Frequency of Thyroid Dysfunction in Patients With Diabetes Mellitus Before and After Liver Transplantation

A. Moura Neto[a,*], T.G. Bovi[a], C.M. Righetto[a], A.R. Fiore[a], L.T. Lot[b], S.R. Perales[b], E.C. de Ataide[b], and I.F.S.F. Boin[b]

[a]Discipline of Endocrinology, Internal Medicine Department, Faculty of Medical Sciences, University of Campinas, Campinas, Sao Paulo, Brazil; and the [b]Surgery Department, Faculty of Medical Sciences, University of Campinas, Campinas, Sao Paulo, Brazil

ABSTRACT

Background. There is mutual influence between the liver and thyroid hormone metabolism. Patients with diabetes mellitus (DM) also have an increased prevalence of thyroid disorders (TDs). The objectives of this study were to evaluate the frequency of TD before and after liver transplantation (LT) in a population of patients with DM as a whole and when categorized by sex.

Materials and Methods. This was a retrospective study involving interview and medical record analysis of 46 consecutive patients followed at the diabetes mellitus and liver transplantation unit of a tertiary university hospital.

Results. Of all patients, 76.1% were men with a median age of 60 years old (interquartile range: 56 to 65 years) and time since LT of 5 years (range, 0.6 to 9 years). Hypertension, hypercholesterolemia, hypertriglyceridemia, alcoholism, and smoking were present in 47.8%, 34.8%, 23.9%, 34.8%, and 30.4% of the patients, respectively. The most frequent immunosuppressant in use was tacrolimus (71.1%). TD was present in 4.3% and 13% before and after LT, respectively ($P = .058$). In women and men, these frequencies were 9.1% and 18.2% ($P = .563$), and 2.9% and 11.8% ($P = .045$), respectively.

Conclusions. Frequency of TD was high both before and after LT. After transplantation, prevalence of TD increased in men and differences between males and females almost disappeared. Further studies are needed to assess if screening for TD before and after LT in patients with DM might be beneficial, especially in men.

THERE is a mutual influence between the liver and thyroid hormone (TH) metabolism. TH dysfunctions can compromise liver processes such as cholesterol synthesis and metabolism [1]. On the other hand, the liver is one of the main organs responsible for peripheral TH metabolism. Advanced liver disease can present with alterations in the laboratorial profile of TH, the nonthyroidal illness syndrome, which sometimes is indistinguishable from primary diseases of the thyroid [2]. Immunosuppressants that are commonly used after liver transplantation (LT) have been linked to increased incidence of autoimmune diseases, which in turn are the main cause of thyroid dysfunctions (TDs), in the form of Hashimoto's thyroiditis and Graves' disease [3]. Autoimmune thyroid disorders are much more common in female patients. Autoimmune diseases of the liver also increase the risk for thyroid disorders [4].

Moreover, patients with diabetes mellitus (DM) have an increased frequency of TD compared to the healthy population [5]. Hypo- or hyperthyroidism can influence the recover and morbidity of patients after LT, while also impacting on the metabolic control of DM [6].

Studies evaluating the influence of LT on the frequency of TDs, especially in those patients with DM, are lacking. Therefore, the aims of this study were to assess the frequency of TD (primary hypo- or hyperthyroidism) in

*Address correspondence to Arnaldo Moura Neto, MD, PhD, Discipline of Endocrinology, Internal Medicine Department, University of Campinas, UNICAMP, 126, Tessalia Vieira de Camargo Street, Barao Geraldo, 13084-971, Campinas, Sao Paulo, Brazil. E-mail: arnaldo.mouraneto@gmail.com

0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.02.043

patients with DM before and after LT as a whole and when categorized by sex.

PATIENTS AND METHODS

This was an observational, retrospective study involving 46 consecutive patients evaluated at the Diabetes Mellitus and Liver Transplantation Unit of a tertiary university hospital (Hospital das Clinicas, University of Campinas). Data were reviewed from medical records of all patients and were collected in April 2016. All patients referred for DM evaluation were screened for TDs with serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4). All had been screened for TD before LT, as part of routine pretransplantation laboratorial screening.

Data analyzed included clinical and epidemiological characteristics such as sex, age, etiology of cirrhosis, time since LT and diagnosis of DM, body mass index (BMI), frequency of hypertension, hypercholesterolemia and hypertriglyceridemia, smoking and alcohol abuse, and immunosuppressants used. The last TSH and fT4 before LT as well as the latest measurements after the procedure were used and we recorded the proportions of patients with abnormal serum TSH and/or fT4 values. TSH and FT4 were measured by electrochemiluminescence (Roche Hitachi-Elecsys Cobas, São Paulo, Brazil) using reference values TSH 0.45–4.5 IU/L; FT4: 11.6–23.2 pmol/L.

