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Imaging of transplanted islets by positron emission tomography, magnetic resonance imaging, and ultrasonography

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Keywords: islet transplantation, positron emission tomography (PET), magnetic resonance imaging (MRI), ultrasonography or ultrasound (US), islet, diabetes mellitus (DM)

Abbreviations: BLI, bioluminescence imaging; CT, computed tomography; DM, diabetes mellitus; DO3A-VS, 1,4,7-tris(acetic acid)-10-vinylsulfone-1,4,7,10-tetraazacyclododecane; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7-10-tetraacetic acid; DTBZ, dihydrotetrabenzine; FDG, 2-[18F] fluoro-2deoxy-D-glucose; FHBG, 9-[4-fluoro-3-(hydroxymethyl)butyl]guanine; FIAU, iodo-1-(2-deoxy-2-fluoro-b-D-arabinofuranosyl)uracil; Gd, gadolinium; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HF-US, high-frequency ultrasonography; IBMIR, instant blood-mediated inflammatory reaction; IL, interleukin; Mn, manganese; MN-NIRF, magnetic nanoparticles modified with a near-infrared fluorescent; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; SPIO, superparamagnetic iron oxide; T1WI, T1-weighted images; T2WI, T2-weighted images; US, ultrasonography or ultrasound; VMAT2, vesicular monoamine transporter 2

While islet transplantation is considered a useful therapeutic option for severe diabetes mellitus (DM), the outcome of this treatment remains unsatisfactory. This is largely due to the damage and loss of islets in the early transplant stage. Thus, it is important to monitor the condition of the transplanted islets, so that a treatment can be selected to rescue the islets from damage if needed. Recently, numerous trials have been performed to investigate the efficacy of different imaging modalities for visualizing transplanted islets. Positron emission tomography (PET) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities for this purpose. Some groups, including ours, have also tried to visualize transplanted islets by ultrasonography (US). In this review article, we discuss the recent progress in islet imaging.

Introduction

Islet transplantation is a useful therapeutic option for severe diabetes mellitus (DM), including type 1 DM and pancreatomized DM.[1-3] The procedure involves dripping isolated islets into the portal vein to engraft them in the liver. This is a safe and relatively fast procedure that can be performed under local anesthesia. According to the most recent report from the Collaborative Islet Transplant Registry, 571 diabetic recipients received islet allotransplantation from the pancreata of 1,010 donors from 1999 to 2009 (http://www.citregistry.org). However, the outcome of islet transplantation, though improving, remains inadequate. Approximately 40% of the islet-transplanted recipients require daily insulin injection at 3 y after transplantation, and many recipients require multiple donors. The worse transplant efficacy is brought about by rejection,[4] a thrombotic and inflammatory reaction called instant blood-mediated inflammatory reaction (IBMIR),[5] islet toxicity due to immunosuppressants,[6-9] or islet ischemia[10,11] in the early transplant stage. Thus, it is important to monitor the condition of the transplanted islets. If damage to the islets can be detected, then an appropriate treatment can be selected to rescue the islets from damage. The classical monitoring parameters for assessing islet viability and function, such as blood glucose level, serum C-peptide level, glucose tolerance test, or HbA1c, are based on the metabolic function of islets. Because abnormalities in these parameters arise after actual damage to the islets, they can be considered relatively late markers of islet graft dysfunction.[12] Needle biopsy of the liver is another method for monitoring transplanted islets, and can show direct evidence of islet damage such as hypoxia, apoptosis, and immune or inflammatory response by immunohistochemistry. However, needle biopsy is an invasive procedure with a low success rate for detecting islets (according to Toso and colleagues, the success rate was 31%).[13]

Numerous experimental trials have been performed to investigate the efficacy of different imaging modalities for visualizing transplanted islets. Bioluminescence imaging (BLI)

