplantation in 12 % of patients out of the 14% of patients who had it pre-transplantation. All pre-transplantation diabetic, hypertensive & hypertriglyceridemic patients remain having the same criterion post-transplantation respectively. Nine patients who had impaired FPG pre-transplantation became diabetics on treatment post-transplantation while only one patient continued to have normal FPG all over the post-transplantation period of follow-up of this study. Obesity persisted in 19% of patients post-transplantation out of 22 % of patients pre-transplantation. Low HDL persisted in 29% of patients post-transplantation out of 89% of patients pre-transplantation.

Statistically significant effect of both pre-transplantation history of DM & impaired FPG and family history of DM on PTMS was detected in table (6).

Table (7) showed statistically significant effect of post-transplantation BMI & use of Cyclosporine (CS) as the main immunosuppressant medication on prevalence of PTMS.

(Table 2): Pre-transplantation Demographic & Aetiological data:

Item	**No. = 85**	**%**
Age (years) Mean ± SD Range	 52.1 ± 6.6 (23 - 66)	
Gender Male Female	 72 13	 84.7 15.3
Smoking No Stopped (Ex.) Current	 45 31 9	 52.9 36.5 10.6
Alcohol intake Yes No	 1 84	 1.2 98.8

Family history of : DM HTN DM &HTN None	 44 4 3 34	 51.8 4.7 3.5 40
Chronic Hepatitis C	81	95.3
Chronic Hepatitis B : Hepatitis B only Combined hepatitis B &C	 2 5	 2.4 5.9
Combined hepatitis C & Bilharziasis	6	7.1
Congenital biliary atresia	1	1.2
Primary sclerosing cholangitis	1	1.2

N.B: No. = number of patients, DM= Diabetes mellitus, HTN= Hypertension

(Table 3): Comparison between mean ± SD of pre- & post- transplantation clinical & laboratory data **:**

Parameter	**Pre-transplantation** (Mean ± SD)	**post-transplantation** (Mean ± SD)		***p- value**	**Significance**
		1st month	**12th month**		
Blood pressure: Systolic: Diastolic:	 116.8 ± 10.7 70.4 ± 7.9	 130.5 ± 18.6 79.8 ± 13.7	 124.2 ± 9.6 77.2 ± 7.0	 **<0.001** **<0.001**	 **Significant**
BMI	27.3 ± 3.7	27.1 ± 3.6	28.9 ± 3.3	**<0.001**	**Significant**
FPG	103.9 ± 32.0	172.3 ± 71.2	129.9 ± 38.0	**<0.001**	**Significant**
Serum TG	74.3 ± 38.6	75.1 ± 38.3	153.7 ± 39.5	**<0.001**	**Significant**
Serum HDL	32.5 ± 14.96	32.6 ± 14.7	52.7 ± 12.0	**<0.001**	**Significant**

N.B: MS= Metabolic syndrome, FPG= Fasting plasma glucose, HDL= High density lipoprotein, TG= Triglycerides, BMI= Body mass index

(Table 4): Comparison between prevalence of MS & its constituents before & after LT:

Item	**Before LT**		**After LT**		**P- value***	**Significance**
	No.	**%**	**No.**	**%**		
M.S Yes No	 12 73	 14.1 85.9	 41 44	 48.2 51.8	**<0.001**	**Significant**

Impaired FPG Yes No	 10 75	 11.8 88.2	 12 73	 14.1 85.9	0.96	Non -Significant
DM Yes No	 26 59	 30.6 69.4	 65 20	 76.5 23.5	**<0.001**	**Significant**
HTN Yes No	 9 76	 10.6 89.4	 50 35	 58.8 41.2	**<0.001**	**Significant**
Obesity Yes No	 19 66	 22.4 77.6	 30 55	 35.3 64.7	0.29	Non -Significant
-Hypertriglyceridemia Yes No	 2 83	 2.4 97.6	 43 42	 50.6 49.4	**<0.001**	**Significant**
Low HDL Yes No	 76 9	 89.4 10.6	 27 58	 31.8 68.2	**<0.001**	**Significant**

