# Nutrición Hospitalaria

## Original

# Incidence and risk factors for diabetes, hypertension and obesity after liver transplantation

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## Abstract

*Aim:* Metabolic disorders are widely described in patients after liver transplantation (LTx).

**Material and methods:** Arterial hypertension, diabetes mellitus and obesity incidence and risk factors were assessed in 144 post-LTx patients at least one year after transplantation (59% male; median age 54 y; median time since transplantation 4 y). Risk factors were assessed using logistic regression analysis according to demographic, socioeconomic, lifestyle, clinical, anthropometric and dietetic variables.

**Results:** The incidence of hypertension was 18.9%; diabetes, 14.0% and obesity, 15.9%. Risk factors for the incidence of hypertension were abdominal obesity (OR: 2.36; CI: 1.02-5.43), family history of hypertension (OR: 2.75; CI: 1.06-7.19) and cyclosporine use (OR: 3.92; CI: 1.05-14.70). Risk factor for incidence of diabetes were greater fasting glucose levels (mg/dL) pre-LTx (OR: 1.04; CI: 1.01-1.06) and on the diagnosis of alcoholic cirrhosis as an indication of LTx (OR: 2.54; CI: 0.84-7.72). The incidence of obesity after LTx was related to lower milk consumption (mL) (OR: 1.01; CI: 1.001-1.01; P < 0.05), greater donor BMI (kg/m²) (OR: 1.34; CI: 1.04-1.74; P < 0.05), greater BMI prior to liver disease (kg/m²) (OR: 1.79; CI: 1.36-2.36; P < 0.01) and a per capita income twice the minimum wage (OR: 5.71; CI: 4.51-6.86; P < 0.05).

*Conclusion:* LTx was associated with significantly increased rates of hypertension, diabetes and obesity. Furthermore, the incidences of these disorders were related to immunosuppressive therapy and have risk factors that are common in the general population.

(*Nutr Hosp.* 2013;28:643-648)

**DOI:10.3305/nh.2013.28.3.6193**

Key words: *Liver transplantation. Arterial hypertension. Diabetes mellitus. Obesity.*

## INCIDENCIA Y FACTORES DE RIESGO PARA LA DIABETES, LA HIPERTENSIÓN Y LA OBESIDAD DESPUÉS DEL TRASPLANTE HEPÁTICO

**Resumen**

*Objetivo:* Los trastornos metabólicos han sido ampliamente descritos en los pacientes sometidos al transplante hepático (TH).

*Material y métodos:* La incidencia de hipertensión arterial, diabetes mellitus y obesidad además de los factores de riesgo se evaluaron en 144 pacientes post-TH al menos un año después del trasplante (59% hombres, edad promedio 54 años, mediana del tiempo desde el trasplante 4 años). Los factores de riesgo se evaluaron mediante análisis de regresión logística de acuerdo con variables demográficas, socioeconómicas, estilo de vida, así como variables clínicas, antropométricas y dietéticas.

*Resultados:* La incidencia de hipertensión fue del 18,9%, la diabetes, el 14,0% y la obesidad, el 15,9%. Los factores de riesgo para la incidencia de la hipertensión fueron la obesidad abdominal (OR: 2,36, IC: 1,02-5,43, p < 0,05), los antecedentes familiares de hipertensión arterial (OR: 2,75, IC: 1,06-7,19, p < 0,05) y el uso de la ciclosporina (OR: 3,92, IC: 1,05-14,70, p < 0,05). Los factores de riesgo para la incidencia de diabetes fueron niveles más altos de glucosa en ayuno (mg/dL) pre-TH (OR: 1,04, IC: 1,01-1,06, p < 0,05) y el diagnóstico de cirrosis alcohólica como indicación de TH (OR: 2,54, IC: 0,84-7,72, p < 0,05). La incidencia de obesidad después del TH se relacionó con el bajo consumo de la leche (mL) (OR: 1,01, IC: 1,001-10,01, p < 0,05), donante con IMC más grande (kg/m²) (OR: 1,34, IC: 1,04-1,74; p < 0,05), mayor índice de masa corporal antes de la enfermedad hepática (kg/m²) (OR: 1,79, IC: 1,36-2,36, p < 0,01) y ingreso per cápita dos veces el sueldo mínimo (OR: 5,71, IC: 4,51-6,86, p < 0,05).

