Open Access

OBM Transplantation

LIDSEN Publishing Inc.

Original Research

Contribution of a Single Islet Transplant Program to Basic Researchers in North America, Europe, and Asia through Distributing Human Islets

Tatsuya Kin [1, 2, *], Doug O'Gorman [1], Wendy Zhai [1], Jennifer Moriarty [1], Kyle Park [1], Advaita Ganguly [1, 3], Shawn Rosichuk [1], AM James Shapiro [1, 2]

1. Clinical Islet Laboratory, University of Alberta Hospital, Edmonton, Canada; E-Mails: tkin@ualberta.ca; Douglas.O'Gorman@albertahealthservices.ca; Wendy.Zhai@albertahealthservices.ca; Jennifer.Moriarty@albertahealthservices.ca; Kyle.Park@albertahealthservices.ca; Advaita.Ganguly@albertahealthservices.ca; Shawn.Rosichuk@albertahealthservices.ca; jshapiro@ualberta.ca
2. Department of Surgery, University of Alberta, Edmonton, Canada
3. Centre for Healthy Communities, School of Public Health, University of Alberta, Edmonton, Canada

* **Correspondence:** Tatsuya Kin; E-Mail: tkin@ualberta.ca

Academic Editor: Chirag S. Desai

OBM Transplantation
2024, volume 8, issue 2
doi:10.21926/obm.transplant.2402212

Received: February 23, 2024
Accepted: April 18, 2024
Published: April 23, 2024

Abstract

There has been a steady expansion in islet isolation and transplantation activity worldwide. In addition to preparing human islets for transplantation, we have been providing human islets to basic researchers. The aim of this study was to review the activity of distribution of human islets to basic researchers in North America, Europe, and Asia, and to investigate if there are any differences in utilization rate of islets among three continents. We reviewed our islet isolation batch files, donor records, and documents related to shipping from 2007 to 2023. We have distributed islets to a total of 49 researchers (11 at the University of Alberta campus, 21 in North America, 7 in Europe, 10 in Asia). The yearly average [±SD] of islets distributed was 6,607,443 [±1,782,547] islet equivalents obtained from 28 [±5] pancreases, resulting in 230 [±88] shipments. Standard delivery to Europe or Asia takes at least 2 days whereas researchers in North America receive islets the next day. On top of this fact, we found that

delayed delivery occurred more often in Asia (31.9%, 201/631 shipments) and Europe (30.8%, 134/435) than in North America (6.8%, 114/1682). Interestingly, the utilization rate of islets within delayed deliveries was highest in Asia (91.5%, 184/201) followed by Europe (83.6%, 112/134) and North America (77.2%, 88/114). There were disparities in the frequency of delayed deliveries and in the utilization rate among three continents. Our program with a 17-year track record has been actively distributing human islets to researchers in three continents.

Keywords
Islet isolation; islet transplantation; diabetes mellites; islet shipping; organ donation; research consent

1. Introduction

Deceased human donors are essential for organ and tissue transplantation. They are also essential for research in the basic medical sciences. Islets isolated from deceased donor pancreases have been successfully used for clinical transplantation and basic research. There has been a steady expansion of basic research studies utilizing islets isolated from human pancreases [1]. However, technical and financial challenges for human islet isolation limit the number of centers that can distribute islets for basic research [2-5]. The Clinical Islet Laboratory at the University of Alberta Hospital has been one of the limited centers. The primary role of our laboratory is to extract and prepare islets from deceased donor pancreases for islet transplantation to people with diabetes. However, it is still difficult to constantly obtain adequate amounts of islets for transplantation. When we do not yield sufficient islets for transplantation but consent for research utilization is obtained from donors (medical assistance in dying is legal in Canada) and/or their families, we distribute islets for research to basic researchers, which is the secondary role of our laboratory. In other words, we do not perform islet isolation for the sole purpose of distributing islets for research.

We established the Alberta Islet Distribution Program (AIDP, https://sites.google.com/a/ualberta.ca/alberta-islet-distribution-program/) in 2007 for the distribution of islets to basic researchers [6]. Our operative philosophy is derived from respecting the wishes of donors and their families, from our desire not to waste extremely valuable materials, namely human islets, and from our hope to contribute towards the advancement of medical research.

