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Islet Transplantation: Alternative Sites

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Abstract The portal vein is currently the site of choice for clinical islet transplantation, even though it is far from being an ideal site. Low oxygen tension and the induction of an inflammatory response impair islet implantation and lead to significant early loss. Even if enough islets survive the early implantation period to render insulin independence, few patients maintain it. Therefore, the search for an ideal site for islet transplantation continues. Experimentally, islets have been transplanted into the portal vein, kidney subcapsule, spleen, pancreas, peritoneum, omentum, gastrointestinal wall, testis, thymus, bone marrow, anterior chamber of the eye, cerebral ventricles, and subcutaneous and intramuscular spaces. Some of these sites are suitable for gathering scientific data, whereas others have potential clinical application. Varying degrees of success have been reported with the use of all these transplant sites in an experimental setting. However, the optimal transplant site remains to be finally established.

Keywords Islet transplantation · Sites · Liver · Kidney subcapsule · Spleen · Pancreas · Peritoneum · Gastrointestinal walls · Bone marrow · Subcutaneous

Introduction

The optimal site for islet transplantation should offer an optimal engraftment with long-term graft function. It should also be easy to access with minor surgical complications, and it should be immunologically privileged. In other words, such a site would 1) provide portal venous drainage to permit normalization of blood glucose levels and avoid systemic hyperinsulinemia; 2) provide a rich arterial supply to the islets, thereby increasing oxygen tension; 3) allow for minimally invasive clinical islet infusion; 4) allow easy access for functional and morphologic follow-up of the islets post transplant; 5) provide a microenvironment that prevents early islet loss, thereby enhancing islet engraftment; and 6) protect islets from rejection. Such an optimal site has yet to be defined. Surgical complications may be seen following transplantation to all possible sites and no site is completely immunoprivileged.

The islets of Langerhans consist of endocrine cells embedded in a rich network of specialized capillaries that regulate islet blood flow [1]. In addition, revascularization of grafted islets in a new host organ determines survival and function of these islets [1]. Therefore, an islet graft needs a rich vascularized organ for survival. Numerous sites have been tested for experimental islet transplantation, including the liver, kidney subcapsule, spleen, pancreas, peritoneum, omentum, gastrointestinal wall, testis, thymus, bone marrow, anterior chamber of the eye, cerebral ventricles, and subcutaneous and intramuscular spaces. Despite the success of experimental islet transplantation in rodents using these sites for islet transplantation, few sites went on to be tested in a large animal model. Even though the testis, the cerebral ventricles, the anterior chamber of eye, and the thymus are suggested to be immunologically privileged sites, these sites are only useful for scientific studies and remain clinically irrelevant. For clinical islet transplantation, intraportal infusion remains currently the preferred site. The aim of this manuscript is to review the recent data concerning the clinically relevant alternative islet transplantation sites.

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The Liver

The liver is currently the site of choice for clinical islet transplantation. The advantages of the liver as a site for islet transplantation include the relative ease of transplant with minimal side effects as it can be done through a minimally invasive approach without the need for surgery, as well as portal insulin delivery and thus avoidance of systemic hyperinsulinemia. Conversely, the liver is far from being an ideal site for islet transplantation. Technically, intraportal islet infusion has been accompanied by serious complications, such as portal hypertension, bleeding, or even portal vein thrombosis [2]. In addition, routine biopsies to monitor these islets are difficult. Recent technical developments, such as improving the purity of the islet preparation, heparin supplementation, and occlusion of the tract after islet infusion with coils, have reduced the risk of these complications [2]. Despite these improvements, the liver environment remains hostile to these transplanted islets. Significant percentages of islets die shortly after intraportal transplantation due to activation of hemostasis and thrombotic mechanisms [3–6], macrophage and Kupffer cell–mediated inflammation [7, 8], as well as higher levels of immune suppressive medication such as sirolimus and tacrolimus in the portal circulation that are directly toxic to or impair engraftment of islets [9]. In fact, the portal-to-systemic drug level ratio ranged from 0.95 to 2.71 for sirolimus and 1.0 to 3.12 for tacrolimus [9]. Even after syngeneic islet transplantation into the portal vein of mice, insulin content, glucose-stimulated insulin release, (pro) insulin biosynthesis, and glucose oxidation rate were markedly decreased in islets retrieved from the liver, when compared with both islets transplanted into the pancreas and endogenous islets, suggesting that the liver markedly impaired the metabolic functions of intraportally transplanted islets [10••]. In an autotransplant model in dogs where alloimmunities and autoimmunities are not an issue, Alejandro et al. [11] showed that 30,000 islets were sufficient to reverse diabetes in all animals; however, 80% of animals became diabetic within 15 months suggesting continuous loss of islet function. Consequently, the liver is not an ideal host for transplanted islets for long-term function. In an experimental study in mice, syngeneic islets were transplanted into four sites: kidney, liver, muscle, and omentum. The authors compared operative feasibility, efficiency of implantation (the marginal mass required to cure diabetes), and glycemic control [12]. The results showed that operative feasibility and efficiency of implantation were best for the kidney, whereas glucose kinetics of omental pouch islets was the most similar to controls [12]. In the clinical setting, despite using islets from more than one donor to achieve insulin independence, within 3 years post transplant almost three quarters of the patients were insulin dependent (Collaborative Islet Transplant Registry annual report; http://www.citregistry.org).

