Rapid Publication

Magnetic Resonance–Defined Periportal Steatosis Following Intraportal Islet Transplantation

A Functional Footprint of Islet Graft Survival?

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There is growing interest in more widespread application of isolated islet transplantation for the treatment of type 1 diabetes; however, the sequelae of long-term islet residence within the liver are unknown. We report herein a consequence of intraportal islet transplantation, specifically the development of periportal hepatic steatosis apparently induced by the local secretion of insulin within the liver. *Diabetes* 52:1591–1594, 2003

Provocative success in experimental animals >3 decades ago suggested that isolated islet transplantation might be an ideal therapy for individuals afflicted with type 1 diabetes (1,2). In the ensuing 30 years, >300 human islet transplants were performed but the overall success rate was <10% (3). Some improvement was evident during the final years of the last decade, especially in a series of transplants reported by the team from Geissen (4). However, consistent success was not reported until the Edmonton protocol was described in 2000 (5).

Although we and others have now confirmed the efficacy of the Edmonton regimen, a number of practical problems remain (6–8). The cause of greatest concern is that success generally requires islets transplanted from multiple-donor pancreata. This not only adds significantly to the cost of the procedure and limits the number of transplants that can be performed, but also adds to the risk of the procedure itself (9).

A second concern is reliance on the intrahepatic site for transplantation. An advantage of this site is that success has generally been correlated with the use of this location versus other sites that have been tried (3). An intraportal release of islets also has the theoretical advantage of promoting portal insulin delivery and avoiding systemic hyperinsulinemia. The negative aspects of intraportal islet transplantation include that the portal circulation may experience relatively higher levels of immunosuppression administered by mouth compared with the systemic circulation (10), thereby inducing direct islet toxicity or impaired engraftment (11,12). The portal site also precludes efficient biopsy of the graft, which may be useful in monitoring for graft rejection or evaluating graft dysfunction. Finally, serious complications can result from the infusion procedure, including hemorrhage and portal vein thrombosis (3).

We describe a consequence of intrahepatic islet transplantation, specifically the development of hepatic steatosis surrounding the portal tracts in which the transplanted islets reside. This can be readily detected by noninvasive magnetic resonance (MR) imaging (MRI) and may therefore provide a simple and noninvasive means for following survival of the transplanted graft.

RESEARCH DESIGN AND METHODS

Patients and islet transplant protocol. Our center has now transplanted 10 patients with isolated islets using the Edmonton protocol for immunosuppression (7) under protocols approved by both the Food and Drug Administration and our institutional review board. Eight of the patients have completed the protocol, and each gained insulin independence. The four patients with the longest duration of graft function following intraportal islet transplantation were evaluated by MRI. Of note, for inclusion in the study all patients were required to have an ultrasound examination of the liver that documented absence of hepatic parenchyma or vascular abnormality including steatosis. Posttransplant ultrasound imaging was not routinely performed in our study. Cross-sectional imaging of the initial patient was prompted by attempt at second-dose islet transplant using ultrasound-guided portal vein cannulation at 13 months after the first dose. Ultrasound revealed an unusual pattern of multiple foci of increased hepatic echogenicity that obscured visualization of the portal vein. The study was interpreted as consistent with localized areas of steatosis versus multiple mass lesions or infection. This finding was followed-up with an MR study 1 week after uneventful infusion of the second islet dose. The subsequent three patients were imaged at 8, 11, and 12 months after islet transplantation to assess the universality of the findings in the index case.

MRI protocol. MRI is uniquely sensitive to microscopic lipid deposition in tissues by virtue of chemical shift imaging, whereby voxels of mixed water/lipid content display signal loss on opposed phase images (13). Chemical shift imaging via a modified two-point Dixon gradient echo sequence is routinely performed in clinical MRI of the liver (14) and was utilized to image patients who had received isolated allogeneic islets infused via the portal vein.

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MR, magnetic resonance; MRI, MR imaging.