N.B: LT= liver transplantation

(Table 5): Post-transplantation fate of pre-transplantation MS & its constituents:

Item	**Pre-transplantation** (No.=85)	**Post-transplantation fate** (No.=85)	
		Persistence	**Absence**
M S : No. %	 12 14.1	 10 11.8	 2 2.4
Impaired FPG No. %	 10 11.8	 9 became DM 10.6	 1 became normal PG 1.2
DM : No. %	 26 30.6	 26 30.6	 0 0
HTN : No. %	 9 10.6	 9 10.6	 0 0

Obesity : No. %	 19 22.4	 16 18.8	 3 3.5
High TG: No. %	 2 2.4	 2 2.4	 0 0
Low HDL: No. %	 76 89.4	 25 29.4	 51 60.0

(Table 6): Comparison between demographic data of LT recipients with & without post-transplantation MS:

Item	**Without metabolic syndrome** **No.=44**	**With metabolic syndrome** **No.=41**	**Test of significance**	***P-value**	**Significance**
Age (years) mean +_SD Range	52 ± 6.7 29 – 66	52.2 ± 6.6 23 – 63	t-test = 0.08	0.93	Non -Significant
Gender male Female	38 (86.4%) 6 (13.6%)	37 (82.9%) 4 (17.1%)	X^2= 0.19	0.66	Non -Significant
Smoking Yes No Stopped	5 (11.4%) 23 (52.3%) 16 (36.4%)	4 (9.0%) 22 (53.7%) 15 (36.6%)	X^2= 0.06	0.39	Non -Significant
HCV infection: -absent Present -	1 (2.3%) 43 (97.7%)	3 (7.3%) 38 (92.7%)	X^2= 0.34	0.55	Non -Significant
Pre-LT DM & impaired FPG : absent Present	31 (70.5%) 13 (29.5%)	18 (43.9%) 23 (56.1%)	X^2= 6.13	**0.013**	**Significant**
Family history of DM absent present	26 (59.1 %) 18 (40.9%)	12 (29.3) 29 (70.7%)	X^2 = 7.6	**0.005**	**Significant**

N.B: HCV = Hepatitis C virus

(Table 7): Comparison between post-LT clinical, laboratory & immunosuppression drugs data of LT recipients with & without post-transplantation MS:

Item	Without metabolic syndrome No.=44	With metabolic syndrome No.=41	Test of significance	P-*value	Significance
Blood pressure systolic diastolic	 116.2 ± 10 68.8 ± 7.7	 117.6 ± 11.6 72.1 ± 7.8	 0.55 1.89	 0.57 0.06	Non –Significant
BMI	26.2 ± 3.2	28.5 ± 3.9	2.89	**0.004**	**Significant**
FPG	100.6 ± 32.5	107.4 ± 31.4	0.97	0.33	Non - Significant
TG	74.2 ± 39.1	74.4 ± 38.5	0.01	0.98	Non -Significant
HDL	33.2 ± 14.6	31.7 ± 15.4	0.44	0.65	Non - Significant
Tacrolimus Taken Not-taken	 43 (97.7%) 1 (2.3%)	 40 (97.6%) 1 (2.4%)	 0.003	 0.96	Non - Significant
Cyclosporine Taken Not-taken	36.4%)(16 28 (63.6%)	26 (63.4%) 15 (36.6%)	6.21	**0.012**	**Significant**
MMF Taken Not-taken	20 (45.5%) 24 (54.5%)	14 (34.1%) 27 (65.9%)	1.13	0.28	Non - Significant

N.B: MMF= Mycophenolate mofetil.

* P- value (≤ 0.05) was considered statistically significant and was considered highly significant if P-value (< 0.001).