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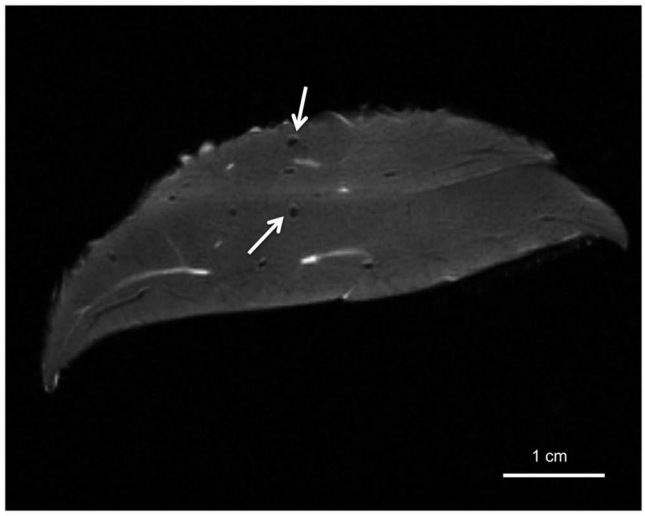

Figure 1. Syngeneic transplanted SPIO-labeled islets were seen as hypointensive spotty areas (arrow) in the livers of mice on T2WI MRI (our unpublished data).

is one of the earliest of these methodologies.[14] This method visualizes transplanted islets with luciferase gene transfection as an optical image by oxidation of luciferin as an injected substrate. BLI is a good technique for evaluating islet engraftment[15] and rejection.[16] However, BLI is not a suitable modality for a clinical setting because it cannot visualize deep tissue. Positron emission tomography (PET) and magnetic resonance imaging (MRI), which are widely used clinical imaging modalities, are the most widely used for this purpose. Some groups, including ours, have also tried to visualize transplanted islets by ultrasonography (US). In this review article, we describe the recent progress in islet imaging using clinical imaging modalities, including our own studies.

PET and SPECT

Early PET studies

PET is a noninvasive nuclear medical imaging modality for evaluating functional processes in the body with high resolution and good sensitivity. It is used especially for detecting tumors. Images are obtained based on the cellular consumption of molecules labeled with positron-emitting isotopes. The first study on islet imaging using PET was reported by Toso and colleagues in 2005. They labeled islets with 2-[^{18}F] fluoro-2deoxy-D-glucose (FDG) (**Table 1**), and certified that the radioactivity of the labeled islets was higher than that of non-labeled islets. Though the radioactivity declined at 6 h after transplantation, this was nonetheless the first successful attempt to detect islets using PET.[17] Many PET trials were published in 2006. In one study, Lu and colleagues succeeded in visualizing transplanted human and rat islets that were transduced with a thymidine kinase gene using 9-[4-fluoro-3-(hydroxymethyl)butyl]guanine (FHBG) as a tracer (**Table 1**).[18] In addition, they showed that labeled islets could be visualized for over 90 d after transplantation.[19] Kim and colleagues also visualized transplanted islets by the same method; moreover, they demonstrated that the radioactivity uptake in transplanted islets was elevated when the function of the islets was improved by induction of the viral *interleukin* (*IL)-10* gene,[20] which promotes glucagon-like peptide-1 (GLP-1) expression.[21]

Recent progress in PET imaging

Because these cell-labeling methods were based on a viral transduction technique, it is difficult to utilize them directly in a clinical setting. Furthermore, because the islets must be labeled before transplantation, these methods cannot be applied to post-transplant islets. To overcome these challenges, novel probes that can label islets specifically by intravenous injection have been developed. Simpson and colleagues successfully visualized islets labeled with [^{11}C] dihydrotetrabenzine (DTBZ) via vesicular monoamine transporter 2 (VMAT2), which is specifically expressed on islets. They performed PET with normal and diabetic rats using this method, and found that radioactivity uptake was present in the normal pancreas but not in the diabetic pancreas.[22] Witkowski and colleagues succeeded in visualizing intramuscular transplanted rat islets on PET using this tracer.[23] In a study using a similar probe, 9-[^{18}F]fluoropropyl-(+)DTBZ, which has a longer half-life than [^{11}C]DTBZ (110 min in [^{18}F] vs 20 min in [^{11}C]), was also specifically taken up into the pancreas following intravenous injection.[24]