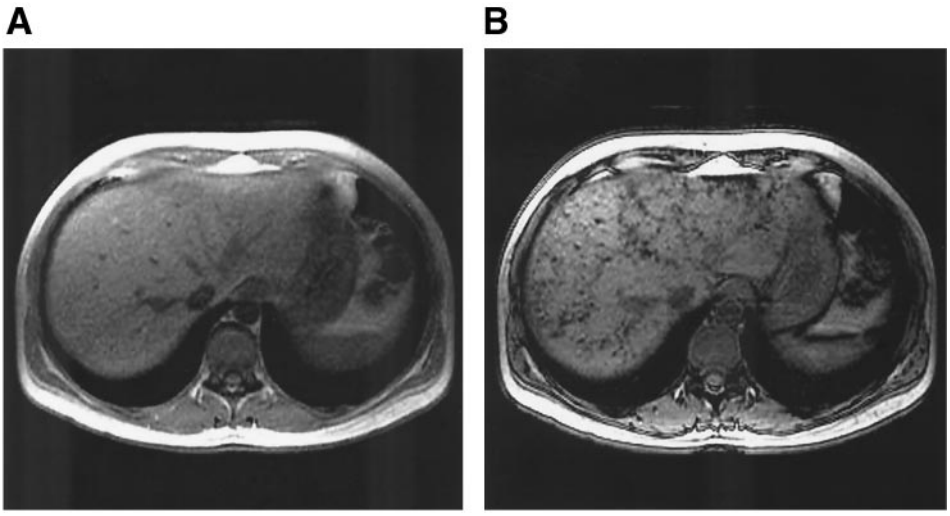

FIG. 1. MR images of the liver from a Horizon Echo Speed 1.5-T magnet (General Electric, Milwaukee, WI) show periportal steatosis 14 months after islet cell transplantation. *A*: T1-weighted in-phase gradient echo image (echo time 4.6 ms) shows normal intermediate-to-high signal intensity liver (L) and low-to-intermediate signal intensity spleen (S). *B*: Corresponding T1-weighted opposed phase image (echo time 2.3 ms) shows periportal loss of signal intensity (arrows), which is diagnostic for geographic steatosis.

RESULTS

Results of MRI. Two of four patients who were imaged following islet transplantation showed a unique pattern of steatosis, with a fine branching linear and reticular pattern of signal loss on opposed-phase imaging (Fig. 1). Two patients did not have hepatic steatosis detectable by MRI. MRI applied in this manner has high sensitivity and specificity for detection of steatosis and adequately discriminates this from other entities such as accumulation of glycogen.

Correlation of MR results with islet graft function. The two patients who had hepatic steatosis on MR each had excellent graft function at the time the imaging study was performed. The first patient had become insulin independent following a single infusion of islets from a single cadaveric donor (8,500 IEq/kg recipient body wt). This patient received a second dose of islets due to development of fasting hyperglycemia at 13 months posttransplant, despite having evidence of a continued high level of graft function with stable C-peptide levels before and after a mixed meal challenge (1.2–3.8 ng/ml) and nearly normal HbA_{1c} (6.2%). Within 3 weeks of the second dose, the mixed meal challenge continued to demonstrate a high level of function (C-peptide 1.2/4.1 ng/ml) and the HbA_{1c} had improved to 5.8% (Table 1). The second patient that showed hepatic steatosis became insulin independent immediately following a second dose of islets 10 months earlier. The combined transplanted islet mass in this patient was 17,100 IEq/kg. This patient also had evidence of excellent graft function (Table 1).

One of the two patients who did not reveal hepatic steatosis had lost the majority of graft function and resumed insulin therapy at 7 months posttransplant, 1 month before the imaging study. Basal C-peptide levels in this patient at the time of imaging indicated marginal graft function (0.5–1.0 ng/ml). Partial graft function remained, as evidenced by a retained response to a mixed-meal challenge (C-peptide 1.9 ng/ml) and the fact that only one-fifth of the pretransplant insulin dose was required. The second patient who was found by MR to be free of

TABLE 1
Characteristics of patients with and without periportal steatosis on MRI

	Patient 1	Patient 2	Patient 3	Patient 4
Periportal steatosis evident on MRI	Yes	Yes	No	No
Dose 1 (IEq/kg)	8,500	8,828	12,768	8,544
Dose 2 (IEq/kg)	5,365	8,333	NA	NA
Packed cell volume of infusion 1 (ml)	5	5	4.9	5
Packed cell volume of infusion 2 (ml)	2	3.5	n/a	n/a
AST peak post–dose 1 (day of peak) (units/l)	653 (day 1)	69 (day 4)	168 (day 1)	101 (day 5)
AST peak post–dose 2 (day of peak) (units/l)	97 (day 1)	1,031 (day 1)	NA	NA
AST at time of imaging (units/l)	68	48	30	29
ALT at time of imaging (units/l)	60	43	23	44
Total bilirubin at time of imaging (mg/dl)	0.3	0.8	0.3	0.4
Daily insulin dose at time of imaging (units)	0	0	5	7
Fasting C-peptide at time of imaging (ng/ml)	1.2	1.5	1.3	0.7
Stimulated C-peptide at time of imaging (ng/ml)	4.1	2.7	2	1.9
HbA_{1c} at time of imaging (%)	5.6	6.9	7.1	6.7
Mean tacrolimus trough levels (range) (mg/l)*	4.9	3.2 (2.1–4.6)	5.6 (3.2–7.7)	3.2 (1.6–5.5)
Mean rapamycin trough levels (range) (mg/l)*	12.3	10.5 (7.1–13.6)	10.8 (9.7–15.1)	8.8 (7.0–10.3)
Peak portal pressure rise with dose 1 (mmHg)†	1	5	4	4
Peak portal pressure rise with dose 2 (mmHg)†	3	1	NA	NA

