Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Alterations in carbohydrate metabolism in cirrhotic patients before and after liver transplant

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ARTICLE INFO

Article history:
Received 1 May 2015
Received in revised form
6 September 2015
Accepted 1 October 2015
Available online 9 October 2015

Keywords:
Diabetes
Carbohydrate metabolism
Liver cirrhosis
Liver transplantation
Insulin resistance

ABSTRACT

Aim: The main objective of this study is to demonstrate whether carbohydrate metabolism alterations identified in patients with advanced cirrhosis show any improvement after liver transplant.

Methods: The study included 86 patients who underwent liver transplant between March 2010 and February 2011. An oral glucose tolerance test was performed before the liver transplant, and 6 and 12 months after. Beta cell function and insulin resistance were also calculated, applying formulae that use basal plasma glycaemia and insulin, and plasma glycaemia and insulin during an oral glucose tolerance test. Risk factors for pre- and post-transplant diabetes were also studied. The diagnosis of diabetes was based on an OGTT.

Results: The proportion of patients with diabetes before transplant, and at month 6 and 12 after transplant were 70.9%, 48.8% and 39.2%, respectively. Compared to baseline, at month 6 the odds ratio of having diabetes was 0.39 (IC 95% [0.21, 0.73]) and at month 12 it was 0.26 (IC 95% [0.14, 0.50]). The composite insulin sensitivity index values at 6 and 12 months were 1.72 units higher (IC 95% [0.84, 2.58]) and 1.58 units higher (IC 95% [0.68, 2.44)] than baseline. A statistically significant association was found between high MELD values and high body mass index, and risk of pre-transplant diabetes ($p = 0.001$ and $p = 0.033$, respectively). Cirrhosis aetiology did not influence the risk of diabetes.

Conclusions: In this study, we were able to ascertain that alterations in carbohydrate metabolism typical of advanced cirrhosis improve after liver transplant. This improvement is mainly due to an improvement in insulin resistance.

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Abbreviations: HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; IR-HOMA, homeostatis model assessment for insulin resistance; ISIc, composite insulin sensitivity index; SecrHOMA, homeostatic model assessment for the beta-cella function; FIP, first insulin release phase; SIP, second insulin release phase; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ADA, American Diabetes Association; MELD, model for end stage liver disease; BMI, body mass index; SD, standard deviation; AUC, area under the curve.

http://dx.doi.org/10.1016/j.diabres.2015.10.002

1. Introduction

Glucose intolerance and diabetes are often observed in liver cirrhotic patients [1,2]. The primary alteration that occurs in cirrhotic patients is insulin peripheral resistance with predominance of postprandial hyperglycaemia. However, liver insulin sensitivity tends to remain unchanged, allowing liver glucose production to remain normal and be suppressed responding to insulin in a similar way to patients without cirrhosis [3]. Therefore, the basal glycaemia is not useful in the diagnosis of diabetes in cirrhotic patients. Neither glycated haemoglobin (HbA1c), nor fructosamine, nor 1,5-anhydroglucitol has proven to be useful for diagnosis of diabetes in cirrhotic patients [4–8]. Therefore, the Gold Standard to study alterations in the metabolism of carbohydrates in cirrhotic patients is the oral glucose tolerance test (OGTT).

It is unclear whether the metabolism of carbohydrates improves after liver transplant. There are two factors that might influence glucose metabolism after liver transplant: the metabolic effects of the immunosuppressive medication and the persistence of pre-transplant metabolic alterations [9–13].

Several studies have shown a high prevalence of glucose intolerance in transplanted patients [14,15], but often these studies have not tested diabetes prevalence before transplant using the OGTT; hence, these studies are inconclusive as to whether there is an improvement or worsening after transplant. Studies that used the OGTT before and after liver transplant have generally used a low number of participants and the results are inconclusive. However, these studies seem to show that the peripheral insulin sensitivity improves after transplant [9,16,17].

The main objective is to study whether carbohydrate metabolism alterations identified in cirrhotic patients awaiting liver transplant show any improvement after transplant. The prevalence of diabetes before and after transplant was studied using the OGTT. Additional objectives were to determine changes to insulin resistance and insulin secretion, and to study risk factors to have pre- and post-transplant diabetes.

