Review Article on Interventional Radiology in Glands

Allo- and auto-percutaneous intra-portal pancreatic islet transplantation (PIPIT) for diabetes cure and prevention: the role of imaging and interventional radiology

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Abstract: Although the life expectancy of patients with type 1 diabetes mellitus (T1DM) has improved since the introduction of insulin therapy, the acute life-threatening and long-term complications from diabetes mellitus are significant causes of both mortality and morbidity. Percutaneous intra-portal pancreatic islet transplantation (PIPIT) is a minimally invasive, repeatable procedure which allows a β-cell replacement therapy through a liver islet engraftment, leading to insulin release and glycaemic control restoration in patients with diabetes. Allo-PIPIT, in which isolated and purified islets from cadaveric donor are used, does not require major surgery, and is potentially less expensive for the recipient. In case of long-term T1DM, islet-after-kidney (IAK) transplantation can simultaneously cure diabetes and chronic renal failure, while islet-transplant-alone (ITA) is performed in brittle, short-term T1DM, based on the infusion of an adequate islet mass and on a steroid-free immunosuppressive regimen according to the Edmonton protocol. Results of the Collaborative Islet Transplant Registry (CITR) demonstrate that allo-PIPIT reduces episodes of hypoglycemia and diabetic complications, and improves quality of life of diabetic patients. Auto-PIPIT, in which the own patient's islets are used, has been investigated as a preventive treatment for pancreatogenic diabetes in patients who undergo extensive pancreatectomy for malignant and non-malignant disease. This Review outlines the role of imaging and interventional radiology in allo- and auto-PIPIT.

Keywords: Type 1 diabetes; islet transplantation; ultrasound; pancreatogenic diabetes; hepatic steatosis; insulin action

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Introduction

In the United Kingdom 10% of the National Health Service budget is spent on diabetes, mainly due to diabetic-induced heart, foot, and renal diseases (1).

The acute life-threatening and long-term complications from type 1 diabetes mellitus (T1DM) are significant causes of both mortality and morbidity (2,3).

Good glycemic control with intensive insulin treatment is known to markedly decrease the incidence of chronic micro-vascular complications and cardiovascular morbidity in patients with T1DM (2,4). However, this treatment is difficult, expensive, and associated with an increased incidence of severe hypoglycemia, which is often accompanied by hypoglycemic unawareness (5), provoking considerable complications (6).

Whole-organ pancreatic transplants into human subjects first performed in the early 1980s (7) are now associated with 1-year insulin independence rates of higher than 80% (8). Long-term T1DM is often associated with chronic renal insufficiency: a combined kidney/pancreas transplantation represented the best therapeutic option for these patients (9,10), normalizing glucose levels and preventing complications (11,12). However, the procedure is also associated with significant perioperative morbidity (11) and the need for long life immunosuppression therapy.

Since the 1990s, islet-after-kidney (IAK) transplantation represents a good alternative to treat diabetes associated with chronic renal insufficiency (13) in case of pancreas unavailability from a cadaveric donor at the time of kidney transplantation. Since the 2000s, according to the Edmonton Protocol (14) based on the infusion of a large islet mass and on a glucocorticoid-free immunosuppressive regimen, islet-transplant-alone (ITA) is performed in patients affected by brittle T1DM with preserved renal function: the preliminary results, published by Shapiro *et al.* (14) demonstrating an 80% of insulin independence rate at 1 year, paved the way for further experiments worldwide. However in both diabetic populations submitted to allo-PIPIT (IAK an ITA), the purpose is to obtain insulin independence or a significant reduction of exogenous insulin requirement, to prevent hypoglycaemic episodes and diabetic complications (15,16) such as nephropathy (17) or retinopathy (18) and to increase life expectancy (19).

Auto-PIPIT has been more recently introduced not to cure but to prevent another type of diabetes known as "pancreatogenic diabetes": it originates from an extreme disruption of glucose homeostasis after extensive pancreatic resection such as total/subtotal pancreatectomy for chronic pancreatitis or tumours (20,21). The percentage of patients undergoing pancreatectomy that develop pancreatogenic diabetes varies from 8% to 23% increasing up to 40–50% during the follow-up (22, 23). Auto-PIPIT is usually performed 12–48 h after surgery, does not require immunosuppression and has a lower rejection rate than allo-PIPIT (24).

After isolation, centrifugation and purification (10) of the islets, the technical procedure of allo- and auto-PIPIT is similar. In our center, allo- and auto-PIPIT are performed using a combined ultrasonographic and fluoroscopic guidance to reduce puncture attempts, procedural time and peri-procedural complications (25).

Imaging and interventional radiology play a crucial role in PIPIT. In the present article we present a review based on our experience started in the early 1990s and focused on radiological and interventional aspects of PIPIT: pre-PIPIT imaging, interventional procedure, early post-PIPIT imaging, and late post-PIPIT imaging will be analyzed, also highlighting the three islet-transplanted populations (IAK, ITA and auto-transplanted patients).

Criteria of analysis

A systematic literature review was performed to investigate the role of imaging and interventional radiology in PIPIT from 1982 to 2017. Studies regarding allo-transplantation for type 1 diabetes treatment and auto-transplantation for diabetes prevention after extensive pancreatectomy were selected. Our experience was compared with the published literature focusing on the crucial role of imaging and interventional radiology in all the phases of PIPIT: pre-PIPIT imaging, interventional procedure, early post-PIPIT imaging, and late post-PIPIT imaging. Shared and different interpretations were discussed and analyzed.

Pre-PIPIT imaging

Prior to PIPIT, all patients undergo clinical, biochemical, and radiological evaluation to determine whether they meet the inclusion/exclusion criteria for allo- (*Tables 1,2)* and auto-transplantation (*Tables 3,4*). C-peptide is a unique and independent marker of insulin biosynthesis and secretion. In patients with T1DM, C-peptide negativity is used to confirm the type 1 status, and therefore, undetectable C-peptide is important in the inclusion criteria for allo-PIPIT.

