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REVIEW

An overview of current advancements in pancreatic islet transplantation into the omentum

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ABSTRACT

Pancreatic islet transplantation to restore insulin production in Type 1 Diabetes Mellitus patients is commonly performed by infusion of islets into the hepatic portal system. However, the risk of portal vein thrombosis or elevation of portal pressure after transplantation introduces challenges to this procedure. Thus, alternative sites have been investigated, among which the omentum represents an ideal candidate. The surgical site is easily accessible, and the tissue is highly vascularized with a large surface area for metabolic exchange. Furthermore, the ability of the omentum to host large volumes of islets represents an intriguing if not ideal site for encapsulated islet transplantation. Research on the safety and efficacy of the omentum as a transplant site focuses on the utilization of biologic scaffolds or encapsulation of islets in a biocompatible semi-permeable membrane. Currently, more clinical trials are required to better characterize the safety and efficacy of islet transplantation into the omentum.

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Introduction

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder in which insulin-producing β-cells, predominant within the islets of Langerhans in the pancreas, are destroyed. This ultimately results in blood sugar elevation and loss of glycemic control.[1] The development of the Edmonton protocol in 2000 introduced islet transplantation as a method to restore glycemic control in insulin-dependent T1DM patients.[2] Under the current standard of care, the liver is considered the primary site for clinical islet transplantation. The islets can be easily infused into the hepatic portal system allowing β-cells to effectively restore glycemic control to the patients. However, there are limitations associated with islet infusion into the portal system. There is a risk of portal vein thrombosis as well as the elevation of portal pressure that can lead to uncontrolled bleeding. Moreover, there is a possibility of islet loss after transplantation due to the IBMIR that can occur when islets encounter the recipient's blood.[3–6] In order to address the limitations associated with intrahepatic islet transplantation, alternative sites have been investigated including but not limited to the omentum, peritoneum, spleen, renal subcapsule, and gastric submucosa. However, some of these sites show limitations in capacity and functional outcome or introduce further complications post-transplant.[3,7–12]

Among these alternative sites, the omentum has been well characterized and has emerged as a potential preferred site for clinical islet transplantation. The ease of access to the surgical site for graft transplantation, the extensive surface area, and the highly vascularized structure of the omentum with a portal venous drainage system makes it an ideal site for islet transplantation. It is also possible to effectively increase the surface area for graft oxygen delivery and metabolic exchange by folding the omentum on itself. A study in 1977 transplanted islet allograft within a folded omentum in guinea pigs which resulted in islet survival with no sign of rejection post-transplant.[13,14] Since then, research on the safety and efficacy of the omentum as a site for islet transplantation has sought to identify novel surgical techniques and cell delivery methods for graft transplantation to restore glycemic control. Such approaches and techniques are briefly discussed.

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Transplantation of non-encapsulated islets into the omentum

The first clinical islet transplantation into the omentum was performed during the 1980s in which three patients received allogeneic islet transplants into the arteriolar epiploic flap of the omentum. Insulin production was observed in all three cases. One patient became insulin-independent at seven months after the transplant and remained normoglycemic up to fifteen months post-transplant.[15] Since then, different approaches to islet transplantation into the omentum and their effectiveness have been investigated. Yasunami et al.[8] described the construction of a peritoneal-omental pouch using the strips of the omentum. Isografts of rat islets transplanted into the omentum pouch resulted in normoglycemia in insulin-dependent diabetic rats, and the removal of the pouch containing the islets resulted in a prompt return to the diabetic state. The creation of an omental pouch, which is technically simple, allows the islets to be localized in one area by the enclosing sheath of the peritoneum and the insulin to be released into the portal venous system.[8] Moreover, graft retrieval is relatively simple compared to intraperitoneal graft retrieval.[16] Ao et al.[17] also reported the construction of an omental pouch for auto- or allotransplantation of canine islets and indicated that the pouch could host a large number of islets and induce glycemic control in diabetic dogs.[17] Another study in animals that have undergone total pancreatectomy demonstrated that the omental pouch could offer a higher rate of survival for unpurified islets compared to other sites. Berman et al. showed that the transplantation of low purity islets (30% endocrine) into the omentum of insulin-dependent diabetic animals resulted in glycemic control comparable to that of purified islets (>95% endocrine). The ability of the omentum to host a large volume of low purity islets makes it an attractive site for allogeneic islet transplantation considering the low purity of isolated human islets and the impracticality of transplanting a large volume of unpurified islets into the liver.[18–20]

