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BRIEF REPORT

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Insulin independence and normalization of oral glucose tolerance test after islet cell allotransplantation

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Abstract To achieve permanent normoglycemia in patients with type I diabetes, it is necessary to renew the insulin-producing β-cells by transplantation of either a vascularized pancreatic graft or isolated islets of Langerhans. Presently, about 10% of patients with type I diabetes undergoing islet allotransplantation achieve insulin independence; however, glucose intolerance remains in the majority of cases. We report a case of long-term insulin independence after islet allotransplantation in a type I diabetic patient. Three years after islet transplantation, the patient remains insulin-independent with a normal oral glucose tolerance test (OGTT). The patient therefore no longer meets the World Health Organization criteria for the diagnosis of diabetes mellitus and demonstrates that islet transplantation can cure diabetes in type I diabetic patients.

Keywords Type I diabetes · Islet allotransplantation

Abbreviations *OGTT* Oral glucose tolerance test

Introduction

Currently, type I diabetes mellitus is treated with exogenous insulin administration. Intensive insulin therapy can delay the onset and slow down the progression of microvascular complications in these patients [10]. Physiological insulin delivery can only be obtained by substitution of the insulin-producing β-cells. Pancreas transplantation is an established option, but is a major surgical procedure with a significant rate of complications [2, 6, 7]. Transplantation of the isolated insulin-secreting islets of Langerhans is an alternative approach. This procedure is easier and safer than whole-organ transplantation since general anesthesia is not necessary and transplantation is performed by a percutaneous transhepatic injection of Langerhans islets into the portal circulation.

Since 1990, clinical trials of islet transplantation have been carried out in a few centers worldwide. The International Islet Registry included 305 human islet allografts at the end of 1995 (latest update of the International Islet Registry). Insulin independence at 1 year was achieved in only 8% of the patients, with a further 20% demonstrating graft function with normal basal C-peptide levels and improved glycemic regulation [4]. Most of the studied cases of insulin independence showed persistent glucose intolerance [8].

Herein, we report the metabolic outcome in one patient who became insulin-independent 2 months after intraportal islet allotransplantation and who remains insulin-independent 3 years later with a normal oral glucose tolerance test (OGTT) and normal glycosylated hemoglobin.

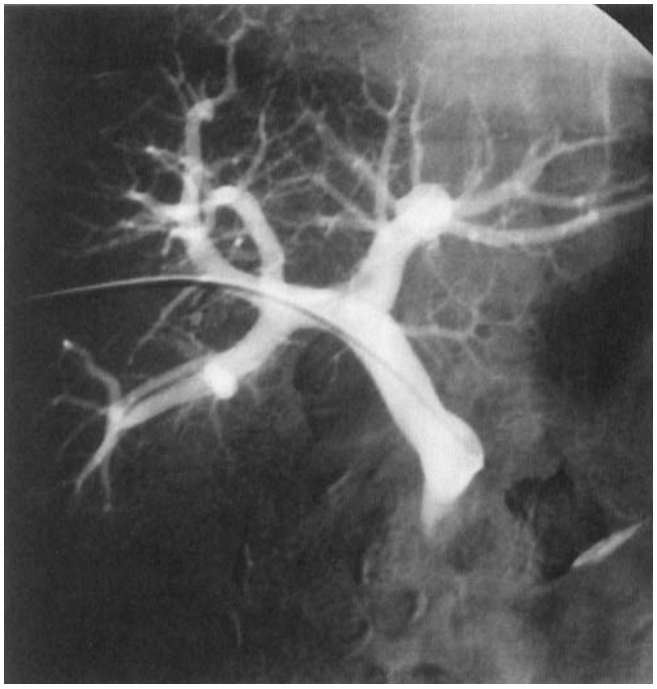

Fig. 1 Transhepatic portography before islet injection; the catheter is placed in the main portal vein

Case report

A 36-year-old woman with a 27-year history of type I diabetes mellitus complicated by proliferative retinopathy, kidney failure, autonomous and peripheral neuropathy, and macrovascular disease received a cadaveric kidney transplant 7 years previously. Because of frequent hypoglycemic events, a whole-organ pancreatic graft was considered, but was contraindicated by the presence of severe iliac vasculopathy. Therefore, transplantation of allogeneic islets was performed by intraportal injection. Before transplantation, basal and stimulated C-peptide levels, measured 6 min after the intravenous injection of glucagon (1 mg), were 0.14 nmol/l and 0.19 nmol/l, respectively (normal range of basal C-peptide: 0.3–1.3 nmol/l). Glycosylated hemoglobin (HbA1c) was constantly between 10% and 12% (normal range: < 6%).

The islets from two cadaveric donors of the same blood group were isolated according to the automated method described by Ricordi et al. [5]. The purification was performed by density-gradient centrifugation on the COBE 2911 cell processor. A total of 106,700 islet equivalents (158,000 total islet number) were obtained from the first pancreas and were maintained in culture overnight. The day after, a second pancreas was processed. After isolation and purification, 421,300 islet equivalents (255,000 total islet number) were obtained. The cells from the two pancreases were pooled for a total of 528,000 islet equivalents, corresponding to 8800 islet equivalents/kg body weight.