Pre-PIPIT imaging consists of chest radiography and liver color Doppler ultrasound (CDU) examination. Portal

Table 1 Inclusion and exclusion criteria for islet-after-kidney (IAK) transplantation according to Clinical Guidelines for Pancreatic Islet Transplantation

Inclusion criteria
Type 1 diabetes
Age between 18 and 65 years
Erratic glucose control, elevated HbA1c and/or hypoglycemic unawareness
Eligibility for whole pancreas (after kidney) transplantation but not suitability due to high peri-operative risk (i.e., cardiac disease) or technical issues (i.e., extensive atherosclerotic disease of iliac vessels)
At least 1 year following successful kidney transplant with stable renal function and without a prior episode of significant acute graft rejection, requiring an anti-lymphocyte antibody treatment
Treatment with standard immunosuppression drug dosages (with or without steroids)
Free from significant immunosuppression-related infection episodes or neoplasms
Exclusion criteria
Fail to meet inclusion criteria
Presence of measurable C-peptide
PRA (panel reactive antibody) percentage greater than 40
Current or recent smokers (more than zero cigarette at any time in previous 6 months)
Body weight >90 kilograms or body mass index >32
High daily insulin requirements (more than 1 unit of insulin/kg body weight
Documented hepatic disease or chronic pancreatitis
Clinically significant anemia or hemophilia
Other health concerns with contra-indication to use of induction therapy or continued immunosuppression (i.e., malignancy or unresolved infection)

Table 2 Inclusion and exclusion criteria for pancreatic islet-transplant-alone (ITA) patients

Inclusion criteria
Diabetes duration of at least 5 years
Absence of endogenous C-peptide secretion
Severe glycemic lability with frequent episodes of undetected hypoglycemia or progressive diabetic complications despite optimization of insulin injection therapy
Exclusion criteria
Age between 18 and 70 years
Diabetes duration less than 5 years
Residual C-peptide secretion (i.e., stimulated C-peptide level >0.5 ng/dL)
Untreated proliferative diabetic retinopathy
Portal hypertension
Coexisting prohibitive cardiovascular disease
Active infection (including hepatitis C, hepatitis B, HIV, and tuberculosis)
Known alcohol or substance abuse
Positive pregnancy test or intent for future pregnancy

Table 3 Inclusion and exclusion criteria for total pancreatectomy and pancreatic islet auto-transplantation

Inclusion criteria
Pancreatectomy for chronic pancreatitis
Recurrent acute or refractory chronic pancreatitis in pediatric patients
Exclusion criteria
C-peptide negative diabetes
T1DM
Portal vein thrombosis/hypertension
Significant liver disease
High-risk cardiopulmonary disease
Known pancreatic cancer

T1DM, type 1 diabetes mellitus.

Table 4 Extended indications for pancreatectomy and pancreatic islet auto-transplantation in patients with known pancreatic malignancy

Inclusion criteria
Completion pancreatectomy for severe pancreatic fistulas after partial pancreatectomy
Extensive distal pancreatectomy for neoplasms of the pancreatic neck
Total pancreatectomy due to preoperative assessment of increased anastomotic risk
Exclusion criteria
Multifocal pancreatic neoplasm at pre-operative imaging or intraoperative evaluation, including multifocal benign intraductal papillary mucinous neoplasm
Suspected or confirmed diagnosis of multiple endocrine neoplasms
Transection margin involvement in the pancreatic pathology, including any degree of dysplasia or ductal disepithelization
Any medical condition potentially compromising the safety of the auto-PIPIT (percutaneous intra-portal pancreatic islet transplantation) procedure

vein course, patency and flow direction are evaluated with CDU (*Figure 1*) to exclude vascular abnormalities. Liver echotexture is also accurately assessed to verify eventual structural changes after PIPIT.

In case of auto-PIPIT, usually performed 12–48 hours after extended pancreatectomy, CDU is also performed to exclude liquid or hemorrhagic post-surgical collections; in some circumstances a contrast-enhanced computed tomography (CT) may be required.

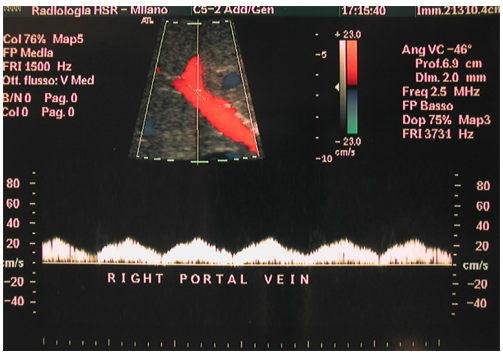

Figure 1 CDU examination of the right portal vein showing its patency and normal flow direction. CDU, color Doppler ultrasound.

Interventional procedure

Patient preparation

PIPIT is usually performed in an angiographic suite under sterile condition with intravenous moderate sedation and routine hemodynamic, cardiac, and oxygen-saturation monitoring (26).

The portal venous system is the anatomic site of choice for islet transplantation, and has advantages of minimally invasive accessibility with avoidance of systemic hyperinsulinemia (27). Although there are few published data on the use of antibiotics in islet cell transplantation, patients typically undergo peri-procedural antimicrobial and antiviral therapy.

Bacteremia and/or sepsis after PIPIT are rare, but sporadic cases related to contamination of cryopreserved islets have been reported (28).

Portal vein access and catheterization

The procedure is usually performed using a combined CDU- and fluoroscopy-guided (25,29) technique. A peripheral portal vein branch is ultrasonically punctured using a right-sided intercostal approach with a 22-gauge needle (*Figure 2*).