Discussion:

Liver transplantation is a life - saving procedure for patients with advanced chronic liver disease, hepatocellular carcinoma and acute liver failure. Improved survival after transplantation can be attributed to refinements in surgical techniques and improved management of early post-LT infections & rejection episodes. All these factors led to increasing numbers of transplant recipients who have long-term consequences of transplantation. **[9]**

These long-term consequences include metabolic complications, cardiovascular complications, renal dysfunction, bone disease and de novo malignancy. MS and its components are the main risk factors of cardiovascular morbidity and mortality. **[10]**

Pre-transplantation prevalence of MS was 14.1% which matches the 16% prevalence reported by **Lunati et al. [11],** but more than the 6% prevalence reported by **Iadevaia et al**. **[12]**. However, PTMS prevalence increased to 48

% of our patients, this goes in agreement with the prevalence of 52%, 45% & 50% reported by **Laish et al., Bianchi et al.** and **Hanouneh et al**. respectively. **[3, 5, 13]** It is less than the 58% & 65% prevalence reported by **Laryea et al.** & **Kallwitz et al.** respectively. **[2, 9]**

Twelve percent of patients had impaired FPG before LT which is more than the 9% prevalence reported by **Anastacio et al. [14]**. Impaired FPG slightly increased to 14 % of patients post-LT.

Before LT, 31 % of our patients were receiving treatment for DM which is more than the 15% & 22% prevalence reported by **Iadevaia et al**. & **Hanouneh et al**. respectively. **[12, 13]** The number of patients with DM increased to 77 % of patients after LT which was more than the 61%, 40%, 52 % & 64 % prevalences reported by **Laryea et al.**, **Laish et al**., **Hanouneh et al**. & **Baid et al.** respectively. **[2, 3, 13, 15]**

Our higher prevalence of post-transplantation DM may be explained, at least in part, by the much higher prevalence of HCV infection as an underlying cause of liver transplantation in our population causing higher prevalence of insulin resistance & DM both pre- & post-LT. Also, most of our patients started on Tacrolimusas, with corticosteroids, as their main immunosuppression drugs with their known diabetogenic effect. **[16]**

Only 11% of patients were on treatment for HTN before LT which goes in concordance with the 10% & 9% prevalences reported by **Laryea et al** & **Laish et al.** respectively. **[2, 3**] Hypertensive patients increased post-transplantation to 59% of patients which is comparable to the 62% prevalence reported by **Laryea et al**., the 58% prevalence by **Laish et al.** & the 64% reported by **Hanouneh et al. [2, 3, 13].**

Immunosuppressive medication is largely responsible for the development of hypertension post LT, with calcineurin inhibitors (CNI) and corticosteroids being the most strongly implicated. The primary mechanism of CNI induced hypertension is through widespread arterial vasoconstriction that results in increased systemic vascular resistance. **[17]**

Hypertriglyceridemia was present in 2 % of patients only before LT which is compared to the 3% prevalence reported by **Laryea et al. [2]**. Hypertriglyceridemia was present in 51 % of patients after LT, this goes in agreement with the 47% prevalence reported by **Laish et al. [3].** But it is more than the 37% prevalence reported by **Bianchi et al. [5]**

Low serum HDL was present in 89 % patients before LT which was much more than the 40% prevalence reported by **Laish et al**. **[3].** Patients with low serum HDL decreased post-transplantation to 32% patients. This was less than the results of **Laryea et al.**, **Laish et al.** & **Bianchi et al.** which were 48%, 49 % & 50% respectively**. [2, 3, 5]**

This high prevalence of dyslipidemia following LT can be explained by the high prevalence of HCV infection in our population because HCV-induced cirrhosis is a risk factor for Hypertriglyceridemia. Also, Corticosteroids can lead to dyslipidemia by increasing the hepatic production of lipids and decreased hepatic LDL reuptake. Cyclosporine inhibits hepatic bile acid 26- hydroxylase, which is thought to decrease transport of cholesterol into bile and its subsequent elimination into the intestines. Additionally, cyclosporine binds to LDL receptor and thereby decreases LDL-cholesterol uptake. **[18, 19, 20]**