The GLP-1 receptor agonist exendin-4 has also received attention as a potentially novel and effective PET probe, because GLP-1 receptors are highly expressed in islets and a probe containing exendin-4 has been shown to bind to islets specifically. In previous studies, [^{64}Cu]Lys^{40}-1,4,7,10-tetraazacyclododecane-1,4,7–10-tetraacetic acid (DOTA)-NH_2-exendin-4,[25] and [^{64}Cu]1,4,7-tris(acetic acid)-10-vinylsulfone-1,4,7,10-tetraazacyclododecane (DO3A-VS)-Cys^{40}-exendin-4[26] have been used to specifically visualize islets in rodent models (**Table 1**). The other novel tracers for specific labeling of islets, such as [^{18}F]dithizon (targeting Zn^{2+} ions in islets),[27,28] and [^{11}C]- and [^{18}F]- labeled L-DOPA (catecholamine precursor),[29] have been developed and used for visualization of islets in pancreatic and islet cell tumors. In particular, [^{18}F]-labeled fallypride (dopamine D2/3 ligand) was used for labeling transplanted islets in a rat model.[30]

These tracers are targeted for binding with a biomarker expressed on islets, but they can also bind to other organs which have the same marker. To identify transplanted islets specifically, studies using a pretargeting approach are underway. In the pretargeting approach, the islets are visualized after receiving pretreatment with materials combined with a tracer.[31] Eriksson and colleagues succeeded in labeling transplanted islets specifically by avidin-biotin interaction. They developed a [^{68}Ga]-labeled biotin tracer and used it to visualize avidin-covered beads transplanted into the liver. They also certified that the avidin-coated human islets could uptake the tracer by means of an in vitro assay. The avidin technique might contribute to the prevention of IBMIR by binding heparin.[32]

Clinical trials of PET

A clinical trial in which PET was used to visualize islets was performed by Eriksson and colleagues in 2009. They performed PET in 6 patients during islet transplantation, and detected

Table 1. Published PET tracers for visualizing transplanted islets

Method for labeling	Tracer	References	Radioactivity	Islet donor species	Comments
Labeling of islets directly	[^{18}F]FDG	[17,33]	4–6 h	human, rat	Available for clinical use already Short radioactivity High uncharacteristic washout
	[^{18}F]FHBG	[18-20]	1–3 mo	human, rat, mouse	Longer radioactivity Use of viral vector
Labeling of islets via intravenous infusion	[^{11}C]DTBZ	[23]	Approximately 30 min	rat	Specific labeling of islets via VMAT2 Short radioactivity
	[^{64}Cu]/[^{18}F]-labeled exendin-4	[26,36]	Over 4 h	human	Specific labeling of islets via GLP-1 receptor
	[^{18}F]- labeled fallypride	[30]	Over 1.5 h	rat	Specific labeling of islets via D2/D3 receptor Available for clinical use already Binds to other organs (mainly the brain)
	[^{68}Ga]-labeled biotin	[32]	Over 30 min	human	Specific labeling of islets via avidin-biotin interaction Prevention of IBMIR

spotty radioactivity uptake in the liver of each patient. The FDG-labeled islets made up 15.0–30.2% of total islets, but there were no adverse events in any of the patients, all of whom showed good glucose tolerance at 1 mo after the transplantation.[33] This was the first report to demonstrate the clinical safety of PET imaging and its usefulness for real-time quantitative and qualitative evaluation of the islet kinetics, and was also the only clinical trial using PET for this purpose. However, the results clearly suggested that PET imaging was a useful method for islet engraftment and that further clinical studies would be warranted. Especially, improvement of the probe is necessary.