The role of ultrasound guidance is essential in order to minimize liver punctures number, procedural time and accidental puncture of other structures (arteries, hepatic

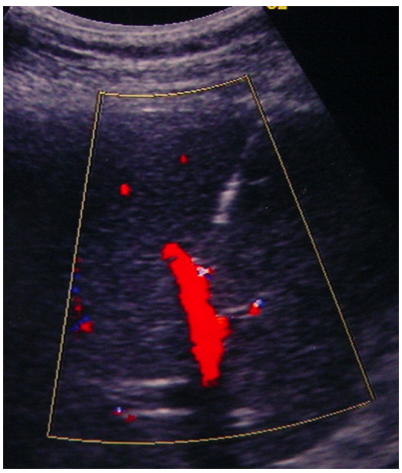

Figure 2 CDU guidance for the puncture of an intrahepatic portal branch. CDU, color Doppler ultrasound.

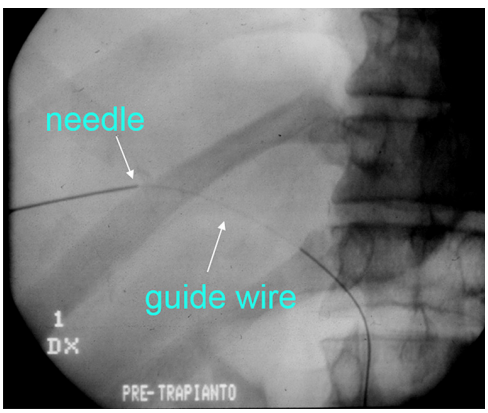

Figure 3 Fluoroscopic image showing a 0.018-inch guidewire insertion in the portal vein through the Chiba needle.

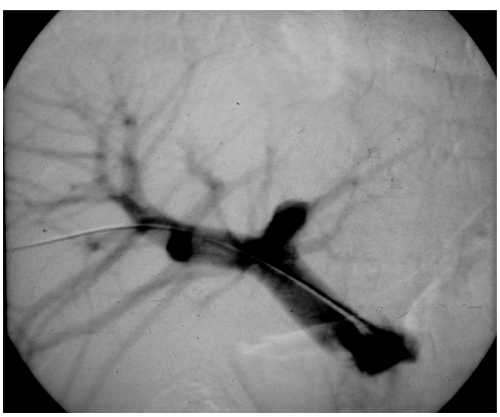

Figure 4 Preliminary portography performed through the 4 Fr catheter.

veins, and gallbladder). In our center, usually the same operator, experienced in both CDU and interventional radiology, performs the right portal vein puncture by inserting the needle with the right hand while holding the probe in the left hand to ultrasonically guide the puncture (25). After the puncture of one wall of a branch of the right portal vein, fluoroscopic guidance is used to perform main trunk portal vein catheterization advancing a 0.018-inch guidewire (*Figure 3*) and then a straight end-hole 4 Fr catheter over the guidewire. Portography (*Figure 4*) and portal venous pressure measurement are performed before and after islets infusion to verify portal patency and pressure increase after PIPIT. Usually portal vein pressure measured prior to infusion is variable from 6 to 12 mmHg and increases by 1–2 mmHg after islets infusion.

Anticoagulation is necessary to reduce the risk of acute portal vein thrombosis. Our institution protocol is based on 1,500–2,000 IU of heparin infused into the portal vein with the islet suspension and 6,000 IU/d of enoxaparin administered subcutaneously for 7 days after the procedure (25). An alternative method reported is based on a systemic anticoagulation with heparin, started after portal vein catheterization, and with a dose of 5,000 U administered during the procedure (26).

Islet infusion

Islet infusion protocol depends on the particular national or institutional protocol used. A typical protocol is based on at least 10,000 islet equivalents per kilogram of body weight. An islet equivalent refers to an average standard diameter of 150 µm, as previously described by Ricordi *et al.* (30). Harvested islets are infused using gravity flow or direct syringe injection (31). The total infusion time is typically 20–30 minutes. A slow injection of the islets is important to avoid their catheter-mediated mechanical damage.

Gravity infusion method allows a better control of islet administration rate allowing gradual reduction of flow preventing any precipitous pressure increases (32). A baseline portal venous pressure over 20 mmHg is a contraindication to transplantation because of increased risk for portal venous thrombosis (31-33). Increased portal pressure indicates embolic saturation of the portal venous system, and increases the risk for thrombotic complications (31).

Tract embolization

Nowadays intrahepatic tract embolization is routinely

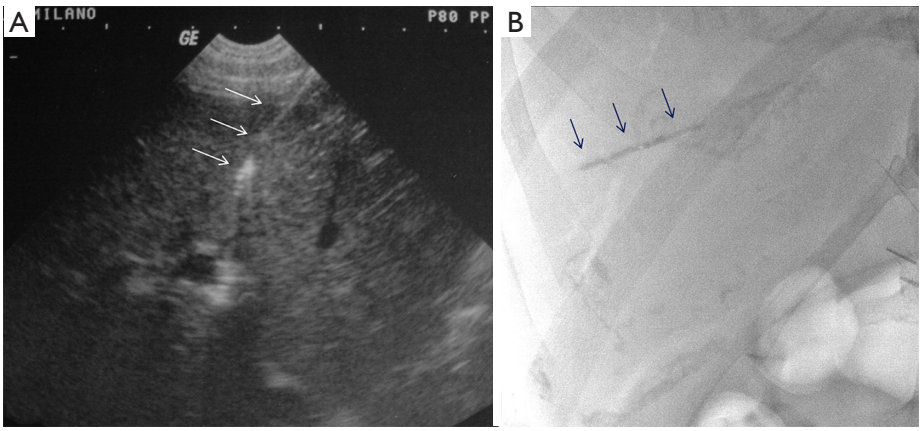

Figure 5 Catheter removal and tract embolization: indicate gelfoam torpedoes in the parenchymal tract (A) at US (white arrows) and (B) at fluoroscopy (black arrows). US, ultrasound.

