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Clinical application of microencapsulated islets: Actual prospectives on progress and challenges ☆

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ABSTRACT

After 25 years of intense pre-clinical work on microencapsulated intraperitoneal islet grafts into non-immunosuppressed diabetic recipients, the application of this procedure to patients with type 1 diabetes mellitus has been a significant step forward. This result, achieved in a few centers worldwide, underlies the safety of biopolymers used for microencapsulation. Without this advance, no permission for human application of microcapsules would have ever been obtained after years of purification technologies applied to the raw alginates. To improve safety of the encapsulated islet graft system, renewed efforts on the capsules' bioengineering, as well as on insulin-producing cells within the capsular membranes, are in progress. It is hoped that advances in these two critical aspects of the cell encapsulation technology will result in wider human application of this system.

Contents

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1. Introduction

Ethiopathogenesis of type 1 diabetes mellitus (T1D) is based on autoimmune β-cell selective killing, driven by autoreactive CD4 clones, also involving a complex cascade of pro-inflammatory and pro-apoptotic molecules. Different working hypotheses on a possible direct role of infection agents on pancreatic (β-cells included) destruction remain unproven [1]. Nevertheless, and regardless of the acquisition of novel β-cell destruction pathways, the near total disappearance of β-cells within the islets leads to endogenous insulin deprivation, which clinically translates into overt diabetes mellitus. Should exogenous insulin supplementation be obviated or delayed, acute and frequently fatal complications would ensue. Hence and so far, exogenous insulin continues to be the mainstay of T1D therapy — virtually the only treatment that allows for T1D patients' survival. In fact, if appropriately modulated, exogenous insulin therapy regimens, implemented by the introduction of the new analogic molecules [2], according to established injection algorithms, may substantially reduce the risk of developing secondary, chronic complications of T1D, with special regard to micro- and macro-angiopathy, a combination that leads invariably to retinopathy, disabling neuropathy, cardiovascular disease and terminal renal failure [2]. However, while life-saving and able to at least restrain the development ofT1D-linked secondary multiorgan damage, insulin therapy is associated with several pitfalls, based on the fundamental principle that exogenous insulin administration can never mimic the stimulus-coupled insulin secretory kinetics of normal β-cells under physiological conditions. Moreover, in a minor cohort of T1D patients, blood glucose (BG) control, despite applied intensive insulin therapy regimens, is brittle, regardless of the insulin delivery system (i.e. conventional vs. minipump). For these reasons and because in general, as mentioned above, BG control using exogenous insulin will be imperfect even in the best conditions, there have been strenuous efforts to substitute the diseased or dead islet β-cells, associated to T1D, with fresh and viable tissue derived from cadaveric pancreatic donors.

While this approach has been pursued for over three decades, using whole donor pancreatic, or isolated islets from donor pancreases, the initial hopes that such a replacement therapy would rapidly and fully succeed have been largely shattered. In fact and in particular, whole pancreatic transplantation remains a quite major surgery, still associated with high morbidity. Isolated islet grafting procedures, *via* transhepatic puncture delivery, in T1D patients, have encountered a series of technical and methodological problems, many of which are still pending. For both procedures, the recipient's systemic pharmacological immunosuppression is a necessary condition for allowing the tissue engraftment and immunologic acceptance. This is not a minor point, considering that β-cell replacement strategies are not a life-saving procedure and per se would not justify the use of dangerous immunosuppressive regimen protocols. Today islet and pancreas transplantation may be reimbursed in some countries, and is even cited in the Clinical Practice Recommendations of the American Diabetes Association [2], intended for a limited cohort of T1D patients; however, both procedures continue to be virtually experimental.

1.1. Clinical islet cell transplantation

Outcomes of clinical islet transplantation (TX) have steadily improved through eras [3] with special regard to 2007–2010, when, according to the data of the Clinical Islet Transplant (CIT) Consortium, 65% of the grafted patients reached insulin-independency at 1 year of post-TX. Less consistent was the maintenance of insulin independence at 5 years of TX — which has significantly improved, reaching 40–50% of all treated patients, only in a few centers worldwide (Edmonton, Minneapolis, Geneva, Lille and Milano) although still unable to match the clinical outcome of whole pancreatic grafts. A major problem is that clinical results obtained by a single whole pancreatic graft may be paralleled by islets obtained from at least 2–3 if not more cadaveric pancreatic donors. In selected instances, review of the CIT Registry (CITR) (www.citregistry.org) data shows that the use of new specific Tc-depleting agents in association with anti-inflammatory molecules allowed extension of insulin independence, in a few cases, by 60–70%. In these successful cases, the pro's supporting the islet TX procedure can be summarized as shown in Table 1.

Such beneficial effects have been deemed to occur, not necessarily in fully insulin-independent patients but also in patients where the TX was functioning, in terms of serum C-peptide detection, and with improvements in HbA1c levels [13,14].

However, in these selected centers, according to CITR, crude mortality associated with the procedure was 3% out of 6 years of elapsed follow-up per patient (including stroke, heart attack, respiratory distress syndrome, ketoacidosis and multiorgan failure); while neoplastic events (0.02/individual/year) also appeared, particularly for lung cancer and skin tumors.

By the same token, several problems, some apparently quite serious, still hamper widespread diffusion of the procedure in a large segment of the T1D population (Table 2).

In summary, these drawbacks remain largely unanswered and restrict islet transplantation to a selected experimental procedure, applicable to only a minor cohort of patients with T1D and available in only a few centers worldwide. To make this approach a cure for T1D, as initially hoped, the gap between dream and reality is yet to be filled.

2. Immunoprotection of the transplanted islets within selective permeable, nontoxic microcapsules

2.1. Introductory remarks

Based on the principle that a possible β-cell substitution cell therapy, envisioned as a cure for T1D, should target all and not only a minority of the patients affected by this metabolic disease, some possible solutions are required. Should grafted islets be enveloped within artificial membranes that selectively regulate cross-permeability of noxious soluble factors, while preventing access to immunoactive cells and molecules, immunosuppressive treatment of the recipients could theoretically be obviated. The physical shield surrounding the islets would attenuate the impact of acute and chronic immune rejection, also offering the opportunity to employ less toxic and possibly locally delivered agents that would generally make the procedure more acceptable.

Additionally, microencapsulation might allow the use of nonhuman tissue as a resource for donor islets, thereby contrasting with the chronic restricted availability of human donor pancreases.

The immunoprotection approach by physical barriers may be pursued by the use of macrodevices or microcapsules, both based on the use of highly selective and nontoxic membranes, variably configured, and comprised of highly purified constituent biopolymers. In the beginning of our research activity on islet immunoprotection, 25 years ago, we selected microcapsules basically made of alginic acid derivatives complexed with amino-acid polycations.

Table 1
Clinical islet transplantation: beneficial effects of quality of life (QOL) and chronic complications.

QOL	Improved	Reference
Cardiovascular	Stabilized/improved	[4] MD Bellin, 2011; [5] T Tharavanij, 2008; [6] P Fiorina, 2005.
Renal	Prevention of GFR decline	[7] Thompson DM 2011; [8] Leitao CB 2009.
Neuropathic	Stabilized/improved	[9] Del Carro U 2007; [10] Lee TC 2005.
Retinal	Stabilized/improved	[11] Warnock GL 2008; [12] Thompson DM 2008.