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The search for a new site for islet transplantation

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Abstract

Good vascularity and large surface for implantation make the omentum a promising site for implant of islet transplantation alternatively to the liver. The first successes of these procedures have further increased the interest toward the omentum. In particular, the strategy suggested by the University of Miami, which includes the use of autologous plasma and thrombin, seems to result in a promotion of the revascularization process and encourages further exploration of this islet transplant site. This transplant strategy could also allow for the introduction of additional local immunoprotective agents, stimulating an even wider interest.

Commentary

Islet transplants have already passed the graduation exam. The procedure is now reliably performed at several centers in many nations and at present it is considered a truly therapeutic option for patients with unstable type 1 diabetes or those who are already on immunosuppressive therapy due to previous organ transplants[1]. In selected centers, the success of islet transplantation is now comparable to that of pancreas transplant alone. The CIT (Clinical Islet Transplantation) Consortium has recently defined a standardized manufacturing protocol, which can be considered a reference procedure for the preparation of islet cell products for transplant applications[2,3]. The results of a new international multicenter trial to evaluate the effect of reparixin as an anti-inflammatory treatment to improve islets engraftment[4] should soon become available and could encourage further refinement of the peri-transplant immunomodulatory strategies. Nevertheless, it is indisputable that many problems still exist, including those linked to the liver as a transplant site. First of all, it is well known that the infusion of the islets inside the portal bed triggers Instant Blood-Mediated Inflammatory Reaction (IBMIR), which is responsible for a significant loss of transplanted islets[5]. In order to obtain a successful transplant, every patient must receive a number of islets twice as large as the one needed to reverse diabetes in the absence of the islet loss due to IBMIR. The islets in the liver are exposed to a high concentration of immunosuppressive drugs and to the phenomenon of glucotoxicity, which could, in the long term, contribute to the exhaustion of islet function[6]. The most important problem presented by the intrahepatic site is the difficulty of introducing local and peri insular immuno-protective or immunomodulating strategies, to avoid, or at least reduce, the need for exposing islet transplant recipients to systemic immunosuppressive therapy. As a matter of fact, the islets dispersed throughout the liver following intraportal infusion are not easily traceable. In addition, islet coating by traditional microencapsulation technologies would be impossible, because of the limited tissue volume that could be infused into the portal system. Furthermore, intra-hepatic islet transplants are not retrievable and this makes future beta cell replacement strategies more challenging in this site. As an example, it would be impossible to recover a stem cell-derived insulin producing cell product, in case it needed to be removed after infusion. At present, this represents a key-limiting factor of islet transplantation. The time has come to find new solutions, new sites for islet implant that facilitate islet engraftment and at the same time allow the possibility to apply techniques to reduce immunosuppressive drugs toxic effects[7]. The results published on the use of other sites for islet transplantation are quite disappointing. Beyond the sporadic evidence of islet function in alternative sites, including the muscle or the bone marrow, there has been no insulin independence reported

by islet transplantation in extrahepatic sites until the very recent report by the Diabetes Research Institute at the University of Miami[8]. There are no new clinical data showing further development of islet transplantation in the skeletal muscle or the bone marrow, following early cases published some years ago. The intramuscular site was originally introduced, for islet autograft, by the Karolinska Institute University[9,10]. Following islet autotransplantation in the skeletal muscle in patients whose pancreas was surgically removed, a significant concentration of circulating c-peptide was detected and the daily insulin requirements decreased. The procedure described is simple, executable in local anesthesia and allows monitoring of the preparation transplanted by means of biopsy or marked antibodies. It is still difficult to scatter the islet properly within muscle bundles to avoid aggregation - which would impair proper oxygenation[11]. After the first reported results, in which insulin independence was not achieved in any recipient, there have been no additional communications in islet allotransplantation. The first cases of islet transplantation within the bone marrow were also recently reported[12], with low post-transplant islet function up to a maximum follow up of 944 days after the transplant, and a modest decrease in insulin requirements[12]. In this site, it was possible to monitor islet engraftment by biopsy, but no allotransplants have been reported. In summary, the results obtained either in the muscle or in the marrow showed only marginal islet function in the autografts, with no data in the allograft setting. For this reason, the first patient who became insulin independent following islet allotransplantation in the omentum received great attention[8] (Figure 1). For the first time, islet transplantation in a site other than the liver not only obtained evidence of a partial function (C-peptide release, reduction of insulin need), but also allowed the patient to completely discontinue exogenous insulin therapy for over one year.

Good vascularity, large surface for implantation, easily performed and minimally invasive surgical procedures, and the possibility of implementing complementary strategies for immune-modulation or immune-protection make the omentum an attractive alternative site[13]. The strategy suggested by the University of Miami, which includes the use of autologous plasma and thrombin, seems to result in a promotion of the revascularization process and encourages further exploration of this islet transplant site. This transplant strategy could also allow for the introduction of additional local immunoprotective agents, stimulating an even wider interest. Immunoprotective agents could allow the discontinuation of continuous recipient immunosuppression, therefore expanding the current indications beyond the very selected subjects in which the risks of systemic immunosuppression are justified. However, the omentum is also a very reactive organ that could easily respond with an encapsulating/fibrotic reaction. Therefore, the quality of the tissue transplanted, details on the preparation of the final islet cell product transplanted, as well the implantation technique, could be critically important and affect islet transplant outcome, as recently discussed by Dr. Ricordi in a plenary lecture at the IPITA Congress in Oxford. So far, while the interest in developing alternative sites for islet transplantation remains strong and the initial results in the omentum site have been encouraging, the liver con-

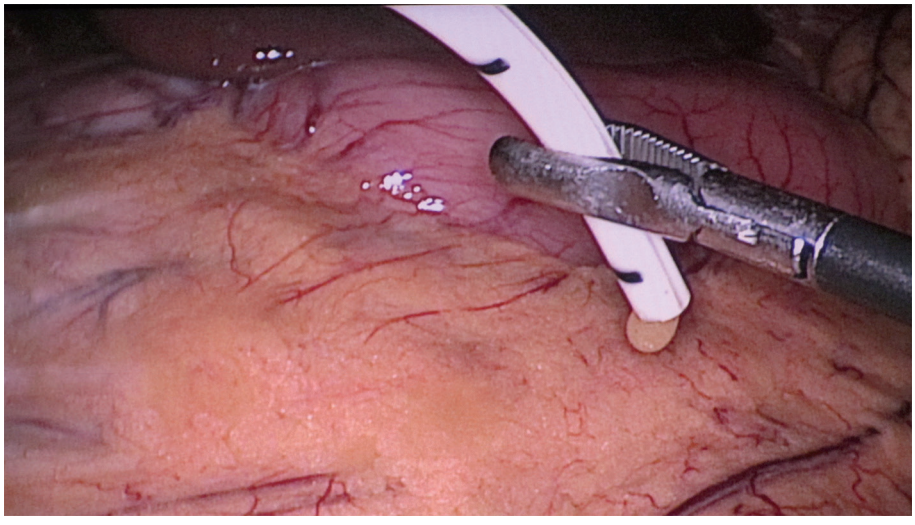

Figure 1. Islet transplantation in the omentum. Human islets, after a dispersion in autologous plasma, are applied on the recipient omentum surface through a small catheter by a laparoscopic approach.

tinues to represent the gold standard for long-term islet function and further studies are needed to develop and validate possible clinically viable alternatives.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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