This study aims to review the activity in the last 17 years, from 2007 to 2023, of the distribution of human islets to basic researchers in North America, Europe, and Asia. Statistical analysis was mainly performed from the researcher's point of view, considering what information is useful to plan in conducting research using islets. We also investigated if there are any differences in utilization rate of islets among researchers on three continents.

2. Materials and Methods

All researchers to whom we distributed islets were approved by the Health Research Ethical Board at the University of Alberta. Material transfer agreements were executed between a researcher's institute and the University of Alberta.

We reviewed our islet batch files, donor records, and shipping documents from 2007 to 2023. We also reviewed feedback forms obtained from researchers. Researchers were instructed to provide us with the form indicating the date of islet arrival and if islets have been used or not as well as any comments. We have been using one courier service for delivery. Standard delivery time from our site to North America is one day (16 to 25 hours), to Europe is 2 days (27 to 44 hours), and to Asia is 3 days (53 to 62 hours) except for the metro Tokyo area in Japan being 2 days. Email notifications were sent to researchers through the courier's web system in the morning of shipping day.

After purification, duplicate samples of the islet preparation were assessed for islet purity and islet quantity expressed in islet equivalent (IEQ) by two independent specialists. Viability assessment was performed using a combination of SYTO green and ethidium bromide as previously described [7].

Islets were placed in a 50 mL polypropylene tube filled with CMRL 1066 culture medium (Corning, Catalogue #99-603 CV). The tube was packaged in a Styrofoam container for shipping, but temperature monitoring during transportation was not carried out.

The number of shipments was counted as follows: when an islet preparation isolated from a donor pancreas was divided, for example, into 10 for 10 researchers, and each researcher received 1/10 of the preparation, we counted 10 shipments in this scenario. When a researcher received islets from two different preparations separately but as one delivery in a common package, we counted 2 shipments in this rare scenario.

Active researchers were defined as researchers who were ready to receive islets for longer than 6 months within a given calendar year. The frequency of shipments per year was calculated as the number of shipments divided by the number of active researchers.

Some researchers requested to receive exocrine fractions (islet purity < 5%), in addition to islet fractions. Shipments of exocrine fractions were excluded from our analysis.

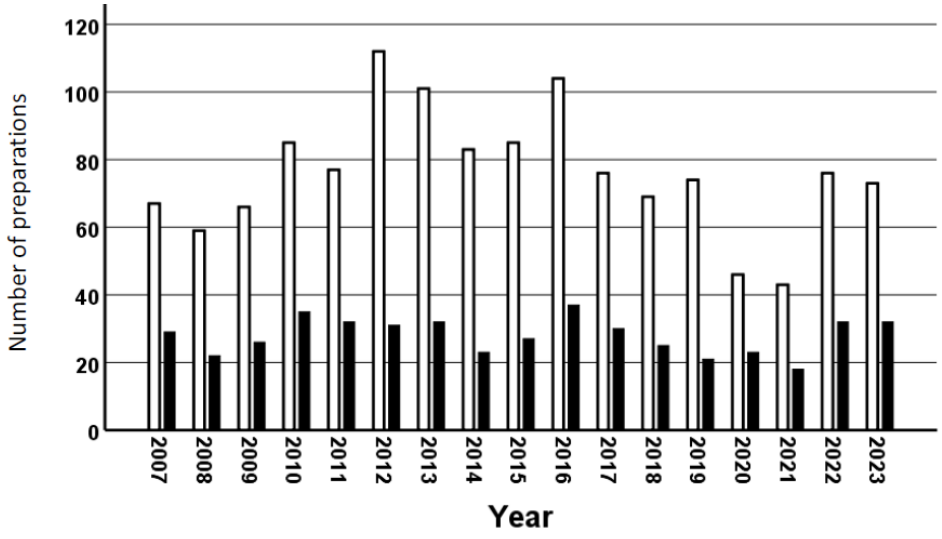
Statistics and graphical presentations were produced using IBM SPSS Statistics 25. Data are presented as mean ± standard deviation or percentages. Data for islet purity, viability, and culture duration were illustrated using box plots. The two-sided chi-square test was used to explore differences in categorical variables across three continents. A p-value < 0.05 was considered to be statistically significant. Bonferroni correction was performed to correct multiple testing.