Injection of the islets was performed under local anesthesia by a percutaneous transhepatic puncture of the portal vein with a 5.5 F catheter. Confirmation of the portal venous placement of the catheter was made by a hypaque injection prior to injection of the cells (Fig. 1), and 3000 units of heparin were injected intraportally as a precaution to prevent intraportal thrombosis. The islets were pooled and loaded in four 50-ml syringes containing Hanks' solution and were infused into the portal vein over 20 min. One concern was the potential development of portal vein thrombosis and/or portal hypertension as a result of introducing a large cell mass into this low-pressure venous circulation. Portal pressures were taken prior to, during, and after islet transplantation. The portal pressure prior to injection was 5 mmHg and immediately after injection was 20 mmHg. The portal pressure normalized within 15 min after the procedure.

Following islet transplantation, the pre-existing immunosuppression consisting of cyclosporine, prednisone, and azathioprine was temporarily reduced to prevent toxicity on the islets. The cyclosporine trough levels were maintained in the range of 100 μg/l. Antithymocyte globulin (ATGAM, 10 mg/kg i.v.) was administered for the first 10 days. Intensive intravenous insulin therapy was administered postoperatively for 15 days to maintain the serum glucose within the limits of 6–8 mmol/l. Subsequently, subcutaneous insulin was given as required to keep the serum glucose within the same limits. Insulin therapy was gradually reduced, and the desired glucose levels could be maintained without insulin after 2 months. This patient remains insulin-independent 3 years after islet transplantation.

Within 3 months after transplantation, the basal and stimulated C-peptide levels were within normal ranges (0.68 and 1.5 ng/ml, respectively) and HbA1c was 4.8%. C-peptide and HbA1c levels have remained normal throughout the 36 months of follow-up (Fig. 2). An OGTT was performed at 3, 6, 12, 24, and 36 months. At 3 months, the OGTT showed normalization of both serum glucose values and insulin secretory response (4.1, 5.3, 6.9, and 4.9 mmol/l and 2.8, 24.4, 52.4, and 30.4 mU/l at 0, 30, 60, and 120 min, respectively) and these responses remain normal 3 years after transplantation. The kidney allograft function remained stable with a mean serum creatinine level of 125 μmol/l and a creatinine clearance of 55 ml/min.

Discussion

Type I diabetes affects approximately ten million people worldwide, and the number of patients with this disease is predicted to increase to as many as 25 million by 2010 [11]. Presently, type I diabetic patients are initially treated with exogenous insulin, and a small proportion undergo whole-organ pancreas transplantation, usually combined with a kidney transplant. An alternative is the transplantation of islets of Langerhans, which has resulted in insulin independence for up to 6 years. Insulin independence after islet transplantation develops in only 8% of patients at 1 year, and seems to be facilitated if: (i) islets are isolated from pancreases with a preservation time of less than 8 h, (ii) more than 6000 islet equivalents/kg body weight are transplanted, (iii) islets are transplanted into the liver via the portal vein, and (iv) induction immunosuppression comprises anti-T- cell antibodies [9]. However, glucose intolerance remains in most insulin-independent patients [1]. Development of insulin independence and normalization of OGTT has so far only been reported for a single patient by the center in St. Louis, Missouri [3].

In the present report, the patient received a high number of freshly isolated islets from two cadaveric donors (8800 islet equivalents/kg body weight) and, after

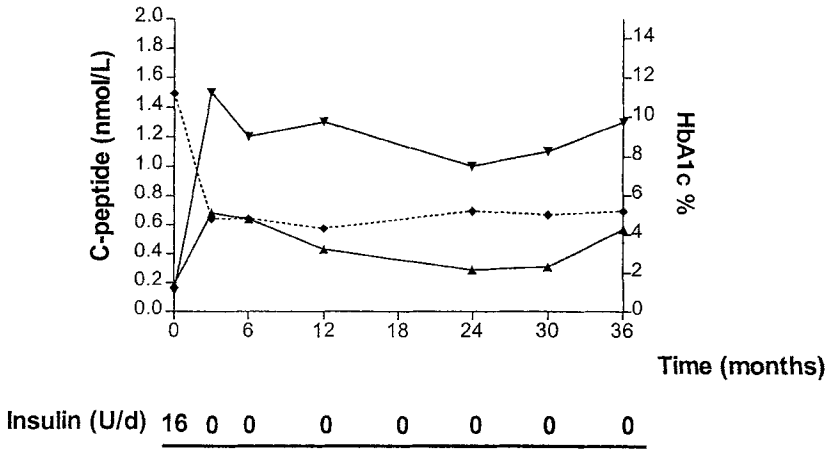

Fig. 2 Basal and stimulated C-peptide levels and HbA1c during the 36 months of follow-up. Within 2 months, the exogenous insulin is stopped with concomitant normalization of C-peptide and HbA1c levels (—▼— stimulated C-peptide, —▲— basal C-peptide, —◆— HbA1c)

transplantation, immunosuppression with a polyclonal anti-T-cell antibody was initiated. We believe that these components were critical factors contributing to the excellent outcome for this patient. Three years later, the patient remains insulin-independent and has normalized her metabolic glucose regulation. Basal and stimulated C-peptide, HbA1c, and OGTT are in the normal ranges. The results of the OGTT indicate that the patient no longer meets the World Health Organization criteria for the diagnosis of diabetes mellitus.

The absence of severe unexpected hypoglycemia has enabled the patient to enjoy a good quality of life. This case demonstrates that type I diabetic patients treated with allogeneic pancreatic islets can achieve long-term insulin independence with normal glucose metabolism.

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