Pharmacological Research 98 (2015) 52–59

Contents lists available at ScienceDirect

Pharmacological Research

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

Hepatic steatosis after islet transplantation: Can ultrasound predict the clinical outcome? A longitudinal study in 108 patients

Massimo Venturini[a,*], Paola Maffi[b], Giulia Querques[c], Giulia Agostini[a], Lorenzo Piemonti[b], Sandro Sironi[c], Francesco De Cobelli[a,d], Paolo Fiorina[e], Antonio Secchi[b,d], Alessandro Del Maschio[a,d]

[a] Department of Radiology, Scientific Institute H S. Raffaele, Milan, Italy
[b] Department of Internal Medicine, Transplant Unit, Scientific Institute H S. Raffaele, Milan, Italy
[c] Department of Radiology, Milano-Bicocca University, Monza, Italy
[d] Vita-Salute S. Raffaele University, Milan, Italy
[e] Transplantation Research Center, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 3 February 2015
Received in revised form 4 March 2015
Accepted 4 March 2015
Available online 23 March 2015

Keywords:
Type 1 diabetes
Islet transplantation
Ultrasound
Hepatic steatosis
Pancreatogenic diabetes
β-Score

ABSTRACT

Percutaneous intra-portal islet transplantation (PIPIT) is a less invasive, safer, and repeatable therapeutic option for brittle type 1 diabetes, compared to surgical pancreas transplantation. Hepatic steatosis is a consequence of the islet engraftment but it is curiously present in a limited number of patients and its meaning is controversial. The aims of this study were to assess hepatic steatosis at ultrasound (US) after PIPIT investigating its relationship with graft function and its role in predicting the clinical outcome.

From 1996 to 2012, 108 patients underwent PIPIT: 83 type-1 diabetic patients underwent allo-transplantation, 25 auto-transplantation. US was performed at baseline, 6, 12, and 24 months, recording steatosis prevalence, first detection, duration, and distribution. Contemporaneously, steatotic and non-steatotic patients were compared for the following parameters: infused islet mass, insulin independence rate, β-score, C-peptide, glycated hemoglobin, exogenous insulin requirement, and fasting plasma glucose.

Steatosis at US was detected in 21/108 patients, 20/83 allo-transplanted and 1/25 auto-transplanted, mostly at 6 and 12 months. Infused islet mass was significantly higher in steatotic than non-steatotic patients (IE/kg: $S = 10.822$; NS = 6138; $p = 0.001$). Metabolically, steatotic patients had worse basal conditions, but better islet function when steatosis was first detected, after which progressive islet exhaustion, along with steatosis disappearance, was observed. Conversely, in non-steatotic patients these parameters remained stable in time. Number of re-transplantations was significantly higher in steatotic than in non-steatotic patients (1.8 vs 1.1; $p = 0.001$).

Steatosis at US seems to be related to the islet mass and local overworking activity. It precedes metabolic alterations and can predict graft dysfunction addressing to therapeutic decisions before islet exhaustion. If steatosis does not appear, no conclusion can be drawn.

1. Introduction

Percutaneous intra-portal islet transplantation (PIPIT) from cadaveric donors represents a less invasive, safer, and repeatable therapeutic option for type 1 diabetes, compared to surgical pancreas transplantation [1]. Combined kidney–pancreas transplantation is the best solution for patients affected by brittle, long-term type 1 diabetes and chronic renal insufficiency [2]. Since the 1990s, islet after kidney transplantation (IAK) has represented a valid solution to simultaneously cure diabetes [3] and chronic renal failure [4] in case of pancreas unavailability from a deceased donor at the time of the kidney transplant. Islet transplantation alone (ITA) is performed in brittle, short-term type 1 diabetic patients with good renal function to achieve insulin independence or, at least, reduce exogenous insulin requirement, prevent hypoglycemic episodes [5] and diabetic complications [6], improving patients' quality of life [7]. Since 2000, ITA is performed according to the Edmonton protocol based on the infusion of an adequate islet

* Corresponding author at: Department of Radiology, Scientific Institute H S. Raffaele, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 02 26436104; fax: +39 02 26432165.
E-mail address: venturini.massimo@hsr.it (M. Venturini).

http://dx.doi.org/10.1016/j.phrs.2015.03.002
1043-6618/

mass and on a steroid-free immunosuppressive regimen [8]. Islet auto-transplantation is a more recent and successful strategy to prevent pancreatogenic diabetes [9,10] which affects 8–23% of the patients undergoing pancreatectomy, increasing at 40–50% during the follow-up [11]. Islet auto-transplantation avoids prolonged cold ischemia [12] and the diabetogenic effect of immunosuppression, determining a lower rejection rate than allo-transplantation.

Hepatic steatosis is a consequence of the islet engraftment within the liver. It can be determined by functioning islets that cause local insulin production, lipolysis inhibition, lipogenesis stimulation, and subsequent fat development [13]. Previous studies, including small series, found steatosis only in a low percentage of allotransplanted patients at US and/or MRI, providing different interpretations of its relationship with graft function [14–19].

The aims of our longitudinal study were the following: to assess first detection, prevalence, duration, and distribution of hepatic steatosis at US after islet transplantation in 83 allo-transplanted (IAK and ITA) and 25 auto-transplanted patients; to compare steatotic and non-steatotic patients for metabolic parameters of islet function; to identify any relationship between steatosis and graft function; and to establish whether US could be useful in the prediction of the clinical outcome.

