

Original

Overweight, obesity and weight gain up to three years after liver transplantation

L. Rezende Anastácio¹, L. Garcia Ferreira², J. Costa Liboredo³, H. de Sena Ribeiro³, A. Soares Lima⁴, E. Garcia Vilela⁴ and M.^a I. T. D. Correia⁴

¹Adult Health Post Graduation Program. Medical School. Universidade Federal de Minas Gerais. ²Surgery Post Graduation Program. Medical School. Universidade Federal de Minas Gerais. ³Food Science Post Graduation Program. Pharmacy School. Universidade Federal de Minas Gerais. ⁴Alfa Institute of Gastroenterology. Hospital of Clinics. Medical School. Universidade Federal de Minas Gerais. Brazil.

Abstract

Introduction: Previous studies have shown that weight gain commonly occurs after liver transplantation (LTx). Few risk factors have been studied.

Objectives: The aim of this study was to assess the weight changes and incidence excessive weight up to 3 years after surgery.

Methods: Post-LTx patients were assessed for their weight changes and incidence of excessive weight before liver disease; on the first outpatient appointment after LTx; 3 and 6mo after LTx; 1; 2 and 3y after LTx. Demographic, socioeconomic, lifestyle and clinical variables were collected to assess risk factors for weight gain, overweight and obesity using linear and logistic regression analysis.

Results: Eighty patients undergoing LTx between 1997/2006 were assessed. Patients lost an average of 9.1 kg during liver disease. This weight was recovered within 1 year after surgery; after 3 years, patients had gained an average of 11.6 kg. The incidence of excessive weight increased over the years, and 56.4% of patients were overweight in the 3 years after LTx; most of them were obese (30.0%). Risk factors for weight gain on the third year after LTx were greater BMI before liver disease ($p < 0.01$); former smoker ($p < 0.01$); family history of overweight ($p = 0.04$); being housewife/unemployed/retired ($p = 0.08$); alcoholic indication for LTx ($p = 0.02$). Risk factors for incidence of excessive weight on the third year after LTx were being married (RR: 13.13; CI: 1.33-125.0); being former smoker (RR: 4.68; CI: 1.16-18.85); greater age at LTx (RR: 1.1; CI: 1.02-1.20).

Conclusions: Post-LTx patients experienced weight gain after surgery, mainly during the 1 year after operation and increased progressive incidence up to 3 years, due to different risk factors, some of them can be prevented.

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Correspondence: Lucilene Rezende Anastácio.
Adult Health Post Graduation Program.
Medical School. Universidade Federal de Minas Gerais.
Avenida Alfredo Balena 110, Faculdade de Medicina, 5º andar.
31270-901. Belo Horizonte, Minas Gerais, Brazil.
E-mail: Lucilene.rezende@gmail.com

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SOBREPESO, OBESIDAD Y AUMENTO DE PESO HACIA TRES AÑOS DESPUÉS DEL TRASPLANTE HEPÁTICO

Resumen

Introducción: Estudios anteriores han demostrado que el aumento de peso suele producirse después del trasplante hepático (TxH). Pocos factores de riesgo han sido estudiados.

Objetivo: Evaluar cambios en peso y incidencia de exceso de peso hacia 3 años después de TxH.

Métodos: Después del TxH los pacientes fueron evaluados en relación a los cambios de peso y a la incidencia del exceso de peso comparada con antes de la enfermedad hepática. Esto ha sido mensurado en la consulta ambulatoria por primera vez después del TxH, y consecutivamente hacia 3 años después del TxH. Variables demográficas, socioeconómicas, de estilo de vida y clínicas se recogieron para evaluar los factores de riesgo mediante análisis de regresión lineal y logística.

Resultados: Ochenta pacientes sometidos a TxH entre 1997/2006 fueron evaluados. Los pacientes perdieron en promedio 9.1 kg durante la enfermedad hepática. El peso fue entonces recuperado en la mayor parte en el primer año después de la cirugía resultando en un incremento promedio de 11.6 kg hacia 3 años después del trasplante. En el tercer año después del TxH, la incidencia del exceso de peso fue de 56,4% de los pacientes con sobrepeso, con 30,0% de obesos. Factores de riesgo para el aumento de peso fueron: mayor índice de masa corporal antes de la enfermedad hepática ($p < 0,01$), ex-fumador ($p < 0,01$), antecedentes familiares de sobrepeso ($p = 0,04$) y indicación para TxH por alcoholismo ($p = 0,02$). Los factores de riesgo para incidencia del exceso de peso en el 3 año después del TxH fueron: estar casado (RR: 13,13; IC: 1,33-125,0), ex fumador (RR: 4,68; IC: 1,16-18,85) y mayor edad en el momento del TxH (RR: 1,1; IC: 1,02-1,20).