*Mean (and range) of last seven measurements prior to imaging study; †peak rise from baseline measured prior to beginning infusion. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

steatosis also had become insulin independent following a single infusion of isolated islets from a cadaveric donor ~12 months earlier (12,800 IEq/kg). At the time of imaging, however, the patient had transiently resumed insulin therapy during a severe systemic allergic reaction to an immunization. Glucose control during this period was poor, as evidenced by a rise in the patients HbA_{1c} to 7.1% despite good C-peptide levels (1.3 and 2.0 ng/ml, pre– and post–mixed-meal challenge, respectively).

There was no obvious difference in the patients who evidenced steatosis on MR for a variety of other factors detailed in Table 1. All patients experienced a transient rise in liver function tests postinfusion that resolved spontaneously. Aspartate aminotransferase levels generally demonstrated the most marked rise and, along with total bilirubin, are shown as markers representative of liver function and liver injury. Liver function at the time of imaging was normal in all patients. Transient elevations in portal pressure also occurred in each of the patients and resolved spontaneously. Each infusion of islets in our series consisted of ≥5 ml packed tissue.

DISCUSSION

We report an unexpected finding of hepatic steatosis in patients undergoing intrahepatic islet transplantation. We found that in two of four transplanted patients who had imaging performed, periportal steatosis was revealed corresponding to where the islets lodge postinfusion in the portal vein. In two other patients who had received an islet graft, no steatosis was present at MRI. These patients differed from those in whom steatosis was detected in that one had lost the majority of graft function 1 month earlier and the other developed a recent deterioration in graft function and transiently required insulin therapy. This may indicate both that the process is reversible (as in many other cases of hepatic steatosis) and that the imaging findings may correlate with the degree of graft function. Study of additional transplanted patients will be required to adequately clarify this hypothesis.

An effective approach to image islets following transplantation has long been sought, but no clinically relevant approaches have been successfully applied. Although the imaging findings detailed herein do not image the islet graft directly, they do provide a functional footprint of graft function that may be suitable to follow graft survival over time.

That high local levels of insulin can result in localized hepatic steatosis is not novel, nor is the fact that this may result in unique findings on MRI. Sohn et al. (15) recently reported analogous findings in two unrelated examples of hepatic steatosis resulting from high levels of local insulin in the liver. The first occurred with an insulinoma metastatic to the liver. In this case, chemical shift MRI revealed a ring of steatosis in hepatocytes surrounding the tumor nodule that was concluded to be a consequence of local insulin release by the tumor. In the same report, a case of subcapsular hepatic steatosis was illustrated that resulted from intraperitoneal administration of insulin during peritoneal dialysis. Again, this was readily detected by chemical shift MR, which is highly sensitive and specific for the detection of lipid (13).

The possibility that intrahepatic islets may cause localized alterations in surrounding hepatocytes has been previously documented. Ryan et al. (16) provided evidence of microvesicular steatosis on a liver biopsy of a patient who had received an intraportal infusion of islets and had increased echogenicity on ultrasound evaluation. In addition, a histologic pattern of peri-islet glycogen deposition has been described following nonhuman primate islet transplantation (17). The pathological significance of these findings to the recipient remains unclear, but it is likely that the development of steatosis is both benign and reversible. It can be reasonably argued, however, that the presence of steatosis (or glycogen) reflects an abnormal local utilization of insulin. Whether this reflects impaired graft function or whether it can result in impaired graft function is unknown.

In summary, islet transplantation has recently been found to be consistently successful using the Edmonton protocol (18). The long-term residence of islets within the liver can result in development of periportal steatosis, which is detected by routine noninvasive MRI. The significance of these findings to the well-being of the recipient and the graft will require further careful study. These findings raise the possibility that the functional status of transplanted islets may be monitored by chemical shift MRI.

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