The Kidney Subcapsule

The kidney subcapsule has been used for a long time as a site for experimental islet transplantation. It has the advantages of graft retrieval for both histologic studies and for confirming the functional effect of the islet graft on experimental diabetes. The kidney subcapsule space possesses special advantages in the clinical setting in the case of combined islet/kidney transplant from the same donor, as islets can be implanted into the kidney subcapsule of the newly transplanted kidney. The kidney subcapsule has also been suggested to be immunologically privileged [13], even though other studies have not supported this conclusion [14, 15]. Nevertheless, experimental islet transplantation to the kidney subcapsule has been used by several authors with good results. In rats, islet transplantation into the kidney subcapsule normalized blood glucose and insulin levels to various stimuli and reversed diabetes complications in the kidney and eyes [16–19].

Despite the success of experimental islet transplantation into the kidney subcapsule, it remains far from an ideal site. The technique of islet transplantation into the kidney subcapsule involves an invasive laparotomy. Incisions are made in the kidney capsule into which the isolated islets are implanted. The oxygen tension in islets implanted beneath the kidney capsule is markedly lower than in native islets up to 9 months after transplantation [20]. In diabetic rats, an even more pronounced decrease in graft tissue oxygen tension was seen [20]. However, the same authors showed a similarly marked decrease in oxygen tension and blood flow into syngeniec islets that were transplanted into the spleen or the liver compared with native islets [21]. There was no difference among the three transplantation sites [21]. Such low blood flow and oxygen tension does not seem to impair successful islet grafting in rodents. In a mouse islet transplant model, the operative feasibility and efficiency of implantation were best for the kidney subcapsule when compared with the liver or omental pouch [12].

In a canine islet transplant model, the number of islets needed to reverse diabetes in a pancreatectomized recipient when transplanted into the portal vein or the spleen was lower than the number needed when placed in the kidney subcapsule [22]. In the pre-human primate islet transplant model, we have shown that the portal vein was superior to the kidney subcapsule as a site for islet transplantation [23•]. In clinical studies, C-peptide level as a marker for islet survival has been shown after transplantation into the kidney subcapsule; however, a higher islet mass was used

compared with transplantation into the portal vein [24]. The required invasive procedure to place the islets in the kidney subcapsule and the high number of islets needed to reverse diabetes may limit the utility of this site to the experimental setting.

The Spleen

In the early era of islet transplantation, the spleen was used extensively as the site for experimental islet transplantation. The advantages of the spleen as a site for islet transplantation include good vascular supply and portal vein insulin delivery. In the pre-human primate model, islet autotransplantation into the spleen after total pancreatectomy was better than the kidney subcapsule for either impure islet preparations, or purified islet preparations, if the mass of tissue implanted was marginal [25]. The spleen allowed fasting normoglycemia, and preservation of islet morphology with numerous islets scattered throughout the spleen [25]. In addition, the number of islets needed to reverse surgical diabetes in dogs was similar when transplanted into the liver or spleen [22]. Intrasplenic pancreatic islet grafts demonstrated functional improvement with time [26]. There was a case report of one patient with juvenile diabetes and subsequent renal failure who was successfully treated with simultaneous kidney and intrasplenic pancreatic islet allotransplants. The patient had normal blood glucose levels without exogenous insulin 1 year after transplantation despite treatment with prednisone [27]. However, the spleen milieu being rich with lymphocytes and the risks of bleeding remain major obstacles for clinical applications.

The Pancreas

The pancreas, being the normal home for the islets, with ideal oxygen tension, is theoretically an attractive site for transplantation. Conversely, the autoimmunity of diabetes may endanger the intrapancreatic transplanted islets, and technically it is an invasive procedure, with the risk of inducing pancreatitis. Few studies have evaluated the pancreas as a site for islet transplantation. In rats, studies have shown fewer islets need to be transplanted into the pancreas to reverse diabetes than when transplanted into the portal vein [28].

