Prevalence of Hepatic Steatosis After Islet Transplantation and Its Relation to Graft Function

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Islet allotransplantation can provide insulin independence in selected individuals with type 1 diabetes. The long-term effects of these transplants on the liver are unknown. Recently, two cases of periportal steatosis after islet transplantation have been described. In this study, we performed ultrasound and magnetic resonance imaging (MRI) in 30 C-peptide−positive islet transplant recipients to detect steatosis and to explore the association of the radiological findings with clinical and metabolic factors. Steatosis was observed on MRI in six (20%) subjects. Histological findings of hepatic steatosis concurred with the imaging findings. Steatosis completely resolved in one subject whose graft failed. More subjects with steatosis required supplementary exogenous insulin than not (67 vs. 21%; $P < 0.05$). The clinical features of subjects with and without steatosis were otherwise similar, although C-peptide levels were higher in insulin-independent subjects with steatosis (0.98 ± 0.12 vs. 0.70 ± 0.18 nmol/l; $P = 0.05$), despite similar blood glucose levels. Serum triglycerides and the use of exogenous insulin were associated with increased odds of steatosis in a logistic regression model (χ^2 [degrees freedom] = 13.6 [2]); $P = 0.001$). MRI-detected steatosis is a common finding; the steatosis appears to be due to a paracrine action of insulin secreted from intrahepatic islets. Hepatic steatosis may be associated with insulin resistance or graft dysfunction. *Diabetes* 53:1311–1317, 2004

Successful islet transplantation using a steroid-free, sirolimus-based immunosuppressive regimen (the Edmonton protocol) has emerged as an effective treatment for type 1 diabetic subjects at major risk from hypoglycemia and metabolic lability (1). Although islet autotransplants have functioned for >18 years without clinical consequence, the long-term effects of persistent allotransplanted islets on the liver after portal venous delivery have not been well defined in large patient cohorts.

Clearly a number of factors might result in structural/functional changes in the liver: *1*) the procedure itself, including ablative approaches used to prevent bleeding from the catheter tract; *2*) the physical embolization of terminal branches of the portal vein by islets and the local effects of peri-islet micro-thrombi; *3*) the local effects on the hepatocyte of high concentrations of insulin released from the transplanted islets; *4*) the effects of immunosuppressive drugs on the liver; and *5*) structural changes, including local scarring after rejection and clearance of islet tissue within the liver. Ultrasound and magnetic resonance imaging (MRI) are noninvasive techniques that facilitate definition of hepatic structure and can be repeated safely to follow changes over time.

An examination of radiological changes after islet transplantation is important for the clinical care of transplant patients and to learn more about the function of transplanted islets over time. Knowledge of normal abdominal appearance after islet transplantation is helpful for future interpretation when these patients present with abdominal pathology unrelated to their islet transplant.

Recently, two cases of periportal steatosis after intraportal islet allotransplantation, apparent on MRI examination, have been described in a small series of four subjects (2). The appearance of steatosis was attributed to intrahepatic insulin secretion and was proposed as a marker of functional islet graft survival. Preliminary data from Maafi et al. (3) also have demonstrated both ultrasonographic and histological evidence of focal steatosis in islets after kidney transplantation.

The purpose of this study was to evaluate long-term ultrasound and MRI findings of the liver after intraportal islet allotransplantation in a large series of subjects and explore the relation of the radiological findings with clinical and histological features and with graft function.

RESEARCH DESIGN AND METHODS

For this study, 30 (17 women, 13 men) of our first 32 consecutive patients receiving islet transplants at the University of Alberta had their livers evaluated using ultrasound and MRI. Of the remaining two patients, one had withdrawn from the program and the other declined MRI. The mean age of the subjects was 43.7 years (range 25–59 years). An MRI and ultrasound of the liver were performed at 447 days (mean), 402 days (median; range 117–1,190 days) after the first islet cell transplant when patients were clinically well, were free from abdominal symptoms, and had stable liver function tests (no elevation >25% above the upper limit of normal). All patients were C-peptide positive at the time of examination. To maintain excellent glycemic control, exogenous insulin was added when fasting or postprandial blood glucose values were >8 or >10 mmol/l, respectively.

Blood was sampled after patients were fasted overnight to estimate liver

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AST, aspartate aminotransferase; FFA, free fatty acid; GFR, glomerular filtration rate; HOMA, homeostasis model assessment; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis.