*Conclusión:* El TH se asoció con tasas significativamente más altas de hipertensión, diabetes y obesidad. La incidencia de estos trastornos se relacionó con la terapia inmunosupresora y otros factores de riesgo que comunes en la población general.

(*Nutr Hosp.* 2013;28:643-648)

**DOI:10.3305/nh.2013.28.3.6193**

Palabras clave: *Transplante hepático. Hipertensión arterial. Diabetes mellitus. Obesidad.*

## Introduction

Survival rates after liver transplantation have reached 85% at five years post-transplant[1] and as high as 56% at 20 years post-transplant[2] in the two last decades. However, the improved survival of patients following liver transplantation (LTx) has been accompanied by an increased prevalence and incidence of chronic diseases over that of the general population.[3]

Although obesity, hypertension and diabetes have been widely described as occurring post-LTx,[4] research to better define the predictors of these diseases is still of paramount importance to identify vulnerable groups and to develop interdisciplinary strategies for prevention and treatment. The aim of this study was to identify the incidence, prevalence and the predictors of arterial hypertension, diabetes mellitus and obesity after LTx.

## Materials and methods

This was a retrospective study on the incidence, prevalence and risk factors for arterial hypertension, diabetes mellitus and obesity among liver transplant recipients from the Alfa Institute of Gastroenterology-Transplant Outpatient Clinic at the Universidade Federal de Minas Gerais in Brazil. Data from patients who underwent liver transplantation between March of 2008 and October of 2008 and were at least 18 years old were retrospectively accessed. Patients who became pregnant, developed ascites or had their transplant less than one year before the evaluation were excluded. The prevalence of these disorders was assessed before transplantation (for diabetes mellitus and arterial hypertension), at the first outpatient appointment post-transplantation (for obesity) and at the time of the final evaluation.

The presence of diabetes mellitus was evaluated by medical diagnosis from medical records and/or by fasting glucose levels above 126 mg/dL that were recorded at least twice.[5] The presence of arterial hypertension was evaluated by medical diagnosis from medical records and/or by arterial systolic blood pressure > 140 mmHg and/or by arterial diastolic blood pressure > 90 mmHg, which were registered at least twice.[6] Obesity was defined as a body mass index (BMI) ≥ 30 kg/m²,[7] Patients were interviewed once to assess potential risk factors for the evaluated disorders according to demographic, socioeconomic, lifestyle, clinical, anthropometric and dietetic variables. This study was approved by the Ethics Committee of the Federal University of Minas Gerais (protocol number ETIC 44 /08).

Demographic and socioeconomic data were collected for age, sex, skin color, marital status, paid professional activity (unemployment and retirement), schooling and income. Lifestyle variables included self-reported hours of sleep per night, smoking or prior smoking and physical activity levels. Patients were asked about their daily activities and their responses were transformed into a corresponding MET (Metabolic Equivalent Energy).[8] These corresponding MET levels were multiplied by the time spent performing these activities, and the results were added together and divided by 24 hours. This value was categorized according to activity level (< 1.3: sedentary; 1.3-1.5: less active; 1.5-1.8: active; > 1.9: very active).[9] The clinical data collected included the indication for patient LTx; donor data (sex, age, BMI); length of time on steroid treatment following LTx; cumulative steroid dose after LTx; tacrolimus or cyclosporine use; arterial hypertension or blood glucose ≥ 100 mg/dL or diabetes mellitus prior to LTx; and a family history of arterial hypertension, diabetes mellitus, excessive weight or cardiovascular disease. Patients were asked about their average body weight before liver disease and were weighed at their first outpatient appointment after LTx.