SPECT studies on transplanted islets

Single-photon emission CT (SPECT) is a nuclear medicine tomographic imaging method using gamma rays. Like PET, SPECT can evaluate functional processes in the body, and thus is useful to detect the early stages of cancer. Also like PET, SPECT is useful to evaluate the conditions of islets based on tracer enhancements as a marker of radioactivity, but the spatial resolution is poor (8–10 mm) and it is impossible to visualize single islets.[34] There have been few studies using SPECT to visualize islets, particularly transplanted islets, but Tai and colleagues succeeded in visualizing transplanted islet cell lines on 5-^{131}I-iodo-1-(2-deoxy-2-fluoro-b-D-arabinofuranosyl)uracil ([^{131}I]-FIAU)-enhanced SPECT using a mouse model in 2007.[35]

MRI

Early MRI studies

MRI is an important imaging modality with advantages such as high spatial resolution, good penetration depth, and strong inhibition of ionizing radiation. However, due to the similar intensity between transplanted islets and liver tissue, MRI cannot be used to visualize islets that have not been pretreated in some way. An experimental trial on the efficacy of MRI for visualizing cells and other tiny structures was started in the late 1990s.[36] The structures or cells to be visualized were labeled with an iron-based MRI agent. Islets are very tiny cellular complexes (generally smaller than 400 μm), but it was expected that they could be visualized on MRI using this agent. In 2004, Jirak and colleagues were the first to succeed in visualizing transplanted islets on MRI; they used a rat model and labeled the islets with superparamagnetic iron oxide (SPIO). The islets were detected in the liver as hypointensive spotty areas on T2-weighted images (T2WI) at 7 d after transplantation, while the transplanted diabetic rats had achieved normoglycemia by that time (**Table 2**; **Fig. 1**).[37] In subsequent studies, the same authors showed that the islets were also visualized at 6 weeks after transplantation,[38] and that the hypointensive areas vanished when the transplanted allogeneic[39] (**Table 2**) and xenogeneic[40] islets were rejected. These data showed that the SPIO-labeled islets could be visualized by MRI, although this technique did not indicate the viability of the islets. A Harvard group developed a novel type of labeling agent that consisted of SPIO and a fluorescent agent (Cy5.5 dye) to evaluate the islet condition. Labeling islets with these SPIO magnetic nanoparticles modified with a near-infrared fluorescent (MN-NIRF) dye, they succeeded in detecting islets both by MRI and immunohistochemical examination in subrenal capsular

Table 2. Progress of islet imaging on MRI

Year	References	MRI condition	Strength in scanners	Donor	Recipient	Contrast agent	Comments
2004	[37]	T2WI	4.7T	rat	rat	Resovist®	The first study for MRI imaging
2005	[39]	T2WI	4.7T	rat (allo)	rat	Resovist®	Rejection model on MRI
2006	[41]	T2WI	4.7T	human	mouse (immune deficient)	SPIO (MN-NIRF)	Certified islets both on MRI and in histological staining
2006	[46]	T2WI	1.5T	rat	rat	Feridex® with poly-l-lysine	Availability of clinical MRI Few toxic agents
2007	[43]	T1WI	7T	mouse and human	mouse (immune deficient)	Gd	The first study of T1WI MRI
2007	[60]	T1 and T2WI	11.7T	mouse	mouse	Feridex® and Gd	Visualized islets by Feridex® labeling and vessels around islets by Gd enhancement
2007	[64]	T2WI	3T	human	pig	Feridex® (encapsulated islets)	MRI for large animals
2008	[66]	T2WI	1.5T	human	human	Resovist®	The first clinical success of MRI imaging
2009	[54]	T2WI	4.7T	rat	rat (allo)	Feridex®, Resovist®, Endorem®	Evaluation of toxicity in various SPIOs
2009	[65]	T2WI	1.5T	baboon	baboon (auto)	Feridex®	Autotranplantation model using non-human primates
2010	[67]	T2WI	3T	human	human	Resovist®	Clinical MRI imaging
2011	[53]	T2WI	1.5T	rat	mouse (immune deficient	Feridex® with heparin	Lower toxicity Improving engraftment