This study followed the ethical precincts of the Declaration of Helsinki and was approved by the University Ethics in Research Committee.

Statistical Methods

Data were described as median and interquartile ranges (IQRs) for continuous variables and frequency and percentages for categorical variables. Comparisons of the frequencies of TD between pre- and post-transplantation periods were performed using the McNemar χ^2 test, corrected as described by Newcombe [7]. Analyses were performed with SPSS v20.0 for Mac OS (DMSS Corp., São Paulo, Brazil) and a significance level of 5% was adopted.

RESULTS

Clinical and laboratorial data of all patients are summarized in Tables 1 and 2. Of all patients, 76.1% were men with a median age of 60 years old (IQR: 56 to 65 years) and time since LT of 5 years (range, 0.6 to 9 years). The most frequent etiology of cirrhosis leading to LT was hepatitis C virus (HCV) infection (69.6%), followed by alcohol abuse (19.6%). Hypertension, hypercholesterolemia, hypertriglyceridemia, alcoholism, and smoking were present in 47.8%, 34.8%, 23.9%, 37.2%, and 32.6% of the patients, respectively. The most frequent immunosuppressants in use were tacrolimus (71.1%) and mycophenolate (48.9%). The median glycosylated hemoglobin (HbA1c) at the time of data recording was 6.5% (range, 5.7% to 7.7%).

The frequencies of TD before and after LT in all patients were 4.3% and 13.3%, respectively ($\chi^2 = 3.571$; $P = .058$). In women, these same frequencies were 9.1% and 18.2%, respectively ($\chi^2 = 0.33$; $P = .563$); and in men these values were 2.9% and 11.8%, respectively ($\chi^2 = 4.0$; $P = .045$).

Table 1. Clinical, Anthropometrical and Laboratorial Characteristics of Patients

Characteristics and Health Status of Patients (N = 46)	%/Median (IQR)
Gender, M/F	76.1/23.9
Age, yrs	60 (56–65)
Time since LT, yrs	5 (0.6–9)
Diagnosis of DM after LT	65.2%
Time of diagnosis of DM after LT, yrs	1.5 (0.5–5.5)
Graft rejection after LT	11.8
Drugs/treatment of diabetes	
Oral drugs	30.4
Insulin	39.1
Oral drugs plus insulin	21.7
Diet alone	8.7
Hepatocellular carcinoma before LT	41.3
Etiology of cirrhosis leading to LT	
Hepatitis C virus	69.6
Alcohol abuse	19.6
Hepatitis B virus infection	4.4
Family history of DM	60.9
Associated diseases	
Hypertension	47.8
Hypercholesterolemia	34.8
Hypertriglyceridemia	23.9
Alcoholism	37.2
Smoking	32.6
Immunosuppressants in use	
Tacrolimus	71.1
Mycophenolate	48.9
BMI, kg/m^2	27.5 (17.1–32.7)
Fasting glucose, mg/dL	112.0 (91.5–157)
Creatinine, mg/dL	1.12 (0.92–1.29)
Total cholesterol, mg/dL	161 (129–182)
HDL-c, mg/dL	42 (34.8–57.3)
LDL-c, mg/dL	88 (66–102)
Triglycerides, mg/dL	121 (89–196)
HbA1c, %	6.5 (5.7–7.7)

Abbreviations: IQR, interquartile range; M, male; F, female; LT, liver transplantation; DM, diabetes mellitus; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol, HbA1c, glycosylated hemoglobin.

DISCUSSION

In this study, TD was diagnosed before LT in a significant proportion of patients, especially in females, with nearly 10% affected compared to 3% in men. This is consistent with the increased prevalence of TD in women in patients with DM and also in the general population [6]. There was a trend toward a significant overall increase in the frequency of TD, with statistical significance only in men.

Liver diseases and DM are associated to abnormalities in serum TH levels, including the total and free forms of triiodothyronine (TT3 and fT3) and thyroxine (TT4 and fT4), as well as the inactive form of TH, reverse T3 (rT3) [2]. The liver plays a central role in conversion of T4 to T3, synthesis of thyroxine binding globulin, T4 uptake and secondary release of T4 and T3 into the bloodstream. Abnormal serum TH is frequent in cases of liver diseases such as cirrhosis, and acute and chronic hepatitis [8–10]. In