Conclusiones: Pacientes sometidos a trasplante hepático experimentaron aumento de peso después Del TxH, sobre todo durante el 1 año después del TxH y con incremento progresivo de incidencia hacia 3 años, en consecuencia a distintos factores de riesgo, algunos prevenibles.

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Palabras clave: Trasplante de hígado. Aumento de peso. Obesidad.

Introduction

Some weight gain after liver transplantation (LTx) seems to be appropriate because most cirrhotic patients on a waiting list for a liver transplant are malnourished¹. However, these patients not only recover their nutritional status but seem to achieve more weight than they should, which increases the prevalence of overweight and obesity after LTx.^{2,3}

As life expectancy of post-LTx patients increases,⁴ the problems associated with excessive weight gain also rise, including greater incidence of metabolic syndrome,⁵ non-alcoholic fatty liver disease⁶ and non-alcoholic steatohepatitis.⁷ It is widely believed that immunosuppressive medication plays a major role in excessive weight gain and, consequently, the onset of obesity. However, this association remains controversial in the literature, and other risk factors have been studied.⁸

The study of weight gain after transplantation and its associated factors is necessary to propose strategies to prevent and treat this problem once the extent and consequences of this condition are well recognized. Until now, few associated factors have been identified. Thus, the aim of this study was to assess weight gain evolution, the incidence of excessive weight and obesity and the associated risk factors within three years post-LTx.

Patients and methods

This was a retrospective study examining LTx patients' weight and body mass index (BMI) changes occurring within the first three years post-LTx. Weight was evaluated before liver dysfunction (informed by patients in the interview); at the first outpatient appointment after LTx; three and six months after LTx; and two and three years after surgery. The weight is usually measured on medical appointments in light street clothing, without shoes, and on a calibrated mechanical scale (Filizola®, São Paulo, Brazil) by trained nurses. The incidence of excessive weight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²)⁹ was examined. Risk factors for weight gain and the incidence of excessive weight and obesity one, two and three years after LTx were also evaluated.

Patients at Alfa Institute of Gastroenterology – Transplant Outpatient Clinic at Federal University of Minas Gerais, Brazil – who underwent transplantation between 1997 and 2006 and who were at least 18 years old at the time of LTx were assessed and interviewed. Patients who became pregnant or those with ascites were excluded.

Patients were interviewed once, from March of 2008 to October of 2008, when they had 5 ± 2 years since transplantation, to assess their demographics, socioeconomic status, current life style habits and clinical characteristics. Retrospective variables were also

collected from medical records. The study was approved by the Ethics Committee of Federal University of Minas Gerais (protocol number ETIC 44/08).

Demographic and socioeconomic data included age, sex, skin color, marital status, paid professional activity, schooling and income. Lifestyle characteristics were based on self-reported habitual hours of sleep per night, current smoking habits and history of smoking. The collected clinical data included the following: indication for LTx, donor data (sex, age and body mass index-BMI), length of time on steroids following LTx, average cumulative steroid daily dose after LTx, tacrolimus or cyclosporine use, arterial hypertension medically diagnosed prior to LTx, blood glucose on the last medical appointment before LTx ≥ 100 mg/dL or diabetes mellitus medically diagnosed prior to LTx and informed by patients' family history of arterial hypertension, diabetes mellitus, excessive weight and cardiovascular disease.

Statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL). Numeric variables were presented in minimum, maximum and median if they did not have normal distribution (Kolmogorov-Smirnov test) or presented as an average and standard deviation when normally distributed. Categorical variables were presented as percentages. The McNemar test was used to determine differences in BMI status over different times after LTx. Risk factors for weight gain one, two and three years after surgery were determined by multiple linear regression. Risk factors for incidence of excessive weight and obesity were determined by univariate (Qui-Square or Fisher test; T Student test or Mann-Whiney) and multiple logistic regression analyses. Variables that had $p < 0.2$ in the univariate analysis were included in the logistic regression model that was undertaken in a stepwise, backward method. Model adjustments were checked by the Hosmer and Lemeshow test ($p > 0.05$). P values < 0.05 were considered to be statistically significant.

Results

We assessed 80 patients (average age of 46.7 ± 12.6 years; 60% male). All of the assessed patients underwent transplants due to chronic liver disease, mainly hepatitis C virus and alcohol abuse. The general characteristics of the patients are depicted in table I.