and intraportal transplant models.[41] They also described that the transplanted xenogeneic islets (human to mouse) had disappeared on T2WI MRI due to immune rejection.[42] Their findings confirmed that islets could be detected on MRI by labeling with SPIO, that the labeled islets could be seen in any transplant site, and that MRI could also reveal the condition of the transplanted islets, including their engraftment status, under the certification of fluorescent stained islets immunohistochemically.

Studies for islet imaging with MRI in a clinical setting

On the basis of this successful islet imaging by MRI in these experimental studies, numerous studies have been performed to overcome the challenges to the clinical use of this modality. First, improvement of the contrast agent was necessary because classic SPIO has some drawbacks in terms of stability, magnetic sensitivity, and toxicity.[37] Biancone and colleagues tried to visualize islets using gadolinium (Gd) instead of SPIO, and succeeded in visualizing human islets transplanted into immune-deficient mice as hyperintensive areas on T1-weighted images (T1WI) MRI. They also proved that the Gd agent did not impair islets in in vitro assessments of viability and insulin-releasing function.[43] Arifin and colleagues developed novel microcapsules for delivering alginate-encapsulated islet cells containing Gd chelates that could be seen as hyperintensive areas on T1WI MRI; the microcapsules conferred immunoprotection against immune-competent cells while responding to changes in blood glucose by releasing insulin.[44] Leoni and colleagues tried to label human islets with a manganese (Mn) agent and performed MRI. They revealed that the Mn-enhanced MRI was useful for evaluating isolated islet functions in in vitro assessments.[45] Regarding SPIO, some novel agents with high stability and low or no toxicity have also been developed. For example, Tai and colleagues used a new SPIO coated with poly-l-lysine, which has lower toxicity.[46,47] Polyvinylpyrrolidone,[48,49] chitosan,[50-52] and heparin[53] have also been used as SPIO coatings. In recent studies, clinical-grade iron nanoparticles, such as ferucarbotran (Resovist®; Bayer Schering Pharma AG), have been used as a more suitable material for labeling islets instead of the classical SPIOs, ferumoxide (Feridex®; AMAG Pharmaceuticals Inc.) and Endorem® (Guerbet). Marzola and colleagues showed that transplanted Resovist®-labeled rat islets could be detected as hypointensive spots in the liver at 42 d after transplantation. The toxicity of Resovist® for islets was weaker than that of Feridex® in an in vitro assay.[54] The lower toxicity was also confirmed by the Park group.[55] Ris and colleagues also compared 3 SPIOs,

Resovist®, Endorem®, and Feridex®, in terms of their stability and function using rat syngeneic and xenogeneic (human to rat) intraportal transplant models, and found that Resovist® had better insulin-releasing ability and signal stability than Endorem® or Feridex®. They also detected Resovist®-labeled islets in the liver for 8 weeks in a syngeneic transplant model, whereas they had disappeared within 8 weeks in a xenogeneic transplant model.[56] Similar data about rejection were also reported by Kriz and colleagues using an allogeneic transplant model.[57]

Another important question is whether a clinical-grade MRI device could visualize transplanted individual islets. A higher magnetic flux density MRI device (over 4.7 tesla [T]) was used in earlier experimental MRI studies,[37,42] and there was no evidence that islets could be visualized using a clinical-grade MRI device with 1.5 T in the mid-2000s. In 2006, Tai and colleagues succeeded in visualizing SPIO-labeled rat islets that were transplanted into the subrenal capsule using a clinical-grade MRI device with 1.5 T (**Table 2**).[46] After their success, 1.5 T became the standard magnetic flux density, and many groups applied this density condition in their experimental studies.[54,58,59]