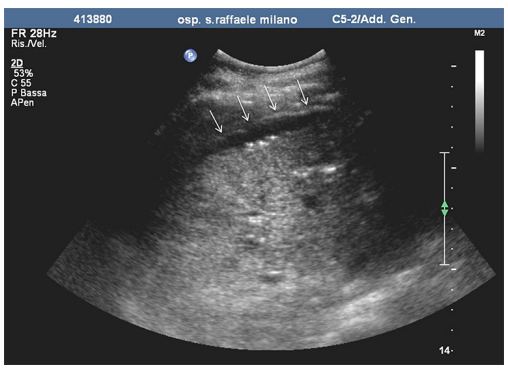

Figure 6 Immediate post-PIPIT ultrasound examination of the abdomen showing a perihepatic fluid collection (white arrows) due to bleeding. PIPIT, percutaneous intra-portal pancreatic islet transplantation.

performed in many centers to minimize the hemorrhagic risk. After completion of final portography, the catheter is retracted into the hepatic parenchymal tract using a combination of US and fluoroscopic guidance. Contrast medium is injected via the catheter to confirm tip position within the hepatic parenchyma before tract embolization. Embolization of the hepatic parenchymal tract can be performed using several hemostatic agents (34,35), in our center with gelfoam torpedoes (*Figure 5*). Care is taken to ensure deployment of the embolic material exclusively within the liver parenchymal tract to avoid intravascular embolization. The ideal embolization material seals the intrahepatic tract, is ultrasonically or fluoroscopically visible, is bioabsorbable, and does not interfere with subsequent radiological or interventional procedures (36).

Early post-PIPIT imaging

Immediate post-PIPIT imaging is based on an accurate, ultrasonographic evaluation in real time of eventual fluid collections around the liver. A strict monitoring with CDU is performed with the patient still lying on the angiographic bed in case of bleeding signs. An early bleeding diagnosis is very important to anticipate possible actions (blood drawings) and therapeutic solutions (blood transfusions, angiographic embolizations, surgical treatments). CDU of the liver is routinely performed at 1, 3 and 7 days. The two most common complications are bleeding (*Figure 6*) and thrombosis (*Figure 7*): bleeding is reported in variable percentage (about 11%), while portal vein thrombosis is more rare and reported in about 3% of the cases (37). The bleeding risk is reduced by an accurate tract embolization during catheter removal. Portal vein thrombosis represents the second most common complication after PIPIT. Complete thrombosis is very rare and a partial thrombosis usually does not determine clinical consequences. Anticoagulation therapy, based on intravenous and intraportal heparin, is routinely administered to minimize this risk. Probably thrombosis may be related to the volume, the purity, and the thrombogenicity of the infused islets (36). Other rare peri-procedural complications include arteriovenous fistulas, hemothorax, trauma to adjacent structures such as biliary tracts and gallbladder. When CDU is not diagnostic a second level imaging examination,

such as contrast-enhanced CT is performed.

Recently, different imaging approaches were developed to directly evaluate transplanted islets viability over time. For example, pancreatic islets labeled with superparamagnetic iron oxide (SPIO) agent were detected at T2-weighted MRI sequences as dark spots scattered in the liver (*Figure 8*). The complete disappearance of all dark spots over time was associated with graft failure (38). Moreover, dynamic contrast enhanced (DCE) MRI was used to assess intrahepatic islet engraftment (*Figure 9*): early perfusion modification resulted predictive of long term function in small groups of patients (39). Several positron emission tomography (PET) tracers were explored in order to quantify liver islet engraftment. Many investigators evaluated biomarkers specific for pancreatic beta cells, with promising but not conclusive results (40). Therefore, the accurate and noninvasive detection of grafted islets remains a challenging goal.

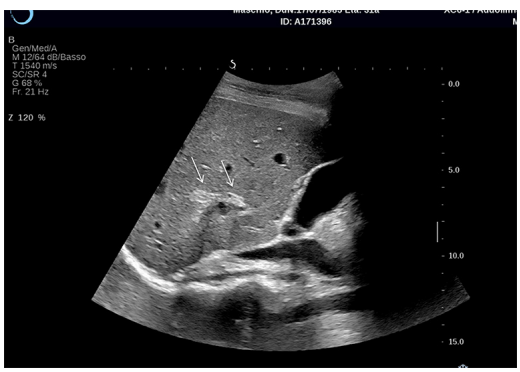

Figure 7 US examination of the liver performed on the first post-procedural day, showing segmental thrombosis of the right portal vein, filled with hyperechoic thrombus (white arrows). US, ultrasound.

Late post-PIPIT imaging

Imaging is also routinely used for PIPIT monitoring. Imaging can be used to monitor late effects due to the infused islets or the immunosuppressive treatment. Life-long immunosuppressive treatment, one of the main limitations of allo-PIPIT especially in IAK patients, can determine neoplastic and infectious complications (41). For example cytomegalovirus infections such as pneumonitis or myocarditis can likely occur after immunosuppression and impact on graft function (41), and can be detected by CT (*Figure 10*) and MRI (*Figure 11*), respectively. Following improved immunosuppressive strategies according to the Edmonton protocol, sirolimus (or tacrolimus) is routinely administered in ITA patients. Sirolimus may be associated to development of ovarian cysts (*Figure 12*) and to nephrotoxic effect: in patients with preserved renal function before ITA, a perinephric edema may appear at US (*Figure 13*) as a rim of anechoic fluid around the kidneys (42).

Immunosuppression-related complications are obviously absent in auto-transplanted patients, who are either donors or recipients and do not need immunosuppressive treatment.