The Peritoneum and Omental Pouch

The greater omentum possesses several features that are sought in an ideal site for islet transplantation. The greater omentum has good arterial pedicles, numerous lymphatic vessels, exclusive portal drainage, a high vascular density, and allows for good neoangiogenesis [29]. An omental pouch can be constructed with long pedicles to be placed in a superficial, subcutaneous area, thereby enabling the monitoring of implanted islets. In rodents, the omental pouch has been shown to offer a safe, convenient, and efficacious alternative to the renal subcapsular space for transplanted islets [30]. Syngeneic islets transplanted into the omental pouch of streptozotocin-induced diabetic rats restored normoglycemia and normal glucose tolerance tests that were different from those transplanted into the kidney subcapsule [30]. Histologic examination of the grafts showed numerous well-granulated insulin-containing cells in both sites and there was no difference in insulin content of the harvested grafts [31]. In diabetic mice, the omental pouch as a site for syngeneic islet transplantation was the best when compared with kidney, liver, and muscle sites in achieving glycemic control and glucose kinetics that were the most similar to controls [12].

The omental pouch of diabetic dogs has been successfully used as a site for autologous islet implant [31–33]. In a study by Ao et al. [32], purified islets autotransplanted into the greater omental pouch successfully reversed surgically induced diabetes in totally pancreatectomized recipients. Compared with intrasplenic islet implantation, insulin levels were lower and an increased graft volume was required to achieve insulin independence in the omental pouch [32].

Recently, the omental pouch has been used as a site for islet transplantation in the pre-human primate model [34••]. Islets were loaded on a synthetic biodegradable scaffold and placed in the omental pouch of diabetic cynomolgus monkeys. Islet engraftment and survival were assessed using blood glucose, C-peptide, exogenous insulin requirements, intravenous glucose tolerance tests, hemoglobin A_{1c} (HbA_{1c}), and histopathology. All animals achieved positive C-peptide levels, a 66% to 92% post-transplant decrease in insulin requirements and reduced HbA_{1c}. Histopathologic analysis of the explanted grafts demonstrated well-granulated and well-vascularized, insulin-positive islets surrounded by T-cell subsets and macrophages. Compared with intrahepatic allogeneic islet transplants, there was a delayed engraftment for omental pouch recipients but similar levels of C-peptide production were ultimately achieved [34••].

The omental pouch also has the advantages of accepting unpurified islets that would carry the risks of portal hypertension and coagulopathy if transplanted into the portal vein [31]. In an experimental study in dogs, the spleen and omental pouch, but not the liver, skeletal muscle, or kidney subcapsule, have been shown to be suitable sites for transplantation of unpurified islets as

evident from achieving islet function with less morbidity [31].

In an experimental study in rodents, Ferguson and Scothorne [35] showed that a small number (12–15) of allogeneic islets implanted in the greater omentum of nonimmunosuppressed guinea pigs were able to survive for long periods of time, with no rejected grafts observed, suggesting that the omentum is an immunoprivileged site. However, from the same study, a larger skin graft in the omentum did not survive as long as a smaller graft [30]. In the nonhuman primate experiments [34], histopathologic examination of omental pouches removed from immunosuppressed monkeys after a minimum of 124 days showed well-granulated islets surrounded by varying amounts of lymphocytes, with minimal signs of lymphocytic infiltration. All these data suggest that the omental pouch has potential as an alternative site for clinical islet transplantation. However, further studies are needed, especially to address the number of islets reported to be required to achieve normoglycemia in rodents [30] and large animals [33, 36].

The Gastrointestinal Wall

The small bowels, as sites for islet transplantation, have easy accessibility for implant and biopsy, and portal vein delivery of insulin. In a small study in rats, islets isografted into small bowel subserosa restored normoglycemia in 80% of recipients. In addition, glucose tolerance tests were comparable with that of the portal vein islet recipients [37].

The submucosa of the stomach and duodenum may represent a better alternative site, because it has a dense vascular network, long-term trophic support in vitro [38], and permits laparoscopic or endoscopic transplantation and follow-up. In a study using the mini pig, the use of the gastric submucosa for islet transplantation was compared with the kidney capsule [39]. At one month post transplantation, islets engrafted in the gastric submucosa demonstrated a better function than those grafted into the kidney subcapsule [39]. The duodenal submucosal space was investigated in Syrian golden hamsters as a site for islet transplantation [40]. Islet function following transplantation into streptozotocin-induced diabetic hamsters, as determined by an intravenous glucose tolerance test, was similar to nondiabetic controls and was significantly greater than diabetic controls [40]. In addition, islets transplanted into the submucosal space became richly vascularized within two weeks, and there was minimal host inflammatory infiltrates. The β cells of the graft remained well granulated with insulin for at least 129 days [40].