MRI is useful for evaluating not only islet imaging but also neovascularization around transplanted islets. Hathout and colleagues focused on neovascularization using experimental animals. They performed syngeneic Feridex®-labeled islet transplantation to the subrenal capsule of mice and performed Gd-enhanced MRI at 3, 7, and 14 d after transplantation. They found Feridex®-labeled islets on T2WI MRI and new Gd-enhanced vessels around the islets on T1WI MRI. The Gd intensity was strongest at 14 d after transplantation, which is the time required to complete neovascularization. Finally, they confirmed the imaging of the vessel network around the islets until 28 d after transplantation[60,61] (**Table 2**). They also performed syngeneic islet transplantation to the right lobe of the liver of diabetic mice, and performed Gd-enhanced MRI at 3, 7, 14, and 28 d after transplantation. The intensity of the right lobe was stronger at 7 d after transplantation than at 3 d, while the intensity of the left lobe had not changed. The degree of intensity was significantly correlated with the number of vessels around the islets.[62] Furthermore, they showed that the intensity of the right lobe was significantly correlated with the blood glucose level, serum insulin level, and change in glucose tolerance.[63] These data revealed that MRI is a useful modality for evaluating neovascularization around transplanted islets and the endocrinal function of the islets when contrast agent is applied.

MRI studies using larger animals for better approximation of the clinical setting have also been performed. The Johns Hopkins group developed encapsulated islets coated with Feridex®, called magnetocapsules. They then intraportally transplanted the magnetocapsules containing human islets into swine, and showed that the capsules could be detected in the liver as hypointensive spots on T2WI MRI at 3 weeks after transplantation, and that the serum human C-peptide level was also elevated at this time (**Table 2**).[64] Medarova and colleagues succeeded in visualizing Feridex®-labeled baboon islets on T2WI MRI in subrenal capsular and intraportal islet autotransplant models.[65]

Clinical trials of MRI in islet transplantation

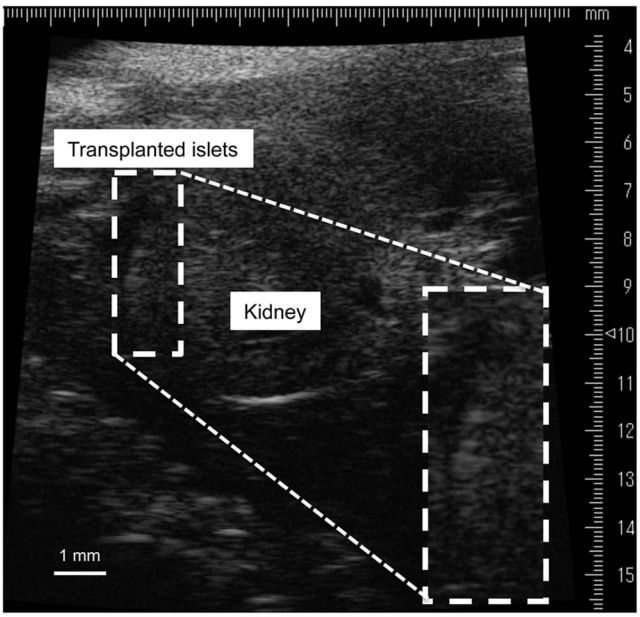

Figure 2. High-frequency ultrasonographic (HF-US) image of transplanted islets in the subrenal capsule. The islets appear as a hyperechoic area on the surface of the kidney. This is a modified version of a figure from a previous study.[75]