Late effects and structural changes within the liver due to the infused islets can be observed from 6 to 12 months after PIPIT. Hepatic steatosis after PIPIT is determined by functioning islets which cause local insulin production, lipogenesis stimulation, and lipolysis inhibition with consequent fat development (43). Hepatic steatosis is related to liver islet engraftment, but curiously not all patients with

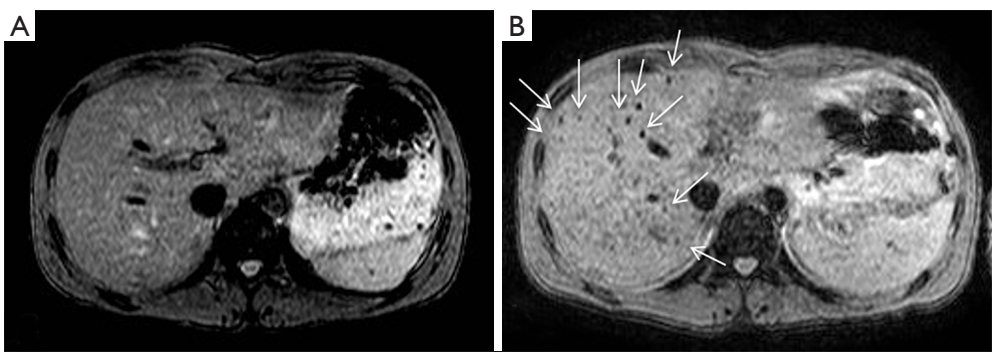

Figure 8 1.5T T2-weighted axial images of liver acquired before (A) and 24 h after (B) PIPIT of iron labeled pancreatic islets. Iron labeled pancreatic islets appear as hypointense spots scattered in the liver (white arrows). MRI, magnetic resonance imaging; PIPIT, percutaneous intra-portal pancreatic islet transplantation.

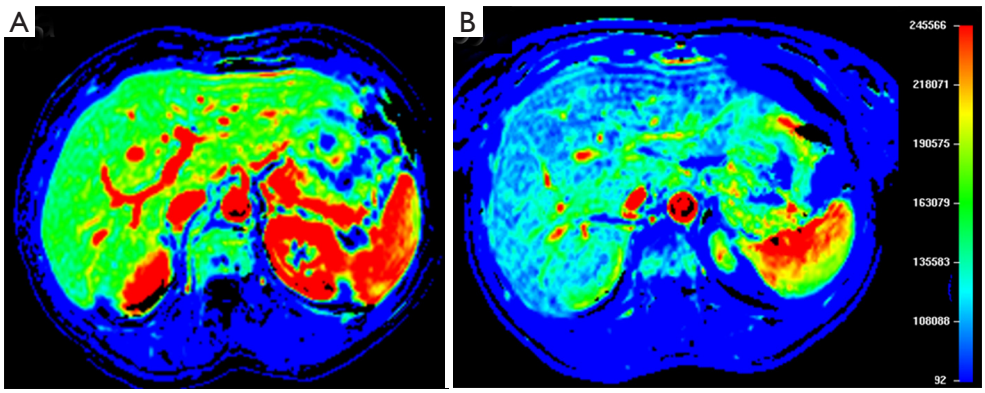

Figure 9 Liver area under the curve (AUC) map obtained with 1.5T DCE-MRI studies before (A) and 24 h after (B) PIPIT of a patient that experienced graft failure. Maps show a significant reduction of liver perfusion 24 h after transplantation. DCE-MRI, dynamic contrast enhanced-magnetic resonance imaging; PIPIT, percutaneous intra-portal pancreatic islet transplantation.

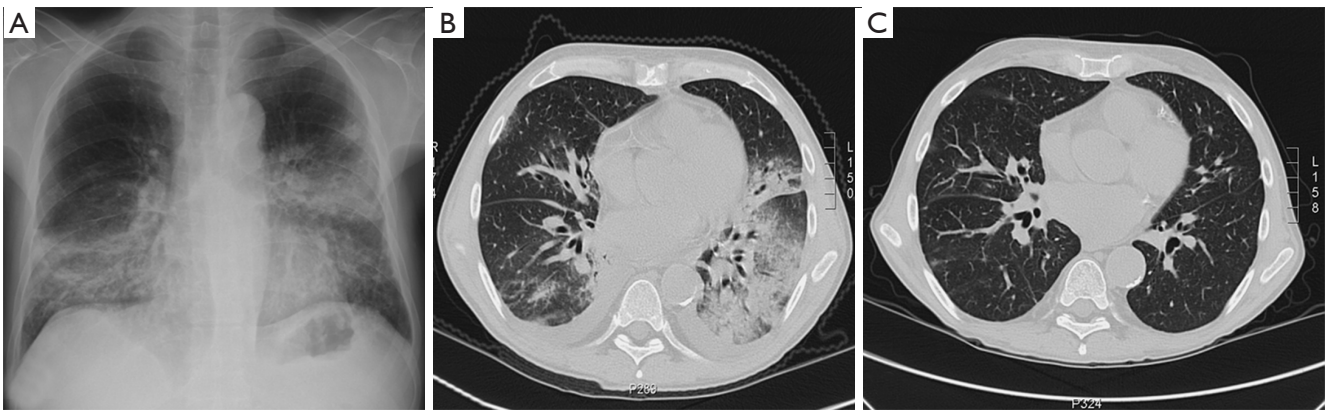

Figure 10 A case of sirolimus-induced pneumonitis. Chest radiogram (A) shows altered density mainly at the pulmonary bases, consistent with interstitial pneumonitis. CT scan (B) demonstrates patchy ground glass opacities with focal consolidations and bilateral pleural effusion. Three months after sirolimus withdrawal CT scan (C) reveals complete healing of the lungs. CT, computed tomography.