An allogeneic islet transplantation study in diabetic mice provided a comparison between the omental and intrahepatic sites. The results indicated that the marginal islet mass in islet equivalent (IEQ), defined as the mass of islets required to cure diabetes in 50% of the engrafted diabetic mice, was lower in the omentum (200 IEQs) than the liver (600 IEQs). Additionally, the mean time to achieve euglycemia was 13.9 ± 3.7 days in the omentum group compared to 15.1 ± 3.3 days in the liver group. Moreover, an intraperitoneal glucose tolerance test three months post-transplant showed that the omentum group had a higher glucose clearance rate, which was not significantly different from the normal control animals.[19] Another study in diabetic monkeys has reported that the released insulin (c-peptide) levels were comparable between the omental and intraportal allogeneic islet transplant recipients.[7] These findings suggest that the omentum can be a promising alternative site to intraportal infusion of islets and control T1DM.

More recently, the use of biologic scaffolds to support islet engraftment has been studied. A novel approach called 'omental-roll-up' was tested in dogs. The procedure involved the preparation of a coagulum of autologous plasma with islets and vascular endothelial growth factors (VEGF) to serve as a temporary *in vivo* culture for the islets during graft revascularization. After the omental implantation of the coagulum containing the islets and VEGF, the tissue was rolled up to secure the graft. Immunohistochemical staining confirmed the presence of islets in the omentum of the animals, and the portal venous samples indicated insulin production. These results suggested that the omental implantation of the three-dimensional islet support in the coagulum of autologous plasma with growth factors could provide a culture-like condition during the progression of graft revascularization. Additionally, compared to islet engraftment without a coagulum, the implantation of islets within a thin plasma coagulum with overlapping layers of omentum does not require the construction of a water-tight pouch to contain the islets. The leakage of islets out of the pouch is associated with failure to establish euglycemia. Consequently, eliminating the need for a water-tight pouch allows fewer sutures to be used, thus reducing the

possibility of ischemia and compromising the islets' blood supply.[17,21] The use of biologic scaffolds has also been investigated in human clinical trials. As a part of an ongoing study at the University of Miami (Allogenic Islet Cells Transplanted onto the omentum; NCT02213003), Baidal et al.[22] implanted the islets into the omentum of a 43-year-old female with T1DM using a degradable biologic scaffold comprised of recombinant thrombin and autologous plasma. The patient discontinued insulin seventeen days after implantation and maintained insulin-independence twelve months post-transplant.[22] Currently, another clinical trial in Italy (NCT02803905) is underway to assess the safety and efficacy of islet implantation into the omentum with the Miami approach.[13]

Lastly, Stice et al.[3] demonstrated the efficacy of a combined transplant site approach in which islets were infused into the hepatic portal vein and an omental pouch. This strategy proved effective in four patients with intraoperative issues that prevented the complete infusion of islets into the portal vein. The researchers created an omental pouch in order to transplant the remaining islets. Follow-up studies indicated that the patients' insulin requirements decreased over time. Compared to intraportal islet recipients, there were no significant differences in glycemic control or graft function three months after transplantation. These results suggest that the omentum may provide a safe alternative site for autotransplantation of islets.[3]