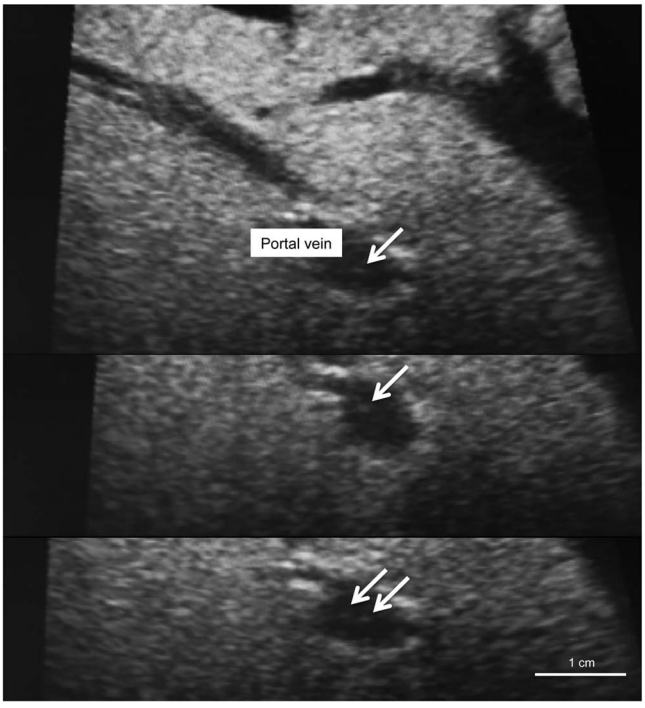

Figure 3. Intraoperative ultrasonographic (US) image for a patient who received islet autotransplantation. The transplanted islets appear as hyperechoic clusters in the portal vein. This is a modified version of a figure from a previous study.[76]

Table 3. Advantages and disadvantages of PET, MRI, and US

	Advantages	Disadvantages
PET	Imaging of islets functionally High resolution Good sensitivity No necessity for islet labeling before transplantation	Ionizing radiation No anatomical information Low spatial resolution (single transplanted islets cannot be visualized)
MRI	High resolution High spatial resolution No ionizing radiation	Necessity of labeling islets before transplantation Toxicity of agent Difficulty of distinguishing between live and dead islets
US	No adverse events for patients Can be performed at bedside	No methodology to visualize single islets at present

The first clinical trial was done by Toso and colleagues in 2008. They performed SPIO-labeled human islet transplantation in 4 patients with type 1 DM. The percentages of labeled islets were 12.6–66.6%. In 3 of the 4 patients, the islets were detected as hypointensive spots in the liver, and in one of the patients, islets were seen at 6 mo after transplantation (**Table 2**).[66] Saudek and colleagues also performed Resovist®-labeled islet transplantation in 8 type 1 DM patients (5 of them achieved insulin independence), and found hypointensive spots on T2WI MRI at 24 weeks after transplantation.[67] On the other hand, an approximately 50% signal loss was detected at 7 d after transplantation and was reduced to 30% at 168 d after transplantation in this clinical trial. This decrease in the signals might reflect early and late islet graft loss.

Summary of MRI studies

In summary, MRI is one of the most advanced modalities for visualization of islets. Some unique studies on contrast agents that function in prolonging the engraftment of islets have been performed by Wang and colleagues.[68,69] Many studies have shown a positive correlation between islet engraftment and function and islet image,[39,70] but there are some obstacles to promoting this methodology at the clinical level. Recently Zacharovova and colleagues confirmed that SPIOs in the transplanted islets were taken into phagocytic cells including macrophages, and that the hypointensive spots on T2WI MRI might not reflect engrafted islets alone.[71] This means that the number of obtained signals might not reflect the number of engrafted islets, which could lead physicians to misinterpret the engraftment of islets (i.e., by leading to false-positive results). Moreover, labeling agents are necessary for MRI examination, and thus the islets cannot be protected from the toxicity of the labeling agents, which might impair the engraftment. The difficulty of long-term visualization of transplanted islets is also a hurdle in the clinical setting. Finally, when reduced islet graft function is observed, MRI cannot be used to evaluate the islet engraftments. All these obstacles should be overcome for the clinical setting of islet visualization using MRI.