Patients who underwent LTx presented with a progressive increase in BMI and excessive weight (table II). The median BMI and the prevalence of obesity three years after LTx were greater than before liver disease. Greater relative weight gain was seen the first year after LTx (an average weight gain of 9.0 kg in relation to the weight the first post-LTx appointment). Patients with overweight or obesity at each evaluation had greater weight loss (in relation to their weight before liver disease and immediately after LTx) and

Table I
Demographic, socioeconomic and clinical characteristics of patients who underwent liver transplantation

<i>Categorical parameters</i>	<i>%</i>	<i>N</i>
Skin color		
White	61.7	49
Brown / black	38.3	31
Married	68.8	55
Housewife/unemployed/retired	55.5	44
Smokers	12.4	10
Former smokers	34.5	28
Indication for LTx		
Hepatitis C virus	33.8	27
Alcohol abuse	30.0	24
Hepatitis auto-immune	11.7	10
Cryptogenic cirrhosis	10.0	8
Cirrhosis with hepatocellular carcinoma	2.5	2
Others	25.0	20
Tacrolimus use	92.5	74
Donor male sex	72.5	58
Arterial hypertension prior to LTx	20.0	25
Hyperglycemia prior to LTx	16.3	13
Diabetes mellitus prior to LTx	6.3	5
Family history		
Arterial hypertension	71.6	58
Diabetes mellitus	58.0	47
Overweight	65.4	53
Cardiovascular diseases	61.7	50
<i>Numerical parameters</i>	<i>Median</i>	<i>Minimum-Maximum</i>
Income (per capita, US\$)	415.0	83.0-4,000.0
Schooling (years)	6.5	0.0-16.0
Amount of sleep per night (hours)	8.0	4.0-10.5
Donor age (years)	27.0	4.0-60.0
Donor BMI (kg/m ²)	23.7	13.5-32.0
Length of steroid use (months)	5.0	1.5-36.0
Average daily cumulative steroid dose (mg/d)	13.4	2.4-48.3

greater weight gain in relation to those with under or normal weight.

A significant number of patients who were overweight or obese one, two and three years after LTx were also overweight before having liver disease (McNemar test; $p < 0.01$), but the percentage of patients with excessive weight was higher within two and three years after surgery than before liver disease (51.3% and 56.3% versus 49.4%). Independent risk factors for weight gain one, two and three years after surgery were the following: past smoking, family history of overweight and obesity or increased BMI before liver disease (table III).

An univariate analysis for the incidence of excessive weight revealed that it was significantly associated with the following: increased age (one year: $p < 0.001$; two years: $p = 0.04$ and three years: $p = 0.001$); past

smoking (two years: $p = 0.006$; RR: 1.59; IC: 1.09-2.31 and three years: $p = 0.03$; RR: 1.44; IC: 1.01-2.06); being married (two years: $p = 0.02$; RR: 4.09; IC: 1.03-16.3 and three years: $p = 0.008$; RR: 4.55; IC: 1.15-17.97); being a housewife, unemployed or retired (three years: $p = 0.02$; RR: 1.38; IC: 1.06-1.79) and greater schooling (three years: $p = 0.048$; median of 9 years of schooling for those who had an incidence of excessive weight versus median of 15.5 years of schooling for others).

The incidence of obesity by univariate analyses was significantly associated with family history of overweight (one year: $p = 0.09$; RR: 1.21; IC: 1.04-1.42); past smoking (two years: $p = 0.01$; RR: 1.54; IC: 1.05-2.24) and increased age (three years: $p = 0.049$). The logistic regression models created for analyzing the incidence of excessive weight are depicted in table III. No logistic regression model could be done for the incidence of obesity because the model could not be adjusted (Hosmer Lemeshow test < 0.05), or the remaining variables in the model were not significant.

Discussion

Patients undergoing LTx lost an average of 9.1 kg while on the waiting list for surgery, but greater weight loss was observed in patients with a past history of overweight and obesity. Most patients recovered the lost weight within one year after operation (53% of patients weighed more than the weight they used to had before liver disease within one year after LTx). Malnutrition is widely described in patients on waiting lists for LTx.¹ Cirrhotic patients generally cannot eat well due to loss of appetite and often have early satiety due to ascites; they also frequently and inadequately follow protein-restricted diets.¹⁰ Having undergone a transplant, these patients once again experience an appetite and the pleasure of prior eating habits after months/years of restrictions. At the same time, they aim to recover their previous nutritional status and are able to enjoy food they could not eat previously.⁸ Furthermore, some studies regarding the role of steroids on weight gain suggest that they could enhance appetite and stimulate the intake of sweet and high fat foods;¹¹ however, steroids' contribution to the incidence of overweight/obesity or weight gain seems to be controversial in LTx patients.^{3,12}