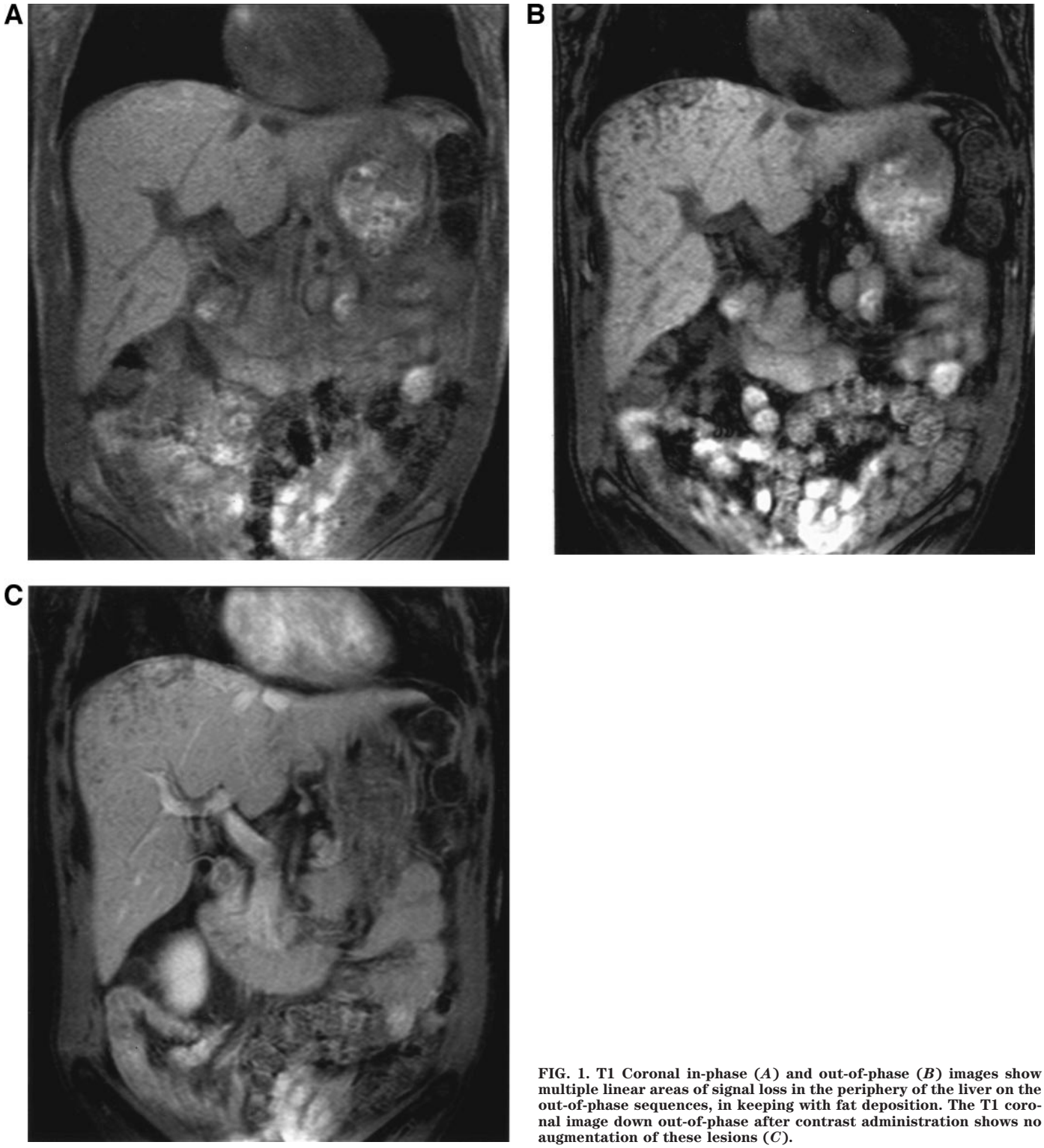

FIG. 1. T1 Coronal in-phase (*A*) and out-of-phase (*B*) images show multiple linear areas of signal loss in the periphery of the liver on the out-of-phase sequences, in keeping with fat deposition. The T1 coronal image down out-of-phase after contrast administration shows no augmentation of these lesions (*C*).

function, lipids, glucose, C-peptide, and HbA_{1c} using a Hitachi 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN). The nondiabetic range for HbA_{1c} is <6.2%. The lower limit for the detection of C-peptide is 0.10 nmol/l. The glomerular filtration rate (GFR) was estimated from the clearance of ^{99}Tc-diethylenetriaminepentaacetic acid and corrected for body surface area. Homeostasis model assessment (HOMA) was calculated in insulin-independent subjects (4).