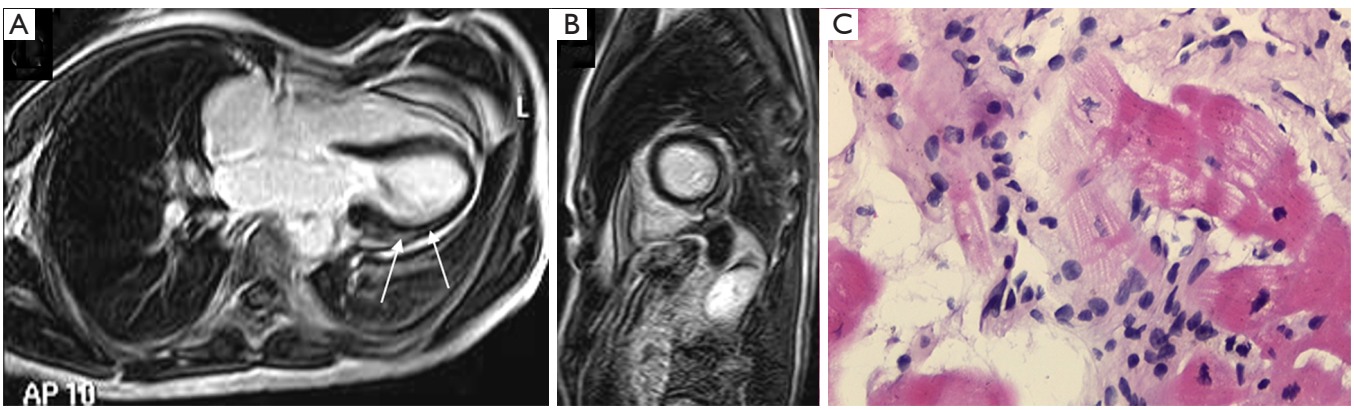

Figure 11 A case of viral myocarditis due to immunosuppressive treatment. 1.5 MRI late-enhancement images on the four-chamber long-axis (A) and short-axis (B) showing left-ventricle subepicardial enhancement (white arrows) consistent with fibrotic infiltration. Myocardial biopsy proved the presence of inflammatory cells and fibrosis (inversion recovery turbo field echo; hematoxylin-eosin, magnification 200×) (C). MRI, magnetic resonance imaging.

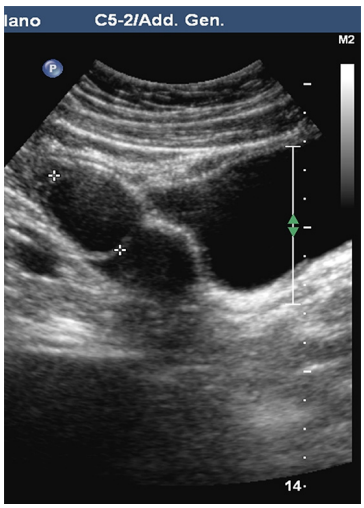

Figure 12 Ovarian cyst at US in a patient manifesting sirolimus-related toxicity. US, ultrasound.

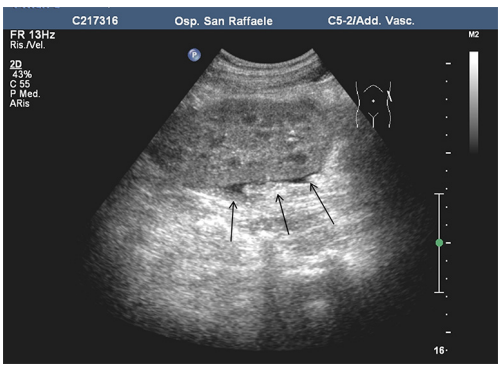

Figure 13 Thin perirenal fluid collection at US (black arrows) in a patient presenting sirolimus-related toxicity. US, ultrasound.

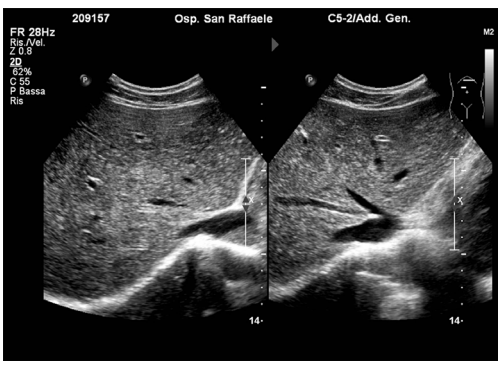

Figure 14 Hepatic steatosis appearance at US preceding graft dysfunction. US, ultrasound.

good islet function develop imaging detectable steatosis. The relationship between graft function and steatosis appearance remains debated. Since the beginning of the 2000s steatosis detection at MRI (44,45) and US (46) after allo-PIPIT was investigated, but no univocal conclusion concerning the best technique nor any correlation between steatosis and graft function was obtained. Even in recent studies steatosis was detected in a variable percentage of patients ranging from 20% to 60% after allo-PIPIT at MRI and US (47,48) and also after auto-PIPIT at US (49): also in these prospective studies a correlation between steatosis and graft function was not clearly defined.

In our recent longitudinal study on 108 patients based on US (50) and involving all the 3 islet-transplanted populations (IAK, ITA and auto-transplanted patients), steatosis at US after PIPIT (*Figure 14*) was interpreted as an early sign of graft dysfunction (51). Our hypothesis is that steatosis appearance at US is related to the overworking activity of some residual vital stressed islets, resulting in insulin overproduction supporting other non-functioning islets: in our opinion, steatosis becomes ultrasonically detectable only when an abnormal peak of local insulin secretion is achieved (50,51). After steatosis detection at US, progressive graft exhaustion was observed until steatosis disappearance in all the patients.