US

US is a useful and safe imaging technique for visualizing subcutaneous body structures, and has the advantage of being performed at the bedside. If islets could be visualized by US with sufficient sensitivity, this might provide many benefits for clinicians in evaluating islet function and condition with little stress on patients. However, there have been few experimental trials.

We have investigated the visualization of islets by US. First, we attempted to visualize transplanted islets with high-frequency ultrasonography (HF-US), evaluating the correlations between HF-US findings and islet function. HF-US uses ultrasound at a high frequency (above 20 MHz), thereby producing higher-resolution images than conventional US.[72] It has been used to diagnose various diseases.[73,74] We transplanted syngeneic (BALB/c mice) and xenogeneic (Sprague-Dawley rats) islets into the subrenal capsular space of diabetic mice. After the transplantation, the mice were examined by HF-US (central frequency 35 MHz, axial resolution 50 μm, focal length 10 mm). In the syngeneic transplant model, a hyperechoic area was detected at the subrenal capsular space during the observation (**Fig. 2**). On the other hand, transplanted islets were visualized as hypoechoic areas that reflected the damage to the islets due to rejection at 3 d after transplantation; they completely disappeared by 28 d in the xenogeneic transplant model. The islet volume calculated by the HF-US device was correlated with numbers of transplanted islets, blood glucose, and serum insulin.[75] These experimental data indicated that US could be used to visualize transplanted islets and to evaluate endocrinal function and condition, including rejection of the islets.

We also clarified that individual islets in the portal vein could be visualized by intraoperative US (the central frequency was 7.5 MHz) in the clinic. We performed total pancreatectomy with islet autotransplantation via the portal vein in a 39-y-old man who had chronic pancreatitis with pancreatic arteriovenous malformation. We examined the portal vein by US during the transplantation, and detected individual transplanted islets as hyperechoic clusters that flowed toward the periphery of the portal vein (**Fig. 3**).[76] This finding and our previously described experimental data clarified some speculations about the use of US imaging for evaluating the islet condition. First, viable islets can be visualized as hyperechoic images not only in rodents but also in humans. It is conceivable that islet imaging in intraoperative US (especially echogenicity) could provide reliable information for predicting the outcome of islet transplantation. Second, islets can be visualized not

only with high-frequency US but also with the usual US used for the human abdomen (central frequency of 7.5 MHz) in spite of their tiny structures. Our data also suggest that US could be an essential component in the examination of islet transplantation.

The next step for US is visualization of transplanted individual islets as in MRI and PET. Recently, Barnett and colleagues developed a new device that contains islets and can be visualized by multimodal imaging techniques. The device was constructed by the encapsulation of islets and a contrast agent including SPIO (perfluorocarbon)[77] or gadolinium chelate[44] using alginate, which is the material used to encapsulate islets. It not only functions in immune-isolation of the encapsulated islets but also can be visualized by MRI at 9.4 T, micro-CT (CT), and HF-US. These trials are considered the first to succeed in individual islet visualization. Further US studies are clearly warranted.

Conclusion

Non-invasive imaging modalities are available for evaluating islet conditions, including the success or failure of engraftment. In particular, the methodologies of MRI and PET have been rapidly improving. Because these methodologies have different advantages and disadvantages (**Table 3**), their use in combination is recommended for accurate assessment of the condition of transplanted islets. As one example of the combination, we consider that US can be used for detecting islets during the infusion, PET for evaluating chronic islet dysfunction and MRI for assessing islet engraftment. Moreover, the combined use of these modalities with classic examinations such as blood and urinary tests could also be used for the same purpose. And although it is difficult to apply US to the detection of islets at present, the studies are just beginning. These imaging examinations may help to improve the outcome of islet transplantation in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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