All ultrasounds were performed on commercially available equipment, including HDI5000 (Philips Medical Systems, Bothell, WA), Acuson XP, Aspen, and Sequoia (Mountainview, CA). All patients underwent abdominal ultrasound during assessment before transplantation. After islet transplantation, patients were routinely assessed on postprocedure day 0 or 1 and again on day 7. These were limited studies to assess the liver and flow in the main, right, and left portal veins (documented with Doppler images) and to look for free fluid. The patients had complete abdominal scans, including Doppler assessment of the main, right, and left branches of the portal vein on the same day as their MRI examination. All exams were checked by a radiologist at the time of the scan and then reviewed by a single radiologist. If there was a difference in interpretation, a consensus was reached between the two radiologists.

The ultrasound studies were reviewed to assess liver echo texture with regard to fatty infiltration. The overall echogenicity of the liver, whether the abnormality was focal or diffuse, and whether the abnormality was heterogeneous or homogenous, were assessed. The overall grade of fatty infiltration was based on the system described by Withers and Wilson (5).

TABLE 1
Clinical and biochemical features of 30 islet transplant recipients undergoing ultrasound and MRI evaluation

	All subjects	Steatosis	No steatosis	*P*
n	30	6	24	—
Age (years)	43.7 (25–59)	42.8 (32–59)	43.9 (25–59)	0.81
Male (%)	13 (43)	1 (16.7)	12 (50)	0.20
BMI (kg/m^2)	22.2 ± 3.0	23.6 ± 4.8	21.9 ± 2.4	0.42
GFR (ml/min)	85 ± 20.6	88 ± 22.5	85 ± 20.6	0.74
AST (units/l)	29 ± 9.6	26 ± 9.9	29 ± 9.5	0.53
Alkaline phosphatase (units/l)	79 ± 26.9	75 ± 18.8	80 ± 28.9	0.71
Bilirubin (mg/dl)	6.9 ± 2.8	5.8 ± 3.4	7.2 ± 2.6	0.29
Cholesterol (mmol/l)	4.8 ± 0.8	4.9 ± 1.1	4.8 ± 0.7	0.71
Triglycerides (mmol/l)	1.15 ± 0.64	1.76 ± 1.1	1.00 ± 0.35	0.15
LDL (mmol/l)	2.65 ± 0.62	2.7 ± 0.8	2.6 ± 0.6	0.93
HDL (mmol/l)	1.61 ± 0.43	1.42 ± 0.39	1.65 ± 0.43	0.24
Fasting glucose (mmol/l)	6.82 ± 1.37	7.65 ± 1.65	6.61 ± 1.25	0.097
HbA_{1c} (%)	6.2 ± 0.67	6.4 ± 0.82	6.1 ± 0.64	0.52
C-peptide (nmol/l)	0.65 ± 0.28	0.62 ± 0.38	0.66 ± 0.25	0.72
C-peptide:glucose ratio	0.098 ± 0.04	0.085 ± 0.05	0.101 ± 0.036	0.39
Exogenous insulin (%)	9 (30)	4 (67)	5 (21)	0.049
Statin therapy (%)	19 (63)	5 (83)	14 (58)	0.37

Data are means ± SD, *n* (%), or *n* (range). *P*, probability of a difference between steatosis and no steatosis.

All MRIs were performed on a 1.5 Tesla Siemens Symphony magnet (Siemens, Iselin, NJ). All patients were imaged using coronal and transverse imaging of the liver consisting of T2-weighted HASTE (Half-Fourier single-shot turbo spin echo) sequences, and T1 in-phase and out-of-phase sequences before and after administration of gadopentetate dimeglumine (Magnevist; 0.1 ml/kg, i.v.; Berlex Canada, Lachine, Canada). The presence of fat was indicated by a loss of signal on out-of-phase T1 images (6).