Dietetic data were based on patient diet history, and the assessed food intake was classified by nutrient and food group using Microsoft Excel software (Microsoft Corp., Redmond, WA) and the table of food composition created by Philippi et al.[10] The nutrients assessed were calories; carbohydrates; proteins; total fat; saturated fat; monounsaturated fat; polyunsaturated fat; cholesterol; total fiber; vitamins A, C, D and E; thiamin; riboflavin; niacin; pantothenic acid; vitamin $B_6$; folic acid; vitamin $B_{12}$; calcium; iron; magnesium; potassium; sodium; and zinc. Food intake was also evaluated by the following food groups or types: cereals, bread, pasta and tubers (g); vegetables (g); fruit (g); milk (mL); yogurt (g); cheese (g); beans (g); meat, poultry, fish and eggs (g); sweet beverages (mL); sugar and sweets (g); and fats and oils (g).

Statistical analyses were performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL). Numeric variables were presented as the median and interquartile interval when they did not follow the normal distribution (by Kolmogorov-Smirnov test) or were presented as the average and standard deviation. Categorical variables were presented as percentages. The prevalence of hypertension, diabetes and obesity before and after LTx was compared using the McNemar test. Risk factors for the incidence of diabetes, hypertension and obesity were determined using multiple linear regression after using a univariate analysis (Qui-Square or Fisher test; T Student test or Mann-Whiney). Variables that had p values < 0.2 in the univariate analysis were included in the logistic regression analysis, which was performed in a stepwise, backwards method. Model adjustment was checked using the Hosmer and Lemeshow test (p > 0.05). P values < 0.05 were considered to be statistically significant.

## Results

There were 144 patients (59% male, median age 54 y, age range 21 to 75 y) who had a median time since

**Table I**

*Demographic, socioeconomic, clinical and anthropometric characteristics of patients who underwent liver transplantation*