Imaging has been largely used to monitor not only the structural changes within the liver but also the beneficial effects of the pancreatic islets in different vascular districts. This has been largely important to confirm that allo-PIPIT may stabilize and reverse diabetic complications. Indeed successful islet transplantation, restoring a good glycometabolic control, improves the overall survival, the cardiovascular outcome and endothelial function in type 1 diabetic patients (19). A reversibility of endothelial dysfunction (52), typically present in type 1 diabetic patients, and an improvement of vasodilatory ability (*Figure 15*) was also associated with a better wellness of endothelial progenitors cells, which appeared to be less apoptotic after a successful islet transplantation (53). Imaging can provide a strong support to clinical data and highlights the benefits obtained after PIPIT. For example, a protective role on diabetic retinopathy can be supposed: a significant improvement of retinal microcirculation revealed by central retinal artery and vein flow velocity increase was found at color Doppler imaging (*Figure 16*) after ITA (18). On the contrary, no retinal microcirculation

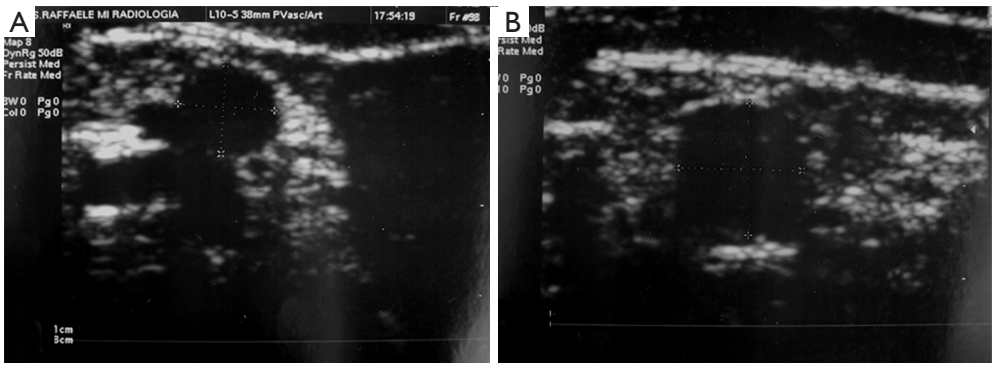

Figure 15 US measurement of brachial artery anteroposterior diameter in response to systemic administration of nitric oxide and local hyperemia to measure endothelial-dependent dilation (EDD). Measurements were performed before (A) and 1 year after (B) islet transplantation, with a significant improvement of nitrate-dependent dilation (B). US, ultrasound.

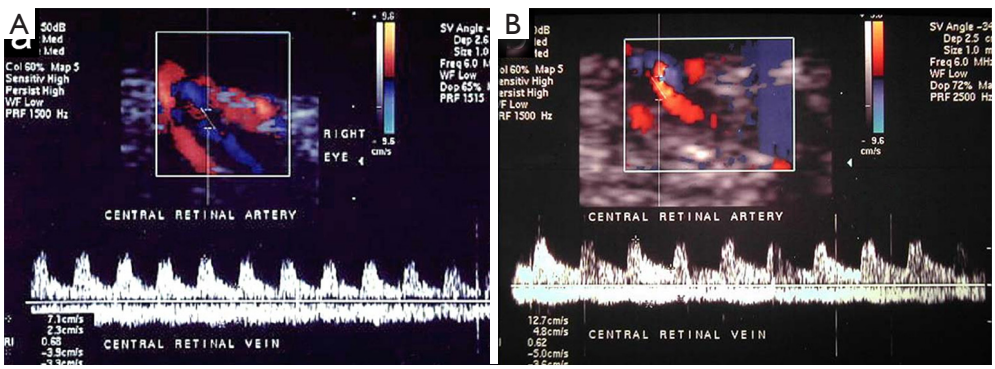

Figure 16 CDU examination of retinal blood flows before (A) and after (B) PIPIT: note the significant blood flow velocity increase in both the central retinal artery and vein 1 year after successful ITA. CDU, color Doppler ultrasound; PIPIT, percutaneous intra-portal pancreatic islet transplantation; ITA, islet-transplant-alone.

improvement was found in long-term type 1 diabetic patients affected by nephropathy and retinopathy, even if successfully submitted to kidney-pancreas transplantation and become insulin-independent (54): probably diabetic retinopathy may be prevented or slowed down by islet (or pancreas) transplantation only at an early stage of T1DM. The protective role of islet transplantation was also demonstrated on the renal blood flow in the transplanted kidney of IAK patients, assessing the arterial resistive index (*Figure 17*) at color Doppler imaging: an enhanced kidney graft survival, hypertrophy and vascular function was found after a successful islet co-transplantation (55,56).

CDU analyzing carotid intima media thickness was also used to demonstrate the beneficial effects of islet transplantation in cardiovascular function (57).

Discussion

PIPIT is an innovative and valid clinical strategy to treat patients affected by brittle T1DM and to prevent pancreatogenic diabetes in patients submitted to extended pancreatectomy. To date, over 1,500 patients have undergone islet transplantation in about 40 international centers (10). Pancreatic islets are extracted, centrifuged, purified and injected via portal vein in the recipients: infused islets engraft at the level of the hepatic sinusoids to release insulin and to restore endogenous C-peptide secretion (58) The liver was deemed the most appropriate site for PIPIT due to many reasons: high regenerative capacity, double vascularization, immunological protection (59). Alternative sites for PIPIT (bone marrow, kidney capsule, gastric submucosa, genitourinary tract, omentum, testis, thymus,

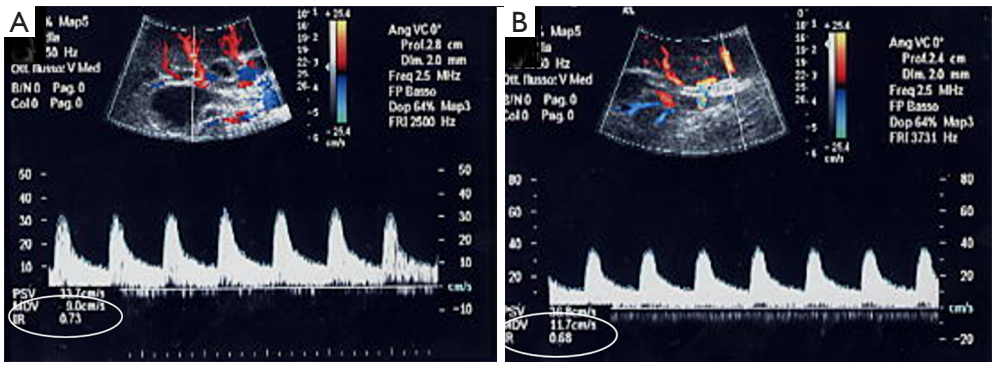

Figure 17 CDU examination of renal arterial resistive index before (A) and after (B) PIPIT, showing reduction of intraparenchymal resistances (0.73 to 0.68) 1 year after successful ITA. CDU, color Doppler ultrasound; PIPIT, percutaneous intra-portal pancreatic islet transplantation; ITA, islet-transplant-alone.