Percutaneous liver biopsies were performed in three subjects. In two subjects, this was done in response to abnormal radiological appearances and in one subject, because of elevated transaminases (aspartate aminotransferase [AST] 226, ALT 314, alkaline phosphatase 222, and bilirubin 3), although these had resolved by the time of the MRI. Further histological material was available from one subject who underwent segmental hepatic resection for control of an intrahepatic hematoma.

Statistical analysis was performed using SPSS 11 for Mac OS X (SPSS, Chicago, IL). Normality of distribution was checked using the Kolmogorov-Smirnow one-sample test. Means were compared using Student's independent *t* test, and proportions were compared using Fisher's exact test.

RESULTS

Imaging findings. Before transplantation, there was no evidence of hepatic steatosis on ultrasound in any subject. After transplantation, MRI demonstrated the presence of fat in the livers of six subjects (20%). The loss of signal on T1 out-of-phase images, which is specific for fat (6), was seen in all six patients (Fig. 1). The pattern of MRI signal loss was striking and distributed throughout these livers. Fatty infiltration of the liver, manifested by diffuse, increased echogenicity of the liver, was also apparent on ultrasound in five of these six subjects.

The MRI abnormalities in one subject with normal ultrasound findings were more focal. In this subject, a 5-cm-diameter region of focal fatty infiltration was present 527 days after transplantation (Fig. 2), when C-peptide levels ranged between 0.11 (basal) and 0.28 (stimulated) mmol/l and the daily insulin requirement was 0.38 units/kg. This patient was insulin independent for only 29 days, and the graft subsequently failed (i.e., basal and stimulated C-peptide levels were consistently undetectable) by day 646. Follow-up MRI at day 1,218 showed normal liver appearance, with complete resolution of this lesion (Fig. 2). An ultrasound also done at day 1,218 showed a normal liver echotexture.

Hepatic hemangiomas were identified in two additional subjects as hyperechoic masses on ultrasound, with peripheral enhancement on MRI; their identity was confirmed by tagged red blood cell nuclear medicine scan (7). The appearance of these lesions was unchanged after transplantation.

MRI abnormalities that did not represent fat were seen in two subjects. In one, imaged 359 days after a segmental liver resection for control of intraparenchymal bleeding, the MRI showed a 2-cm-wide, curvilinear, T1-hypointense, T2-hyperintense subcapsular band of signal abnormality along the resection margin. The ultrasound showed normal liver echotexture. These findings were in keeping with postoperative changes. In the other subject, there was a peripheral, multisegment, wedge-shaped T1 hypointensity on both in-phase and out-of-phase imaging that had a normal T2 signal. This became smaller and linear on follow-up MRIs done 103, 251, and 866 days later and remained hypointense on T1-weighted and normal on T2-weighted sequences. There was no volume loss of the liver associated with this lesion, and it was felt that the signal abnormalities might reflect a perfusion defect, perhaps related to islet transplantation.

Clinical correlates. Liver function tests were normal in all but five subjects who had minor isolated elevations of AST (within 25% of the upper limit of normal). All patients were C-peptide positive, but nine were receiving supplementary exogenous insulin. In subjects receiving insulin, HbA_{1c} and fasting plasma glucose concentrations were higher and fasting C-peptide levels were lower than in insulin-independent subjects (HbA_{1c}: 6.8 ± 0.8 vs. 5.9 ± 0.4%, $P = 0.016$; glucose: 7.5 ± 1.8 vs. 6.5 ± 1.0 mmol/l, $P = 0.05$; C-peptide: 0.48 ± 0.36 vs. 0.73 ± 0.19 nmol/l, $P = 0.02$).

The clinical and biochemical features of the subjects are presented in Table 1. Among subjects with hepatic steato-