Excessive weight gain after LTx has been described by many authors in the literature.^{2-3,12-13} Richards et al.³ studied 597 patients undergoing LTx and found progressive weight gain during the first three years after surgery. In their study, greater weight gain also occurred in the first year after LTx, but the average weight gain in three (-0.8 kg) and six months (1.8 kg) and in one (5.1 kg), two (8.2 kg) and three years (9.5 kg) were lower than the values found in the present study (3.7, 6.0, 9.0, 11.0 and 11.6 kg, respectively).

The incidence of excessive weight also increased

Table II
Body Mass Index (BMI), BMI status, weight difference and percentage up to three years after liver transplantation (LTx)

	Before liver disease	1 ^o time after LTx	3 months after LTx	6 months after LTx	1 year after LTx	2 years after LTx	3 years after LTx
BMI (kg/m²)							
Average	25.9	22.6	24.0	24.8	25.9	26.6	26.9
Standard Deviation	5.6	4.5	4.5	4.5	4.9	5.1	5.0
BMI Status (%)							
Underweight (BMI < 18.5 kg/m ²)	2.5	18.8	10.0	1.3	1.3	0.0	1.3
Regular weight (BMI 18.5-24.9 kg/m ²)	48.1	52.4	56.2	58.7	49.9	48.7	42.4
Overweight (BMI 25-29.9 kg/m ²)	27.9	22.5	20.0	23.7	27.5	22.5	26.3
Obese (BMI ≥ 30 kg/m ²)	21.5	6.3	13.8	16.3	21.3	28.8	30.0
Excessive weight (BMI ≥ 25 kg/m ²)	49.4	28.8	33.8	40.0	48.8	51.3	56.3
Excessive weight incidence¹ (%)			5.0	11.2	20.0	22.5	27.5
Obesity incidence¹ (%)			7.5	10.0	15.0	22.5	23.7
Weight difference (kg)¹							
Average	-9.1		3.7	6.0	9.0	11.0	11.6
Standard Deviation	14.1		5.8	6.9	8.6	8.7	8.7
Weight percentage (%)¹							
Average	115.8		106.7	110.7	115.8	118.9	120.2
Standard Deviation	20.2		9.8	12.0	16.0	16.3	16.6
Weight difference of patients under or regular weight (kg)¹							
Average	-4.8		2.6	4.4	5.4	6.8	7.8
Standard Deviation	9.7		4.9	6.3	6.9	6.6	6.2
Weight difference of patients with excessive weight (kg)¹							
Average	-13.5		5.8	8.5	12.8	14.9	14.6
Standard Deviation	16.6		6.7	7.1	8.8	8.7	9.2
Weight difference of patients with obesity (kg)¹							
Average	-24.5		9.2	11.9	14.8	16.6	17.2
Standard Deviation	14.7		8.3	8.5	9.6	7.9	8.3

¹In relation to the weight on the first time after transplantation.

over the years, and more than half of patients were overweight (56.4%) three years after LTx; most of them were obese (30.0%). Although excessive weight incidence has increased in Brazil, the prevalence of excessive weight (49.1%) and obesity (14.7%) are lower in the general, adult Brazilian population.¹⁴ This indicates that post-LTx weight gain promotes a higher prevalence of overweight and obesity than the prevalence found in the general population of a similar age. Although weight gain is also described in the non-transplanted population with increasing age,¹⁵⁻¹⁶ excessive weight in general population is listed in smaller proportions.

A significant number of patients who became overweight or obese in the early years after surgery also presented with excessive weight before liver disease; this finding is in agreement with other studies^{2,13} and is probably a result of patients returning to old dietary habits and lifestyles. Moreover, obesity and BMI before liver disease were considered independent risk

factors for weight gain in the first and second/third years after LTx, respectively.