The duodenum and gastric submucosal space possess the additional advantage of easy access by endoscopy. The technical success of using endoscopy to transplant islets into the gastric submucosal space was demonstrated recently in pigs [41•]. All the animals in the study tolerated the procedures and there were no signs of perforation, ulceration, or bleeding after transplantation. MRI scans revealed thickening of the gastric wall at sites of islet deposition. Functionally, endoscopic submucosal islet allotransplantation into streptozotocin-induced diabetic pigs resulted in significantly lower exogenous insulin requirement and lower mean glycemia since the first day post transplantation [41•]. The authors concluded that transendoscopic islets transplantation into gastric submucosa is feasible and a safe procedure [41•]. These encouraging results warrant further investigation.

The Intramuscular and Subcutaneous Space

The intramuscular and subcutaneous spaces offer the easiest accessibility for implantation and monitoring with routine biopsies with minimal complications, and are used routinely in clinical practice for parathyroid autotransplantation. However, for islet transplantation, experiences with these sites were disappointing even when postoperative hyperbaric oxygen therapy was applied [42]. Poor oxygen tension and blood supply and lack of early neovascularization may have contributed to the poor outcome. Therefore, induction of angiogenesis in the transplantation sites was promoted as an important factor for successful islet implantation. Several techniques have been used to achieve these goals. In an experimental study [43], angiogenesis was induced at the intermuscular space of diabetic rats by implanting a polyethylene terephthalate mesh bag, which enclosed a collagen sponge and biodegradable gelatin microspheres containing basic fibroblast growth factor. After confirmation of angiogenesis, isolated islets were transplanted into the prevascularized space [43]. Normoglycemia and normal glucose tolerance test were achieved in the rats within three days and maintained for more than 35 days [43]. Induction of neovascularization at the intramuscular site improved islet transplant engraftment and survival compared with controls [44•]. Reversal of hyperglycemia by islet transplantation was most successful in recipients pretreated with bioscaffolds containing angiogenic factors when compared with those who received no bioscaffolds or bioscaffolds not treated with angiogenic factors [44•].

In the subcutaneous tissue, syngeneic islets were implanted into a biocompatible device consisting of a cylindrical stainless-steel mesh [45]. The device was

implanted 40 days prior to islet transplantation to allow neovascularization. Syngeneic islets transplanted into this device restored normoglycemia in diabetic rats and sustained long-term function [45]. No large animal study was conducted to study these sites for islet transplantation. However, three diabetic patients had a subtherapeutic dose of islets transplanted into the forearm. On biopsy, two of the three patients showed β-cell staining and an infiltrate consistent with autoimmune disease [46].

The Bone Marrow

Bone marrow offers an easily accessible site for transplantation. In fact, it is still used for blood transfusion in children. In an experimental study in rats, islet isografts, allografts, and xenografts (tilapia islets to rats) were transplanted into the bone marrow (tibia) of nondiabetic recipients [47]. No immunosuppression was used. The isografts and allografts showed positive staining for insulin and glucagon and no evidence of allograft rejection up to 21 days post transplant, whereas the xenografts were acutely rejected [47]. The authors concluded that the bone marrow is capable of maintaining pancreatic islets in the absence of immunosuppression and, thus, can constitute an immunoprivileged environment for engraftment [47]. In another study from Italy [47], syngeneic islets engrafted efficiently in the bone marrow of streptozotocin-induced diabetic mice, as evident from glucose metabolism that was similar to that of nondiabetic mice [48•]. Islets transplanted into the bone marrow had a higher probability to reach euglycemia than islets transplanted into the liver, and showed a compact morphology with a conserved ratio between α and β cells [48•]. In addition, there was marginal effect on the bone marrow structure [48•]. These encouraging results await confirmation and further testing in a large animal study.

Conclusions

Although the portal vein is the site most often used in clinical islet transplantation, it is not ideal, as evidenced by experimental data and dismal long-term outcomes in the clinical setting. Other sites have been investigated, and some offer promise for future use. However, it has yet to be determined which site will ensure optimal engraftment with long-term graft function.

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- •• Of major importance

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