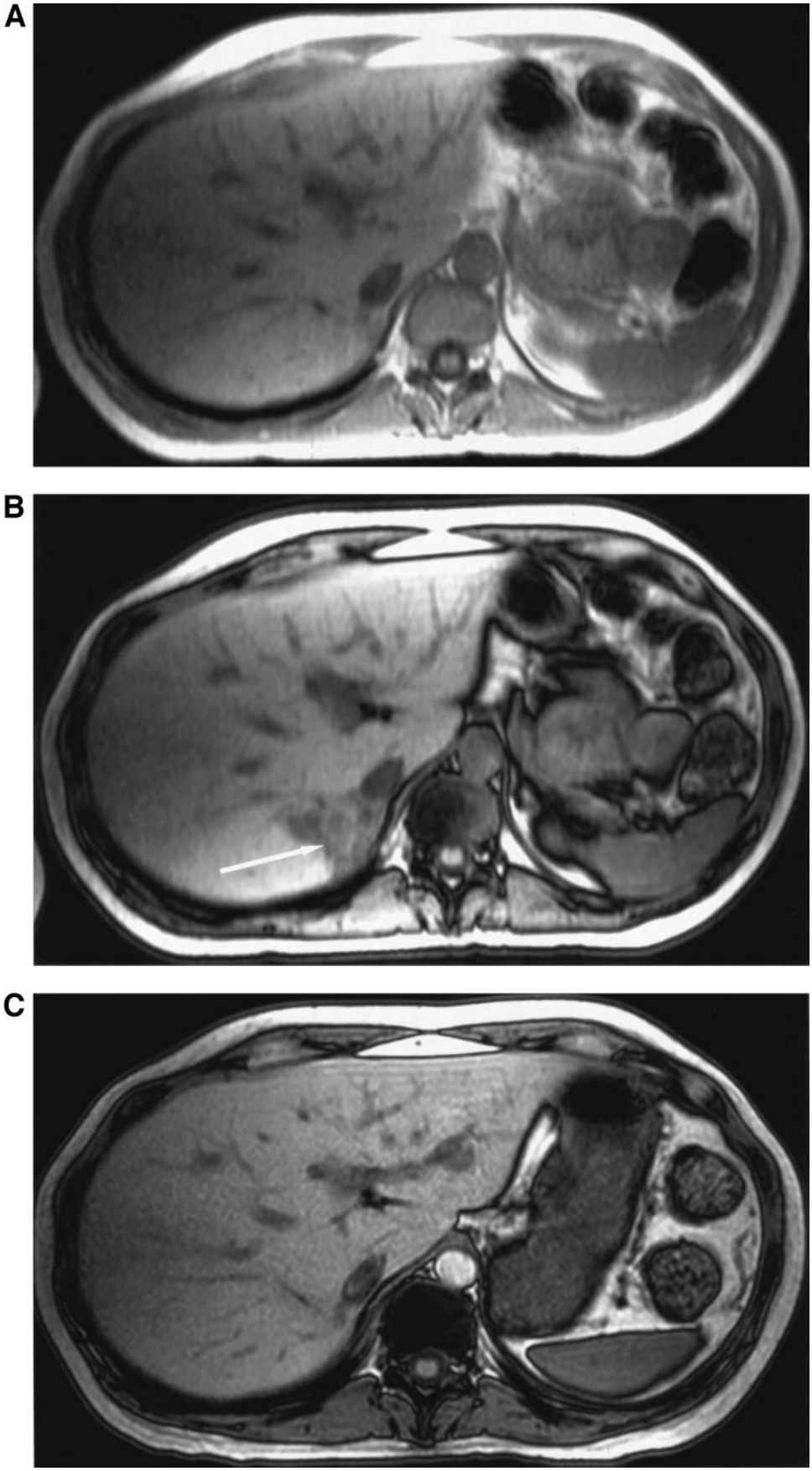

FIG. 2. Out-of-phase T1 imaging (*B*) shows focal signal loss (*white arrow*) in the liver as compared with in-phase T1 imaging (*A*), representing focal hepatic steatosis. A follow-up MRI (*C*) at the time of islet allotransplant failure shows return of the out-of-phase T1 images to normal, indicating resolution of the steatosis.