| Categorical parameters % (n) | | Numerical parameters Median (interquartile interval)/Average ± standard deviation | | | |
|---|---|---|---|---|---|
| Skin color | | Income (per capita, U$) | 500 (300-1,000) | Riboflavin (mg) | 1.3 (0.9-1.6) |
| White | 67.3 (97) | Schooling (years) | 11 (8-16) | Niacin (mg) | 18.1 (13.5-23.6) |
| Brown/black | 32.7 (47) | Sleeping time per night (hours) | 7.7 ± 1.3 | Pantothenic acid (mg) | 3.1 (2.6-4.4) |
| Married | 72.2 (104) | Physical activity level (MET/24 h) | 1.35 ± 0.2 | Vitamin B6 (mg) | 1.5 (1.2-2.0) |
| Unemployed/retired | 43.1 (62) | Donor's age (years) | 26 (20-43) | Folic acid (mcg) | 180.8 (131.9-250.4) |
| Smokers | 10.6 (15) | Donor BMI (kg/m²) | 23.4 (21.8-25.4) | Vitamin B12 (mcg) | 3.5 (1.9-5.4) |
| Former smokers | 40.2 (51) | Length of steroid use (months) | 5 (3-18.5) | Calcium (mg) | 496 (357.0-683.7) |
| Income > 1 min. wage | 47.9 (69) | Cumulative steroid dose (g) | 2.36 (1.57-7.15) | Iron (mg) | 13.0 (9.5-17.2) |
| Income > 2 min. wage | 31.3 (45) | Body mass index (kg/m²) | 26.6 ± 5.4 | Magnesium (mg) | 207.9 (170.9-267.0) |
| Physical activity level | | Waist circumference (cm) | 94.6 ± 15.0 | Potassium (mg) | 2,170.4 (1,819.9-2,896.2) |
| Active | 6.9 (10) | Calories (kcal) | 1,806 (1,451-2,288) | Sodium (mg) | 2,169.4 (1,546.0-2,744.4) |
| Low active level | 30.6 (44) | Carbohydrates (g) | 232.5 (181.1-290.9) | Zinc (mg) | 8.9 (6.4-14.4) |
| Sedentary | 62.5 (90) | Proteins (g) | 66.1 (54.8-87.4) | Food groups | |
| Tacrolimus use | 87.5 (126) | Fat (g) | 61.3 (45.3-85.4) | Cereals, bread, etc. (g) | 379.2 (255.0-550.0) |
| Cyclosporine use | 12.5 (18) | Saturated fat (g) | 18.5 (12.6-25.0) | Vegetables (g) | 104.0 (65-200.0) |
| Donor male sex | 68.5 (98) | Monounsaturated fat (g) | 15.6 (11.6-23.3) | Fruit (g) | 123.4 (45-248.3) |
| Donor overweight | 26.7 (31) | Polyunsaturated fat (g) | 18.0 (11.7-26.2) | Milk (mL) | 125.0 (0-200.0) |
| Donor obesity | 3.4 (4) | Cholesterol (mg) | 168.1 (124.2-259.2) | Cheese (g) | 10.0 (0-15.0) |
| Familiar history of | | Fiber (g) | 16.5 (12.0-23.3) | Yogurt (g) | 0.0 (0.0-0.0) |
| Hypertension | 70.4 (100) | Vitamin A (RE) | 870.6 (423.1-1,377.1) | Beans (g) | 120.0 (60.0-200.0) |
| Diabetes mellitus | 50.0 (71) | Vitamin C (mg) | 74.9 (49.2-139.8) | Meat, poultry, etc. (g) | 120.0 (91.2-185.4) |
| Overweight | 62.7 (89) | Vitamin D (mcg) | 1.4 (0.7-3.0) | Sweet beverages (mL) | 154.0 (0-385.0) |
| Cardiovascular disease | 60.6 (86) | Vitamin E (mg) | 17.2 (10.9-23.4) | Sugar and sweet (g) | 20.0 (0-30.0) |
| Abdominal obesity | 42.7 (61) | Thiamine (mg) | 1.5 (1.2-1.9) | Fat and oil (g) | 19.0 (8.0-28.0) |

transplantation of 4 y (range of 13 months to 14 y). The most common reasons for transplantation were liver cirrhosis due to hepatitis C virus (31.3%; n = 45), alcohol abuse (29.9%; n = 43), cryptogenic cirrhosis (12.5%; n = 18), autoimmune cirrhosis (12.5%; n = 18) and cirrhosis with hepatocellular carcinoma (5.6%; n = 8). Additional reasons for transplantation were found in 21.5% of cases (n = 31). The general characteristics of the patients are depicted in table I.

The incidence of hypertension was 18.9%, that of diabetes mellitus was 14.0% and that of obesity was 15.9%. The prevalences of these disorders before (for hypertension and diabetes) or at the first outpatient appointment after LTx (for obesity) and at the time of evaluation were significantly different ($p < 0.01$; McNemar test) and are shown in figure 1. Independent predictors for the incidence of hypertension, diabetes and obesity are shown in table II.

## Discussion

Increased incidences of metabolic disorders are widely described in patients after liver transplantation. The use of immunosuppressive agents is the most

common explanation for these observations.[11] In the present study, the use of cyclosporine or steroids was also considered to be a risk factor for the incidence of hypertension and diabetes.

The most common disorder was arterial hypertension, as it had an incidence of 18.9% and a prevalence of 40.9%. An increased prevalence (up to 77%) and incidence (36% to 69%) of hypertension has been described in LTx recipients.[12-14] By comparison, the prevalence of hypertension in an aged-matched Brazilian population is 32.5%.[15] The incidence of hypertension was associated with cyclosporine use in our study, which is in accordance with other studies.[16-17] This immunosuppressant agent is reported as being more hypertensive than tacrolimus, although both can cause vasoconstriction and nephrotoxicity.[18] Patients who became hypertensive had more familial cases of hypertension and had greater abdominal obesity, which indicates that the incidence of hypertension in this population is controlled by similar risk factors as the general population.[15]

