JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Advancements and challenges in pancreatic islet transplantation: Insights from the Collaborative Islet Transplant Registry

Since the seminal success of Edmonton protocol in 2000, pancreatic islet transplantation has been very actively pursued worldwide[1]. This breakthrough has provided considerable encouragement to patients affected with type 1 diabetes, particularly those experiencing severe hypoglycemia and poor glycemic control, as well as healthcare professionals dedicated to their treatment. As of the latest report, over 1,300 patients have undergone pancreatic islet transplantation[2]. Notably, several recent studies have presented long-term follow-up results extending beyond 10 or even 20 years[2].

Despite these advancements, the field faces a significant challenge stemming from the diverse criteria employed across studies for assessing graft survival and transplantation success. This challenge is exacerbated by disparate transplantation protocols and confinement of studies to specific countries or institutions, hindering a comprehensive assessment of transplantation responses and the identification of prognostic factors.

To integrate and compile data from islet transplantation, the Collaborative Islet Transplant Registry (CITR) was established in 2001, with participation from more than 39 centers across over 10 countries to date[2]. Over the past two decades, this expansive registry has played a crucial role in aggregating islet transplantation data, significantly advancing our understanding of this therapeutic approach. This year, the CITR has reported three pivotal studies based on the accumulation and long-term analysis of this extensive dataset (Table 1)[2–4].

First, Bernhard Hering and colleagues[4] provided important clinical insights into transplantation protocols and post-transplant management by proposing a common set of four favorable factors. This study involved an extensive and thorough exploration, encompassing various affecting factors such as recipient/donor characteristics, islet graft properties, and immunosuppression methods. Four factors were identified with the highest predictive power, including recipient age of 35years or older, total infused islets of 325,000 islet equivalents or more, induction of immunosuppression with T cell depletion and/or tumor necrosis factor-alpha (TNF-α) inhibition, and maintenance with both the mechanistic target of rapamycin (mTOR) and a calcineurin inhibitor with the highest predictive power. Importantly, with the exception of age, these factors are modifiable and amenable to intervention.

Secondly, David Baidal *et al.*[3] observed a robust correlation between clinical outcomes and concurrent measurements of fasting and stimulated C-peptide levels, along with the C-peptide-to-glucose ratio. This finding implies that retention of C-peptide function should be regarded as another potential goal of islet transplantation.

Lastly, in *The Lancet Diabetes & Endocrinology*, Mikaël Chetboun *et al.*[2] reported the primary graft function (PGF; islet graft function after islet the last islet infusion) and 5 year outcome results. They utilized the BETA-2 score (derived from fasting C-peptide, fasting plasma glucose, HbA1c, and insulin dose expressed as continuous variables), based on 28 days after last islet transplantation, as an indicator to predict the 5 year success rate of islet transplantation[2]. This is significant as it introduces an indicator for predicting the success rate of transplantation, which, until now, either did not exist or was challenging to apply in practice due to diverse standards in various studies. Notably, the correlation analysis between PGF and long-term outcome considered all possible confounding factors, enhancing the reliability and verification power of the study, given its multi-center nature involving more than 1,000 transplants. It is important to note that the PGF was evaluated at 28 days after the last islet infusion. As the authors have already mentioned[2], this timeframe is considered appropriate, taking into account graft engraftment and vascularization. Additionally, it could allow sufficient time for stabilizing glucose homeostasis after transplantation. Previous studies have measured the BETA-2 score at 3 months or continuously after islet transplantation to analyze its relationship with transplantation outcomes[5]. However, given the rapid decline in graft function during the first month after transplantation and a gradual decrement thereafter[5], the 1-month time point suggested in this study appears to be appropriate for evaluating graft function to predict clinical outcomes. Lastly, they are unveiling a prediction model based on the results of this study (accessible on http://pgf.diabinnov.com/), providing crucial information for predicting the prognosis after islet transplantation, determining the need for additional islet transplantation, and offering valuable guidance to healthcare professionals and patients before and after islet transplantation.