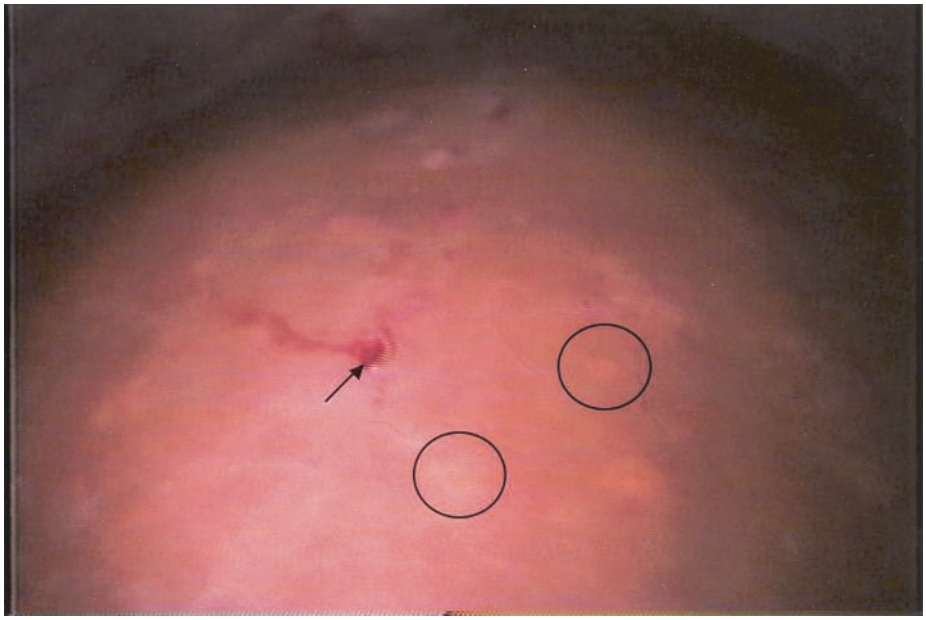

FIG. 3. Multiple hepatic subcapsular yellow fat deposits are seen in a patient undergoing laparoscopy for control of bleeding within 24 h of a second islet infusion. ○, Patchy sites of steatosis seen on liver surface; →, site of intraperitoneal bleed from the portal vein catheterization site.

sis, the proportion of those requiring exogenous insulin was higher. However, there were no differences in age, BMI, lipid profile, liver or renal function, or HbA_{1c} between subjects with and without steatosis, although fasting glucose levels tended to be higher. Similarly, the interval between first transplant and MRI scan did not differ between subjects with and without steatosis (484 ± 197 vs. 405 ± 194 days; $P = 0.38$). When only insulin-independent subjects were considered, subjects with steatosis had higher C-peptide levels than subjects without steatosis, whereas glucose levels and insulin sensitivity, as indicated by HOMA, were similar (Table 2). There was no relation between the presence of steatosis and the number of transplants, islet mass, or time to insulin independence.

Increased serum triglycerides and the use of exogenous insulin were independently associated with increased odds for the presence of hepatic steatosis in a logistic regression model (Table 3). The overall model was statistically significant ($P = 0.001$) and explained 58% of the variability, predicting 87% of responses correctly.

Macroscopic findings. The macroscopic appearance of the liver of a patient with a previous islet transplant undergoing laparoscopy after a second islet infusion is illustrated in Fig. 3. Pale yellow areas are visible on the surface of the liver, representing peripheral deposits of hepatic fat.

TABLE 2
Biochemical features relevant to glycemia in insulin-independent subjects with or without hepatic steatosis on imaging

	Steatosis	No Steatosis	*P*
n	2	19	—
Fasting glucose (mmol/l)	7.0 ± 1.1	6.5 ± 1.1	0.54
HbA_{1c} (%)	5.7 ± 0.14	6.0 ± 0.44	0.42
C-peptide (nmol/l)	0.98 ± 0.12	0.70 ± 0.18	0.05
C-peptide:glucose ratio	0.14 ± 0.003	0.11 ± 0.02	0.14
HOMA-IR	0.39 ± 0.067	0.57 ± 0.035	0.47

Data are means ± SD. HOMA-IR, homeostasis model assessment for insulin resistance.

Histological findings. Biopsies of the liver, performed in two patients because of increased echogenicity on ultrasound, showed perivenular micro- and macrovesicular steatosis (Fig. 4) (8). Glycogen, though present in normal amounts in adjacent hepatocytes, was not present in these lipid-laden vacuoles and glycogenosis was not observed. Histology of a segmental resection of the liver in a third patient, performed after an intrahepatic hematoma secondary to anticoagulation for branch portal vein thrombosis, showed no steatosis. Imaging of the patient's liver with ultrasound before surgery showed no increased echogenicity to suggest fat. A liver biopsy in a fourth patient with elevated transaminases and normal liver imaging showed no abnormality.