Diabetes mellitus was observed in 20.7% of liver recipients, and its incidence was 14.0%. This incidence of diabetes was similar to that described by Stegall et al.[14] (13%), but other studies have found incidence rates
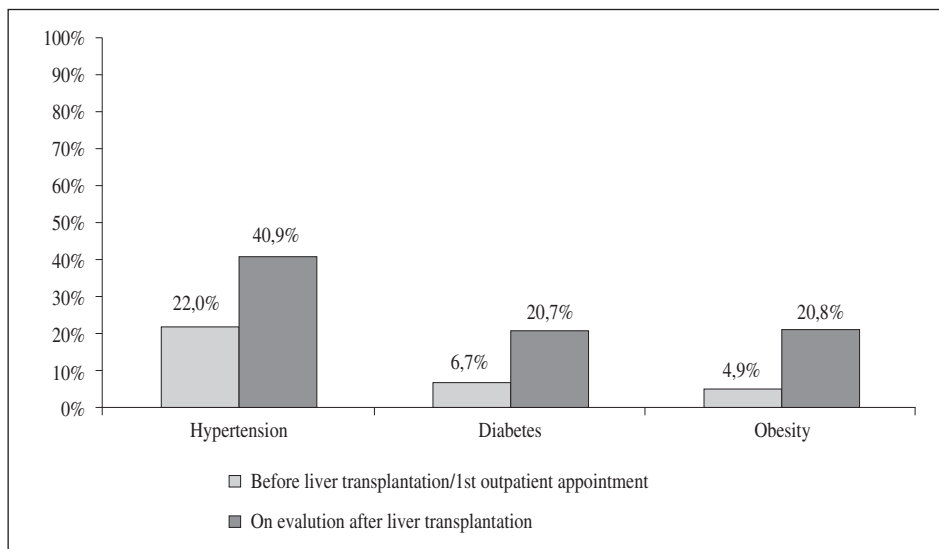
Fig. 1.—*Prevalence of arterial hypertension, diabetes mellitus and obesity before and after liver transplantation.*

**Table II**
*Predictors of arterial hypertension, diabetes mellitus and obesity incidence after liver transplantation*

| Risk factors for aterial hypertension incidence arter LTc (Hosmer Lemeshow test = 0.92) | OR | CI |
|---|---|---|
| Abdominal obesity | 2.36[a] | 1.02-5.43 |
| Family history of arterial hypertension | 2.75[a] | 1.06-7.19 |
| Cyclosporine use | 3.92[a] | 1.05-14.70 |
| *Risk factors for diabetes mellitus incidence after LTx (Hosmer Lemeshow test = 0.54)* | OR | CI |
| Greater fasting glucose pre-LTx (mg/dL) | 1.04[a] | 1.01-1.07 |
| Greater length of time on steroid use following LTx (months) | 1.03[a] | 1.01-1.06 |
| Alcoholic cirrhosis as the indication for liver transplantation | 2.54[a] | 0.84-7.72 |
| *Risk factors for obesity incidence after LTx (Hosmer Lemeshow test = 0.32)* | OR | CI |
| Lower milk consumption (mL) | 1.01[a] | 1.001-1.01 |
| Greater donor BMI (kg/m$^2$) | 1.34[a] | 1.04-1.74 |
| Greater BMI before liver disease (kg/m$^2$) | 1.79[b] | 1.36-2.36 |
| Income per capita ≥ 2 monthly minimum wage | 5.71[a] | 1.36-2.36 |

Multiple logistic regression; [a] $p < 0.05$; [b] $p < 0.01$.