2. Patients and methods

2.1. Participants

This was a prospective and unicentric study. The use of the OGTT was recommended to screen for diabetes in patients who are on the hospital's liver transplantation waiting list. The study included patients who underwent liver transplant between March 2010 and February 2011. Excluded from this study were: patients who had been recipients of other solid organ grafts (5), patients undergoing simultaneous transplant of another organ (3), and patients undergoing transplant due to fulminant liver failure (8). Eleven patients did not give consent and therefore were excluded from the study. In all, 86 patients participated in this study. Patients with known diabetes before liver transplant did not undergo an OGTT.

The OGTT was repeated 6 and 12 months after liver transplant. Patients who showed basal glycaemia greater than 126 mg/dl or required anti-diabetic treatment were classified as patients with diabetes and they did not undergo an OGTT.

Patients with known pre-transplant diabetes did not undergo OGTT and these patients were treated with steroid-free immunosuppression, according to the protocol used in our hospital.

The hospital's ethics commission approved the study and all patients gave their informed consent for their participation.

2.2. Procedures

During 72 h prior to the OGTT, all patients were on a normocaloric diet with carbohydrate intake greater than 150 g/day and maintained a normal physical activity. The OGTT was done after an overnight fast for at least 12 h. Venous blood samples for determination of plasma glucose and insulin were taken from participants immediately before and at 30, 60, 90 and 120 min after oral intake of 75 g glucose. Plasma glucose was measured using enzymatic methods. Insulin was measured using immunoassay. The area under the glycaemia curve was calculated by the trapezoidal method. Insulin resistance was estimated using the following formulae: the HOMA index for insulin resistance (IR-HOMA) [18] and the composite insulin sensitivity index (ISIc) [19]. Insulin secretion was estimated using the following formulae: the HOMA index for the beta-cell function (SecrHOMA) [18], first insulin release phase (FIP) [20] and the second insulin release phase (SIP) [20]. IR-HOMA was calculated as follows: IR-HOMA = [basal insulin (pmol/L) × basal glucose (mmol/L)]/135. ISIc was calculated as follows:

$$\mathrm{ISIc} = 10000 \Big/ \sqrt{\begin{array}{l}[\text{basal glucose (mg/dl)} \times \\ \text{basal insulin } (\mu\text{U/ml})] \times \\ [\text{mean glucose} \times \text{mean insulin during OGTT}]\end{array}}$$

SecrHOMA was calculated as follows: SecrHOMA = [basal insulin basal(pmol/l) × 3.33]/[basal glucose(mmol/l) − 3.5]. FIP was calculated as follows: FIP = [1283 + 1.829 × Insulin in minute 30 (pmol/l)] − [138.7 × glucose in minute 30 (mmol/l) + 3.722 × basal insulin]. SIP was calculated as follows: SIP = [287 + 0.4164 × Insulin in minute 30 (pmol/l)] − [26.07 × glucose in minute 30 (mmol/l) + 0.9226 × basal insulin].

Diabetes was diagnosed according to the American Diabetes Association (ADA) criteria: patients with basal plasma glycaemia equal to, or greater than, 126 mg/dl, glycaemia equal to, or greater than, 200 mg/dl 2 h after the OGTT and patients requiring anti-diabetic treatment. Impaired fasting glucose (IFG) was defined as fasting plasma glucose values of 100–125 mg/dl. Impaired glucose tolerance (IGT) was defined as glucose levels of 140–199 mg/dl 2 h after the OGTT. Patients with either IFG or IGT were classified as having pre-diabetes.

Diabetes prevalence was compared before, at 6 and at 12 months after transplant. Changes in the area under the glucose curve and changes in insulin resistance and secretion were compared in patients who underwent an OGTT.

Pre-transplant risk factors taken into account were: age, gender, body mass index (BMI), model for end stage liver disease (MELD) index [21], hypertension, dyslipidaemia and hepatitis C infection. The following factors were studied as risk factors for the occurrence of diabetes 12 months after