DISCUSSION

The results of the current study demonstrated that the presence of fat in the liver of islet transplant recipients is a common finding on hepatic imaging and can be confirmed histologically. The fat infiltration on imaging, which was not present before transplantation, had either a focal or diffuse, though not homogeneous, pattern of hepatic involvement. Diffuse fatty infiltration of the liver with heterogeneous granular appearance on ultrasound is not a common finding in the general population. The benign nature of this has been confirmed with MRI by the normal T2 signal and lack of enhancement with gadolinium. The presence of fat was confirmed in all six of our patients by the decrease in signal on T1 out-of-phase images as compared with the signal on T1 in-phase images (6).

TABLE 3
Logistic regression model of factors predicting the presence of steatosis

	OR	95% CI	*P*
Exogenous insulin required	25.5	1.5–436	0.025
Triglyceride (mmol/l)	15.5	1.03–233	0.047

Dependent variable: steatosis (present = 1). Model χ^2 (df) = 13.6 (2); Nagelkerke $r^2 = 0.576$, $P = 0.001$.

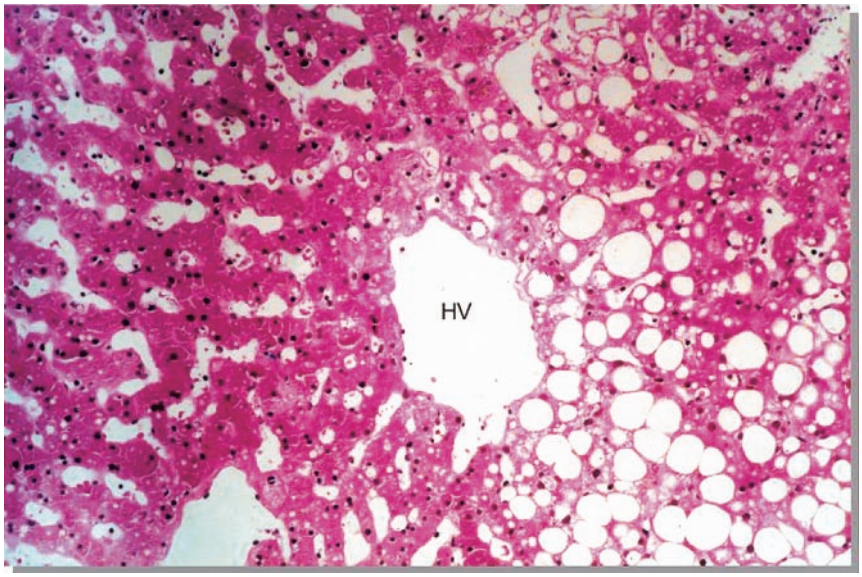

FIG. 4. Hematoxylin and eosin scan showing multiple vacuoles of fat deposited in the liver. Similar steatosis was observed in another patient (8). The vacuoles did not stain for glycogen nor is hepatocellular glycogenosis observed, although normal amounts of glycogen are apparent in hepatocytes. HV, hepatic vein.

Previous studies comparing ultrasound and MRI have found that MRI is less sensitive for the detection of steatosis (9). However, previous MRI studies did not use chemical shift imaging, which markedly increases the sensitivity and specificity for steatosis (6). T1 out-of-phase imaging, a chemical shift imaging technique used in our study, is now felt to be the gold standard for the noninvasive diagnosis of steatosis (10).

In contrast to previous reports suggesting that hepatic steatosis could be an index of islet function, it is striking that hepatic steatosis was not a uniform finding in our islet recipients, even though all were C-peptide positive. Graft function varied among subjects, but higher HbA_{1c} and fasting glucose and lower C-peptide levels suggested graft function was poorer in subjects requiring exogenous insulin. Indeed, the majority of subjects were insulin independent. Nevertheless, the presence of hepatic steatosis on MRI in one subject completely resolved after the patient became C-peptide negative, which supports a causative role for the intrahepatic secretion of insulin by transplanted islets in the genesis of hepatic steatosis.

The only clear difference in clinical or metabolic parameters between subjects with or without evidence of hepatic steatosis was that the proportion of subjects with steatosis requiring exogenous insulin was higher. When only insulin-independent subjects were considered, as the use of supplemental exogenous insulin confounds the interpretation of fasting glucose and C-peptide levels, C-peptide was higher in subjects with steatosis, even though fasting glucose levels did not differ. Although this finding could be associated with some degree of insulin resistance, the HOMA, an index of insulin sensitivity, did not differ.