as high as 38%.[19] By comparison, the prevalence of diabetes in the Brazilian population is no greater than 8%.[20] The length of steroid treatment following LTx was found to be a risk factor for the incidence of diabetes. For each additional month on steroid treatment, the likelihood of a transplant patient becoming diabetic increased 1.03 times. For each additional 10 months, this probability was found to increase by 10.3 times. Glucose intolerance is a well established side effect of corticosteroid therapy[21] and can induce insulin resistance and enhance hepatic gluconeogenesis.[22] Although many patients present with diabetes in the early post-operative period, the prevalence of diabetes decreases with tapering doses and discontinuation of immunosuppressive drugs.[23] In our study, all patients had transplants more than one year before analysis, and the amount of time since transplantation was not asso-

ciated with the incidence of diabetes. Greater fasting levels of glucose prior to liver transplantation were predictive of diabetes onset after treatment. Thus, it can be inferred that these patients had an increased risk of developing diabetes before the LTx. In discordance to other studies, older age,[19] obesity[24] and family history of diabetes[24] were not considered to be risk factors for the incidence of diabetes in the present study. Although infection with the hepatitis C virus is the primary etiology of liver disease associated with the incidence of diabetes after transplant,[19] we found that the only cause of liver disease related to this affection was previous alcohol abuse. Maintenance of this variable in the final model of diabetes incidence was important for better adjustment of the model (Hosmer and Lemeshow test = 0.54). Moreover, although cirrhosis resulting from alcohol abuse has been weakly associated with the

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incidence of diabetes (p = 0.10), this etiology has been associated previously with higher blood glucose levels[25] and insulin resistance or metabolic syndrome.[26-28]

Obesity affects 14.7% of the adult population in Brazil,[29] which is lower than that found in the current study (20.8%). At the first outpatient appointment after liver transplantation, 15.9% of patients were obese. This incidence is similar to that observed during the second and third years after transplant (16% to 18%).[30-31] Although this incidence seems high, obesity affected 16% of the patients before the development of liver disease. Malnutrition is common in patients waiting for a LTx,[32] and this leads to decreased fat and muscle mass. Following transplantation, patients gain more weight than is healthy,[31,33] which increases the prevalence of obesity after the operation. Having a greater body mass index, which is a risk factor for obesity and overweightness, prior to the development of liver disease is also associated with these conditions after LTx.[16,30-31] A larger donor BMI was also found to be a risk factor for the incidence of obesity, and this association has previously been documented by Everhart et al.[30] Although some have hypothesized that changes in body composition after LTx may be the result of a failure to monitor energy intake by the brain-liver axis,[34] the association between donor and recipient BMI could be due to the need for compatible sizing, as a graft from a heavier donor only matches a heavier recipient.[26] Lower milk consumption and a greater per capita income (≥ 2 minimum monthly salaries) were present in the final logistic regression model for obesity incidence following LTx. An increased likelihood (10.1 times) for the development of obesity was found for every 100 mL of reduced milk intake, while other variables remained constant. Although reduced milk, dairy and calcium intake have recently been associated with weight gain and obesity in the general population,[35-36] we must emphasize that these data cannot be assumed to represent a risk factor for obesity incidence due to the cross-sectional nature of the dietary data collection. These data are frequently representative of the current rather than chronic dietary intake. The effect of per capita income on obesity and weight gain in the general population is still controversial, and this study was the first to evaluate this variable as a predictor of obesity incidence in the post-liver transplant population. Some studies have shown low income to increase obesity prevalence and weight gain,[37] while others have shown the opposite effect in the general population.[38]

Our data confirm the high incidence and prevalence of arterial hypertension, diabetes mellitus and obesity after liver transplantation. In transplant patients, the incidence of these disorders was related to the immunosuppressant regimen (for hypertension and diabetes), higher blood fasting glucose levels pre-LTx, greater BMI prior to liver disease, 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, such as abdominal obesity, a familial history of hypertension, decreased milk intake and a greater per capita income, were also found to be risk factors for transplant patients. Because some of these variables are capable of modification, interdisciplinary teams should aim to prevent hypertension, diabetes and obesity in transplant patients by promoting life style changes and better managing immunosuppression, especially in groups with pre-existing risk factors.

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