Older age at the time of LTx was also an independent risk factor for weight gain and increased incidence of excessive weight in the first and third years after surgery; this finding is similar to the study by Richards et al.³ Being a former smoker was also a risk factor for weight gain and excessive weight any time after LTx. This has not been studied by other authors yet;^{2-3,12-13} however, smoking cessation is largely associated with weight gain in the general population.¹⁷⁻¹⁸ Mechanisms of weight gain after smoking cessation include increased energy intake, decreased resting metabolic rate, decreased physical activity and increased lipoprotein lipase activity.¹⁹

Family history of overweight was also identified as an independent risk factor for weight gain in the early years after LTx and for increased incidence of excessive weight in the second year after surgery. This variable has not been assessed in other studies,^{2-3,12-13} but

Table III
Independent risk factors by multiple linear and logistic regression for post liver transplant weight gain and excessive weight incidence, respectively, within one, two and three years after surgery

<i>Independent risk factors for weight gain</i>	<i>Constant</i>	<i>p value</i>	<i>Independent risk factors incidence of excessive weight</i>	<i>RR</i>	<i>IC</i>	<i>p value</i>
<i>One year after LTx</i>						
Family history of overweight	2.59	0.02	Former smoker	5.95	1.39-25.51	0.02
Former smoker	2.32	0.03	Greater age at LTx	1.13	1.03-1.23	0.01
Obesity before liver disease	1.97	0.06				
Greater age at LTx	1.78	0.08				
Alcoholic cirrhosis indication for LTx	-2.04	0.05	Hosmer Lemeshow test			0.81
<i>Two years after LTx</i>						
Former smoker	3.03	< 0.01	Former smoker	7.77	1.87-32.35	< 0.01
Body Mass Index before liver disease	2.49	0.02	Being married	7.46	1.24-45.45	0.03
Family history of overweight	2.11	0.04	Family history of overweight	5.96	1.18-30.13	0.03
Alcoholic cirrhosis indication for LTx	-2.54	0.01	Hosmer Lemeshow test			0.89
<i>Three years after LTx</i>						
Body Mass Index before liver disease	2.90	< 0.01	Being married	13.16	1.33-125.00	0.03
Former smoker	2.68	0.01	Former smoker	4.68	1.16-18.85	0.03
Family history of overweight	2.11	0.04	Greater age at LTx	1.10	1.02-1.20	0.02
Housewife/unemployed/retired	1.79	0.08	Constant	0.002		
Alcoholic cirrhosis indication for LTx	-2.32	0.02	Hosmer Lemeshow test			0.60

post-LTx, overweight patients have reported having a family history of diabetes mellitus, arteriosclerotic heart disease, and hypertension more frequently than have patients who were not overweight.¹³ Family history of overweight may be an indicator of favorable genetics and an environment inducing excessive weight.

Marital status was a risk factor for the incidence of excessive weight two and three years after surgery, which was also pointed out by Everhart et al.² Marital status is also associated with body changes in the general population.²⁰ It has been suggested that marriage may lead to increased body weight as a consequence of increased food intake because the couple eats together, influencing one another's diet.²¹ Additionally, it can also be hypothesized that married patients receive excessive spousal care after LTx.⁸

In this study, the absence of paid employment (in the case of housewives, unemployed and retired patients) was minimally associated with weight gain two years of surgery ($p = 0.08$). This variable could not be removed from the model because other variables would lose their significance; this also occurred with "alcoholic cirrhosis as an indication for LTx".

Immunosuppressive medication (tacrolimus or cyclosporine; length of steroid use or average daily cumulative steroid dose) did not have any association with weight gain or the incidence of excessive weight or obesity. Some authors have found that steroids² and cyclosporine⁵ contribute to the genesis of post-LTx excessive weight. Although immunosuppressive drugs

are frequently blamed for excessive weight gain after the operation, this association is not clear.^{3,12} Although no association was observed between the use of steroids and weight gain, the greater weight gain was observed in the first year of operation. In this period, patients usually receive the highest doses of immunosuppressive drugs. It is also possible that in this period due to the large number of medical consultations, examinations and care, they have reduced daily energy expenditure and increased food intake.

Limitations of this study could have affected the results. The small sample size may have contributed to a type two error in statistical analyses. Also, the retrospective review nature of this paper and some data obtained by patients' information could have impacted the outcomes observed.

In conclusion, patients undergoing LTx lose weight while they are ill and recover it within one year after surgery. The weight gain is progressive; up to three years after LTx, more than half of the patients are overweight or obese. Weight gain and incidence of excessive weight are related to many potential modifiable risk factors. Thus, patients, especially those who were overweight or obese prior to liver disease, older, have stopped smoking, report a family history of overweight and are married, should be encouraged to follow rehabilitation programs to prevent excessive weight gain after LTx. Interdisciplinary teams must be engaged in advising lifestyle modifications, such as incentives to increase physical activity levels and proper nutritional interventions. The latter should be offered early to

patients who undergo LTx to prevent excessive weight gain and other co-morbidities.

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