It is becoming clear that insulin resistance plays a central role in the pathogenesis of steatohepatitis, as in nonalcoholic steatohepatitis (NASH), obesity, and type 2 diabetes. In NASH, the suppression of lipolysis by insulin is impaired (11,12), resulting in increased delivery of free fatty acids (FFAs) to the liver. Increased delivery of FFAs to the liver, particularly in association with hyperinsulinemia, will promote steatosis and is associated with hepatic insulin resistance and an increase in hepatic glucose output (13).

However, the hepatic steatosis seen in association with insulin resistance (e.g., type 2 diabetes and NASH) is diffuse and homogeneous. In our islet transplant recipients, the steatosis was either focal or patchy. Furthermore, type 1 diabetic subjects are generally insulin sensitive. The subjects in this study were not obese and did not exhibit any clinical features commonly associated with severe insulin resistance.

It seems most likely, therefore, that this pattern of steatosis is due to a paracrine action of insulin promoting the esterification of FFAs within hepatocytes. The steatosis was predominantly perivenular and located peripherally in the liver. Transplanted islets, infused into the main portal vein, embolize within small branches of the portal venous system that are predominantly in the liver periphery (14). Similar findings of focal hepatosteatosis have been reported around insulinoma deposits metastasizing to the liver via the portal venous system (15). The ability of insulin to promote the local accumulation of lipids has long been recognized in the development of lipohypertrophy in individuals who fail to rotate the site of subcutaneous insulin injections. A paracrine action for insulin is also suggested by the hepatocellular glycogenosis observed around small and sparse transplanted islets in one nonhuman primate that required supplementary exogenous insulin (16). Hepatocellular glycogenosis develops in the presence of insulin when cytoplasmic glucose levels are high and seems to be associated with wide fluctuations in blood glucose levels, which were not apparent in our subjects (17).

Our observations confirmed previous reports of hepatic steatosis after intraportal islet transplantation; similar changes have been observed in both islet allograft and autograft recipients (2). Furthermore, our results indicated that this is observed in ~20% of C-peptide−positive subjects and 10% of insulin-independent subjects. Because steatosis was not seen in the majority of our insulin-independent subjects, it is unlikely that steatosis represents an index of functional islet mass. The resolution of

steatosis in one patient with complete loss of graft function indicates that hepatic steatosis is related to the presence of functioning islets. It is unclear, however, whether the islets in patients with steatosis are healthy or stressed.

Our data do not permit us to draw firm conclusions regarding the etiologic factors responsible for hepatic steatosis after islet transplantation. Nevertheless, our logistic regression model indicated that the use of exogenous insulin and increases in serum triglyceride levels were independently associated with increased odds of steatosis. The need for exogenous insulin suggests some graft dysfunction, although it is unclear whether elevated triglycerides cause or are a consequence of steatosis. It is clear that other factors are involved, however, as the model explained only 58% of the variation. The presence of steatosis may reflect some degree of graft dysfunction that would accord with observations of hepatic fat on ultrasound in patients receiving islet transplants after kidney transplants with marginal islet graft function (3). Longitudinal MRI studies of the progression or resolution of steatosis and its relation to graft function may provide insight into the exact significance of steatosis.

The use of immunosuppressive drugs could be postulated as an alternative explanation for the genesis of these radiological abnormalities. Sirolimus can cause an elevation of serum lipids, and tacrolimus has the potential to be diabetogenic. Tacrolimus does not appear to be associated with steatosis in liver transplantation (18). Sirolimus, though widely used in solid organ transplantation, has not been associated with the presence of steatosis. The immunosuppressive drugs, however, may accentuate the development of steatosis by insulin.

It seems most unlikely that either the procedure itself or the presence of islets are responsible for the appearance of steatosis, given that the radiological changes were not evident on ultrasound tests performed in the week after transplantation. There was a substantial interval between transplantation and MRI imaging.

In summary, the focal deposition of fat within the liver in patients who have received an islet transplant is a common and expected finding. The typical appearance is of an ill-defined, heterogeneous granularity with increased echogenicity on ultrasound or signal loss on T1-weighted out-of-phase sequences on MRI. The radiologist should recognize these abnormalities as a benign finding in patients who have received an islet transplant. Although it is reassuring that the patients in our study were asymptomatic and had no derangement of liver function tests, the long-term clinical significance of focal steatosis is not clear. These apparently benign appearances raise intriguing questions about the paracrine effects of intrahepatic secretion by transplanted islets and warrant further study.

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