anterior chamber eye) were recently investigated (60) but without promising results (61). In case of allo-PIPIT, either in IAK or in ITA patients, pancreatic islets are extracted from cadaveric donors; while in case of auto-PIPIT patients are simultaneously donors and recipients. In allo-PIPIT patients need a life-long immunosuppressive treatment, while they don't need in auto-PIPIT. Functioning islets represent an effective β-cell replacement therapy able to normalize metabolic and glycaemic control. The most important islet transplantation centers report an insulin independence rate of 50–70% by 5 years after allo-PIPIT (10,62-64), according to the Edmonton protocol. Although insulin independence is the ideal outcome from islet transplantation, it is usually not the primary endpoint. Reduction of severe hypoglycemic events and diabetic complications are other important measures of transplant outcomes (65), that can be obtained also in case of partial islet function considering also that PIPIT is a repeatable procedure. The largest series of auto-PIPIT for chronic pancreatitis report insulin independence in 15–41% of patients (66-71). The University of Minnesota reported that 30% of 409 patients submitted to auto-PIPT were insulin independent at 3 years follow up and an additional 33% had partial graft function defined by the presence of C-peptide (67).

Imaging and interventional radiology play a crucial role in PIPIT. In our experience CDU is largely used in all the phases of an islet transplant: as pre-transplant imaging to evaluate portal vein patency, as guidance in the interventional procedure to safely and quickly access the portal vein, as early post-transplant imaging to diagnose eventual complications, and as late post-transplant imaging to assess liver structural changes and vascular modifications. CDU as pre-PIPIT imaging can provide hemodynamic information about the portal vein blood flow (patency or thrombosis, flow direction, anatomic variants). In our center (and nowadays in many others) CDU is routinely used as guidance to interventional procedures and to safely access in real time the portal vein. The portal vein visibility at CDU may be slightly reduced in auto-PIPIT, performed 12–36 hours after a surgical treatment. Combined use of US and fluoroscopy for percutaneous portal venous access is associated with a low risk of complications and shorter procedure time compared with fluoroscopy alone (25,29). A combined CT and fluoroscopy approach was also used for PIPIT (72): but a very prolonged procedural time (the patient needs to be transferred to the interventional suite following the CT-guided puncture) and an increased radiation dose are significant disadvantages. Although a right or left transhepatic puncture may be used, most series report the use of a right transhepatic approach for PIPIT (29,73). CDU as early post-PIPIT imaging is important to early diagnose peri-procedural complications as bleeding and portal vein thrombosis, the two main complications of PIPIT: an early diagnosis is important to anticipate eventual therapeutic solutions (transfusions *vs.* anticoagulation therapy). Theoretically IAK patients affected by long term T1DM and chronically submitted to aspirin administration, should have a higher bleeding risk than ITA (and auto-transplanted) patients. In our experience, no statistically significant differences in terms of bleeding were found between IAK and ITA patients. A slightly higher bleeding rate was found in allo-transplanted patients submitted to a third PIPIT procedure than those submitted to

second or first transplant (18): probably the higher portal vein pressure usually recorded during a third transplant procedure can determine a greater bleeding risk (74). An accurate intrahepatic tract embolization at the end of the procedure under ultrasonographic and/or fluoroscopic guidance can contribute to reduce the bleeding risk (74). CDU is also used as late post-PIPIT imaging to monitor liver structural changes: the appearance of steatosis after 6 months has been universally detected by US and MRI (46) but curiously not in all patients and without a shared relationship with the islet function. In our opinion, steatosis represents an early marker of islet dysfunction (51). Our hypothesis is strengthened by a recent prospective study involving all the 3 islet-transplanted populations (50). As expected, auto-transplanted patients, not needing immunosuppression, achieved better clinical outcomes than allo-transplanted patients but the percentage of steatosis ultrasonically detectable was significantly lower (4% *vs.* 24%). The relevant advantage of detecting steatosis at US is to early identify patients still maintaining good values of islet function (C-peptide, β score) but evolving towards graft exhaustion: these patients might receive additional immunosuppressive treatment, insulin therapy or might be listed for a further PIPIT before complete graft failure. CDU is also used to monitor vascular modifications after PIPIT. In case of successful islet transplantation, not only in case of insulin independence but also of partial islet function, restoring a good metabolic control, beneficial effects on renal (17), ocular (18) and carotid (19) blood flow at CDU have been demonstrated. Retinal microcirculation improvement is particularly relevant because diabetes is still the major cause of blindness in western countries (75). Other imaging techniques, such as MRI and PET, are under investigation to detect the engrafted islets: both techniques require ex-vivo islets to be labeled before PIPIT with SPIO and fluorine 18 fluorodeoxyglucose (FDG). Labeled islets can be visualized at MRI (40) and PET (42) allowing the monitoring of islet engraftment. DCE-MRI has been also used to study liver perfusion changes after PIPIT and their correlation with graft function (41).

In conclusion, allo-PIPIT is a minimally invasive, innovative and repeatable therapeutic option to treat brittle T1DM, reducing the impact of its complications. Auto-PIPIT, in case of extensive pancreatectomy, prevents pancreatogenic diabetes without need of immunosuppression. Interventional radiology and imaging both play a key role in PIPIT. CDU represents an useful tool to obtain hemodynamic information about portal vein before transplant, to provide real time guidance to the interventional procedure reducing puncture attempts, to early diagnose peri-procedural complications, to monitor hepatic and vascular changes and, in our opinion, to predict the clinical outcome in case of steatosis detection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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