Correspondence
Kun-Ho Yoon
Tel.: +82-2-2258-3589
Fax: +82-2-595-2534
E-mail address: yoonk@catholic.ac.kr

Received 16 November 2023; revised 9 December 2023; accepted 18 December 2023

Table 1 | Summary of recent findings from the Collaborative Islet Transplant Registry (CITR)

Author	Objective	Subject	Defined outcomes	Findings
Bernhard Hering *et al.*[4]	To determine factors associated with favorable long-term outcomes in islet transplant recipients	398 non-uremic islet transplant alone recipients with type 1 diabetes and SHEs between 1999 and 2015 and with at least 1 year follow-up	• HbA1c <7.0% and absence of SHEs • HbA1c <7.0% • Absence of SHEs • Fasting C-peptide ≥0.1 nmoL/L • Fasting glucose 59.4–140.4 mg/dL • Insulin independence, defined as >14 days with no exogenous insulin use	Four factors associated with the highest rates of successful outcomes • Age ≥ 35 years • Total infused islets ≥325,000 islet equivalents • Induction immunosuppression with T cell depletion and/or TNF-α inhibition • Maintenance with both mTOR and calcineurin inhibitor
Mikaël Chetboun *et al.*[2]	To clarify the distinct effect of PGF on 5-year transplantation outcomes	1,210 islet transplantation alone or islet-after-kidney transplantation recipients with type 1 diabetes between 1999 and 2020, with a calculable PGF	Primary outcome • Cumulative incidence of unsuccessful islet transplantation, defined as an HbA1c of 7.0% or higher, or severe hypoglycemia, or a fasting C-peptide <0.2 ng/mL Secondary outcome • Graft exhaustion (fasting C-peptide <0.3 ng/mL) • Inadequate glucose control (HbA1c ≥7.0% or severe hypoglycemia) • Requirement for exogenous insulin therapy (≥14 consecutive days)	An inverse, independent, and linear association between PGF (measured 28 days after last islet infusion) and the cumulative 5 year incidence of unfavorable outcomes, including unsuccessful islet transplantation, graft exhaustion, inadequate glucose control, and the need for exogenous insulin therapy
David Baidal *et al.*[3]	To determine C-peptide measures and levels associated with positive glycemic control outcomes following islet transplant	677 islet transplantation alone recipients whose C-peptide was negative (<0.3 ng/mL) before transplant	Primary outcome • Absence of SHEs • HbA1c <7.0% • HbA1c <7.0% and absence of SHEs • HbA1c ≤6.5% • HbA1c ≤6.5% and absence of SHEs • Insulin independence • Absence of SHEs, HbA1c ≤6.5%, and insulin independence (the optimal outcome)	High predictability of C-peptide for primary outcome The higher the C-peptide level, the greater the likelihood of achieving each outcome Cut-off value of C-peptide for optimal graft function: ≥1.0 ng/mL Outperformance of the mixed-meal tolerance test-stimulated C-peptide-to-glucose ratio in predictive ability for all primary outcomes except absence of SHEs, compared with both fasting and stimulated C-peptide

mTOR, mechanistic target of rapamycin; PGF, primary graft function; SHE, severe hypoglycemic events; TNF-α, tumor necrosis factor-alpha.

It is imperative to emphasize that the BETA-2 score at 28 days after transplantation is derived from the composite outcomes of various donor and recipient factors, encompassing islet number and function, immune responses, metabolic factors, and even unknown or poorly measured elements. Therefore, considering a multivariate analysis incorporating PGF in the model, it is necessary to re-evaluate their conclusion that the number of islet infusions and the transplanted islet mass had no significant impact on major clinical outcomes. While the BETA-2 score can serve as a useful indicator for assessing graft function and predicting long-term outcomes, successful islet transplantation still requires meticulous

preparation and vigilant post-transplant management, addressing factors ranging from islet number, mass, and function to post-transplant immunosuppressants[1,3].