2. Materials and methods

2.1. Patient characteristics

IRB approval of our Institution and informed written consent was obtained from all patients.

From 1996 to 2012, 108 patients (51 men/57 women; mean age: 50.8 ± 11.0 years, range: 25–77 years; mean body weight: 64.2 ± 11.5 kg) were consecutively enrolled and submitted to percutaneous intraportal transplantation of pancreatic islets (Table 1). Allo-transplantation was performed in 83 patients (39 men/44 women; mean age: 48.8 ± 9.4 years, range: 27–72 years; mean body weight: 62.0 ± 9.7 kg) and auto-transplantation was performed in 25 patients (12 men/13 women; mean age: 57.6 ± 11.4 years, range: 25–77 years; mean body weight: 70.7 ± 14.1 kg).

2.2. Allo-transplantation

Eighty-three patients affected by brittle type 1 diabetes underwent allo-transplantation. Among these, 33 patients, with a history of long-term diabetes and chronic renal failure, underwent IAK transplantation (15 men/18 women; mean age: 53.3 ± 7.4 years, range: 36–72 years; mean body weight: 60.7 ± 10.9 kg), and 50 patients, affected by short-term diabetes, underwent ITA (24 men/26 women; mean age: 45.8 ± 9.4 years, range: 27–71 years; mean body weight: 62.8 ± 9.1 kg), according to the Edmonton protocol [8]. Exclusion criteria were previous stroke, major amputation, severe dilated cardiomyopathy, and coronary heart disease.

The whole pancreas removed with the duodenum was obtained from a brain-dead multiple organ donor through the North Italian Transplant Organization. A relative of the donor gave written informed consent to organ withdrawal.

Immunosuppressive therapy in IAK patients included induction with metilprednisolone (500 mg in a single intravenous bolus) and antithymocyte globulin (ATG 6 mg/kg for 4–7 days), and maintenance with the same protocol established for the previously transplanted kidney (cyclosporine 100–250 ng/ml, or tacrolimus 4–6 ng/ml + micofenolate mofetil 2 g/day or azathioprine 50–150 mg/day). Immunosuppressive therapy in ITA patients included induction with anti IL-2 receptor antibody and maintenance with sirolimus (10–12 ng/ml) and tacrolimus (4–6 ng/ml).

A second islet infusion was performed when C-peptide secretion was less than 0.5 ng/ml, no improvement in glycated hemoglobin (Hb1Ac) or substantial decrease (more than 50% of preprocedural dose) in exogenous insulin requirement (EIR) were found after transplantation.

2.3. Auto-transplantation

From 2008 to 2012, 25 patients were submitted to auto-transplantation to prevent pancreatogenic diabetes, 24–48 h after total ($n = 16$) or subtotal ($n = 9$) pancreatectomy, consequent to a pancreatic tumor in all patients except one who was affected by painful chronic pancreatitis.

Exclusion criteria were multifocal pancreatic tumor or Multiple Endocrine Neoplasm.

Open or laparoscopic surgery was performed under general anesthesia and included total or extensive left pancreatectomy. The spleen was preserved or removed, as appropriate. If a tumor was the reason for pancreatic resection, one centimeter of the pancreatic remnant proximal to the pancreatic margin was resected and sent for frozen examination to confirm margin negativity. Immunosuppression was obviously not required.

2.4. Islet preparation

The pancreas to be used was stored in University of Wisconsin solution at 4 °C. Pancreatic islets were isolated using an automated procedure and purified by centrifugation with a discontinuous gradient [20]. Islet preparations were considered adequate for transplantation according to the following criteria: sterility, defined as the absence of aerobic and anaerobic bacteria, fungi, and mycoplasma; presence of more than 6000 Islet Equivalents (IE) per kg of body weight (20); purity greater than 20%, assessed with morphometric analyses at optical microscope examination; and islet cell viability, determined with propidium iodide stain.

2.5. Procedure

Islet transplantation was performed 12–48 h after islet isolation in all patients, in an angiographic suite using a combined US and fluoroscopic guidance, under local anaesthesia, using a 4-Fr catheter [21].

About 150 ml of a preparation containing 300,000–800,000 purified islets in suspension was slowly injected (20–30 min) through the catheter. Enoxaparin (6000 IU/day) was administered subcutaneously for 7 days after the procedure.

2.6. US assessment

Exclusion criterion for this study was the detection of either focal or diffuse parenchymal hyperechoic areas at baseline US, suggestive for hepatic steatosis.

Liver US examination (ATL-HDI 3000; ATL-HDI 5000; ATL-IU22, 2–5 and 5–9 MHz transducers, Philips Medical Systems, Bothell, WA, USA) was regularly performed at 6, 12, and 24 months after transplantation to assess liver parenchymal changes with regard to fatty infiltration due to steatosis. Steatosis was evaluated with follow-up US in terms of prevalence, first detection, duration, and distribution.

All examinations focused on echotexture variations and were performed and evaluated by the same radiologist (MV) with more than 20 years of experience blinded to the patients' clinical condition. US was the only imaging technique used for monitoring allotransplanted patients while a triphasic contrast-enhanced MDCT (Brilliance 64, Philips, Best, The Netherlands) was routinely