Obesity was present in 22 % of patients before LT which matches the 15 - 30% prevalence of pre-LT obesity reported by **De Luca et al**. **[21],** and is similar to the 21% prevalence reported by **Ruiz-Rebollo et al. [22],** less than the 26% prevalence reported by **Hanouneh et al. [13],** but more than the 18% & the 15 % prevalence in the study of **Bianchi et al.** & **Anastacio et al.** respectively. **[3, 14]**

Obesity was present in 35 % of patients post-LT, this goes in agreement with **Wawrzynowicz-Syczewska et al. [23],** who reported that Obesity (body mass index (BMI>30 kg/m²) is affecting 21 – 42% liver transplant recipients. Our results are similar to the 36% prevalence reported by **Laryea et al.**, the 31 % prevalence of post-transplantation obesity mentioned by **Laish et al.** & the 32% prevalence by **Bianchi et al. [2, 3, 5].** But less than the 53% prevalence reported by **Kallwitz et al.** & the 45% prevalence in the study of **Hanouneh et al. [9, 13].**

Highly significant changes in all parameters of PTMS compared to pre-transplantation parameters were observed, indicating that PTMS was an early & prevalent phenomenon after LDLT.

There was no statistically significant effect of the age, gender or smoking on the occurrence of PTMS. Similar results were reported by **Bianchi et al**. & **Ruiz-Rebollo et al. [5, 22].**

Our study shows that there was no statistically significant effect of HCV infection on prevalence of PTMS. Similar results were reported by **Laish et al.** & **Ruiz-Rebollo et al. [3, 22].** However, **Laryea et al.** considered HCV infection as highly associated with PTMS**. [2]**

A statistically significant relationship was found between pre-transplantation history of DM & impaired FPG and PTMS. This goes in agreement with the results of **Bianchi et al**., **De Luca et al**., **Ruiz-Rebollo et al. [5, 21, 22]**

This can be attributed to that, once DM is established in the pre-transplantation period, LT does not always produce a complete clinical regression probably due to an established B-cell defect with its subsequent metabolic derangements. **[24]**

A statistically significant relationship was reported in our study between pre-transplantation family history of DM and prevalence of PTMS. Similar result was reported by **Ruiz-Rebollo et al. [22]**

A statistically significant effect of post-transplantation BMI on prevalence of PTMS was shown in our study. This goes in agreement with that reported by **Laryea et al.**, **De Luca et al.** & **Anastacio et al. [2, 21, 25]**

Our study showed that using Cyclosporine **(**CS**)** as the main immunosuppressive medication had statistically significant effect on the prevalence of PTMS. While both Tacrolimus (FK) & Mycophenolate Mofetil (MMF) had no statistically significant effect on the prevalence of PTMS. Similar results were reported by **Iadevaia et al. , De Luca et al.** & **Francioso et al. [12, 21, 26].** However, this was rejected by **Laryea et al., Laish et al.** & **Bianchi et al. [2, 3, 5]**

This effect of CS on the occurrence of PTMS can be explained by that CS produces significant weight gain especially in the first year post-transplantation. In addition to the hypertensive & diabetogenic effect of CS**. [7]**

Conclusion:

PTMS is an early and prevalent phenomenon after LDLT and its possible risk factors are pre-transplantation diabetes & family history of diabetes, post - transplantation Obesity and Cyclosporine use.

The main Strengths of this study were the prospective design of the study and the focus on the early post-LT period. While the main limitations were the relative small number of patients, it is a single center experience, the use of BMI as a substitute for waist circumference and absence of nutritional assessment and surveillance before &after transplantation to evaluate the relationship between our regular diet & the prevalence of metabolic syndrome.

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