Chetboun *et al.*[2] applied the Igls 2.0 criteria (revised from the original version), which distinguishes clinical outcomes based on glucose regulation from beta cell graft function using C-peptide and insulin requirement. Consequently, they excluded insulin dependence from the category of unsuccessful islet transplantation but considered fasting C-peptide as low as 0.2 ng/mL as a favorable outcome. This aspect warrants careful attention when interpreting their findings. As noted in another CITR report this year, the retention of C-peptide is closely tied to outcomes such as metabolic restoration, loss of severe hypoglycemic events (defined as hypoglycemia associated with loss of consciousness or requiring third-party assistance for recovery), and achieving insulin independence[3]. Despite the use of more lenient criteria for defining unsuccessful islet transplantation, the 5 year transplant success rate in this integrated registry remains below 30%. If more stringent parameters, such as insulin independence or a significant reduction in insulin requirement as suggested in the initial Igls criteria (a consensus definition for outcomes of beta cell replacement therapy in the treatment of diabetes from the international pancreas and islet transplantation association (IPITA)/European pancreas and islet transplantation (EPITA), consisting of four factors: HbA1c, severe hypoglycemia, insulin requirement, and C-peptide), and a higher C-peptide level (at least 0.3 ng/mL or more) are employed, the success rate could be anticipated to be even lower. This underscores that, despite significant progress in pancreatic islet transplantation, there is still considerable more room for improvement in achieving successful islet transplantation in the future.

Over the past two decades, remarkable advancements have transpired in islet transplantation. The outcomes delineated by the CITR, spanning this period and involving more than 30 centers, provide valuable insights that could significantly contribute to the broader adoption of islet transplantation. We are now able to systematically address common favorable factors associated with successful transplantation outcomes, and there is a growing recognition that maintaining C-peptide levels after transplantation may be another critical goal for successful outcomes. Furthermore, it is now pertinent to deliberate the utilization of the BETA-2 score, measured at 28 days after islet transplantation, as a pivotal tool for guiding re-transplantation decisions in patients. Prospective clinical trials are warranted to explore the BETA-2 score threshold at 28 days, guiding re-transplantation decisions, assessing the target goal of graft function, and validating these findings across diverse ethnic groups including Asian populations. In addition to benefiting from this extensive registry data, the development of modalities capable of assessing islet function before transplantation, such as islets-on-chip, along with the advancement of innovative immunomodulatory approaches, may pave the way for more successful islet transplantation in the future.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1C1C1013016) to E.Y.L.; by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health &Welfare, Republic of Korea (grant number: HI13C0954) and Cooperative Research Program for Agriculture Science and Technology Development (Project No. PJ01345301) Rural Development Administration, Republic of Korea to K.H.Y. Editorial services were provided by Caron Modeas, Evolved Editing, LLC.

DISCLOSURE

Kun-Ho Yoon is an Editorial Board member of *Journal of Diabetes Investigation* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

Eun Young Lee[1], Kun-Ho Yoon[1,2]
[1]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea,*
[2]*Institute of Catholic Ubiquitous Health Care, The Catholic University of Korea, Seoul, Korea*

REFERENCES

1. Shapiro AM, Lakey JR, Ryan EA, *et al.* Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; 343: 230–238.
2. Chetboun M, Drumez E, Ballou C, *et al.* Association between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: A retrospective, multicentre, observational cohort study in 1210 patients from the Collaborative Islet Transplant Registry. *Lancet Diabetes Endocrinol* 2023; 11: 391–401.
3. Baidal DA, Ballou CM, Rickels MR, *et al.* Predictive value of C-peptide measures for clinical outcomes of β-cell replacement therapy in type 1 diabetes: Report from the Collaborative Islet Transplant Registry (CITR). *Diabetes Care* 2023; 46: 697–703.
4. Hering BJ, Ballou CM, Bellin MD, *et al.* Factors associated with favourable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry. *Diabetologia* 2023; 66: 163–173.
5. Forbes S, Oram RA, Smith A, *et al.* Validation of the BETA-2 score: An improved tool to estimate Beta cell function after clinical islet transplantation using a single fasting blood sample. *Am J Transplant* 2016; 16: 2704–2713.

Doi: 10.1111/jdi.14140