Transplantation of encapsulated islets into the omentum

In 1980, Lim and Sun[23] first reported that single implantation of encapsulated islets into insulin-dependent diabetic rats restored glycemic control for almost three weeks post-transplant. Additionally, the encapsulated islet recipients had significantly lower blood glucose levels compared to rats that received non-encapsulated islets.[23] Since then, advancements have been made to improve islet encapsulation procedures for insulin delivery and expand its clinical application. Encapsulation involves the coating of islets in a biocompatible semi-permeable hydrogel membrane, which can then be transplanted into diabetic patients.[24] The semi-permeable membrane allows the passage of oxygen, glucose, insulin, and nutrients while preventing the attachment of the immune cells and antibodies to the graft, which can delay rejection.[25] Overall, there are two approaches to cell encapsulation for immune isolation of islets. Microencapsulation involves the containment of individual or small groups of islets within a chemically stable microsphere. In contrast, macroencapsulation is the coating of a large mass of islets within a biocompatible planar or cylindrical scaffold.[26,27] Currently, the transplantation of microencapsulated islets into the omentum has been investigated.

Commonly, microencapsulated islets are transplanted into the peritoneal cavity due to ease of access to the surgical site, and more importantly, its ability to host large volumes of islets, which is a requirement for transplantation of microencapsulated islets. However, the peritoneal cavity is an avascular site where limited oxygen and nutrient diffusion expose the transplanted islets to prolonged periods of hypoxia and hamper their ability to survive and function. Additionally, the graft retrieval for biopsy and further evaluation is difficult.[28–31] The omental site is highly vascularized, can accommodate and localize a large number of islets, and allows the graft retrieval post-transplant; thus, it provides a large volume and an ideal site for the transplantation of microencapsulated islets.[17,32] Kobayashi et al.[33] demonstrated that the transplantation of agarose microencapsulated alloislets into the omentum reversed hyperglycemia in diabetic NOD mice. The results indicated that nine out of ten recipients of the microencapsulated islets remained normoglycemic for more than a hundred days post-transplant. In contrast, all ten recipients of non-encapsulated islets in the control group experienced a short-term period of normoglycemia after the transplant and returned to hyperglycemia three weeks post-transplant. Furthermore, the removal of the omental pouch containing the microencapsulated islets prompted a return to the diabetic state, which indicated that the microencapsulated islets were

responsible for maintaining normoglycemia in diabetic animals.[33] Another study showed alginate-microencapsulated islets transplanted into the omentum produced glycemic control in insulin-dependent diabetic rats.[30] These findings suggest that the omentum could be a viable site for the transplantation of microencapsulated islets.

Conclusion

Nearly all body tissues have been investigated as alternatives to intrahepatic islet transplantation. Although pre-clinical *in vivo* studies in alternate sites have demonstrated an ability to restore glycemic control, very few have reached clinical practice and studied in properly designed randomized clinical trials.[13] In addition, limitations in capacity and functional outcome or the introduction of further complications post-transplant render these sites either impractical or unsafe to use for islet transplant.[3]

Preliminary data show that the omentum proves a viable alternative site for islet transplantation. Its highly vascularized structure and large surface area, as well as the accessibility of the site for graft transplantation and retrieval, makes the tissue an attractive site for clinical islet transplantation.[13,16] Unlike intraportal islet transplantation, the omentum can allow transplantation of unpurified islets, a characteristic of great importance in allogeneic transplantation of low purity islets.[18,19] Furthermore, the ability of the omentum to host large volumes of islets, which is a requirement for the transplantation of encapsulated islets, makes the site ideal for the transplantation of encapsulated insulin-secreting cells.[17,32]

For all the benefits the omentum offers, one of its major limitations is the inability to receive multiple transplants; thus, the site may not be an option for patients that require laparotomy.[19] Relaparotomy is associated with pain, incisional hernia, ileus, and increase the risk of wound and abdominal infection.[34] In spite of this, the omentum is the only alternative site that has shown efficacy in clinical islet transplantation and provided a short period of insulin independence in a small population of patients with T1DM.[13] However, more clinical evidence is required to better characterize the safety, efficacy, and suitability of the omentum as the preferred site for clinical islet transplantation.

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Disclosure statement

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