3. Results

We have been distributing islets to 49 basic researchers, including 11 at the University of Alberta campus, 21 in North America (7 in Canada and 14 from United States of America), 7 in Europe (4 from Israel, 2 in United Kingdom, and 1 in Germany) and 10 in Asia (8 from Japan and 2 in Singapore). Among 49 researchers, 12 received islets from AIDP for longer than 10 years. There were two non-academic institutes to which we distributed islets, however, the active period was less than 12 months.

Figure 1 shows the number of islet isolation procedures and islet preparations distributed for research by year. There was a wide range of the number of islet isolation procedures per year, from 43 to 112. The lower number of islet isolation procedures in 2020 and 2021 was, in part, attributed to the fact that our program was placed on hold for 10 weeks (starting from March 2020) and 12 weeks (starting from November 2020) due to COVID-19. Accordingly, the number of research

preparations was low as well in 2020 and 2021. However, the range in the number of research preparations was narrower, from 17 to 36, compared to islet isolation procedures.



White bars indicate the number of islet isolation procedures. Black bars indicate the number of preparations distributed for research.

Figure 1 The number of islet isolation procedures and preparations distributed for research.

In Table 1, islet distribution activity by year is listed, including IEQ distributed, the number of pancreases, islet mass (IEQ) per pancreas, the number of shipments, and the number of active researchers. Figure 2 shows the islet quantity per shipment received by a researcher and the frequency of shipments per researcher over a 17-year period. This figure summarizes how many islets researchers received in a shipment and how often they received islets in a year. In 2007 when AIDP had only 4 active researchers (Table 1), each researcher received 85,010 IEQs per shipment. This quantity gradually decreased over time, down to 25,091 IEQs in 2015, as the number of active researchers gradually increased, reaching 15 researchers in 2015 (Table 1). Then the quantity became stable at around 25,000 IEQs, as the number of active researchers became stable, ranging from 15 to 20 (Table 1). The frequency of shipments ranged from 8.5 in 2021 to 26.6 in 2010 and fluctuated throughout the years as shown in Figure 2. The lowest frequency in 2021 was associated with the lowest number of pancreases destinated to research distribution (n = 17, Figure 1) due to COVID-19. Except for 2021, researchers received islets more than 12 times a year.

Table 1 Islet distribution activity from 2007 to 2023.

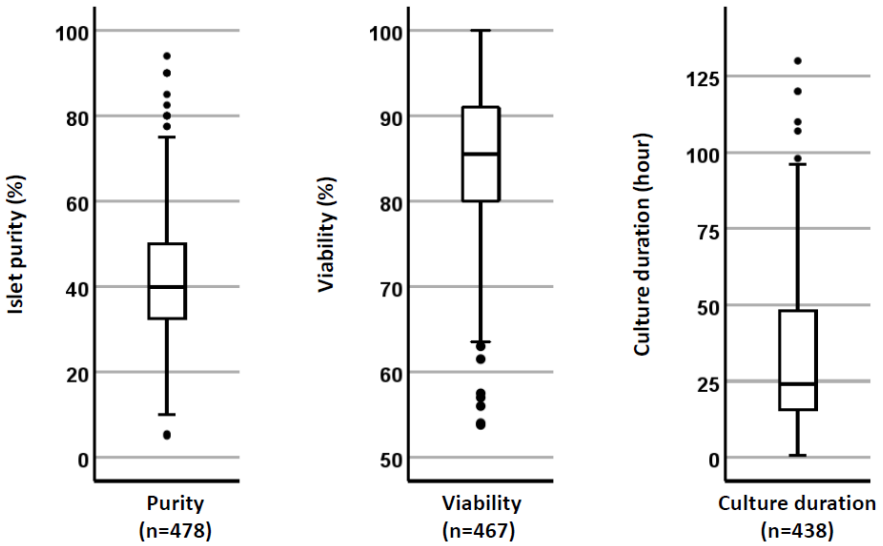
Year	IEQ distributed	# Pancreases	IEQ/pancreas	# Shipments	# Active researchers
2023	7,477,966	32	233,686	214	15
2022	7,791,448	32	243,483	307	18
2021	3,800,260	17	223,545	169	20
2020	5,438,377	23	236,451	225	19
2019	5,555,979	21	264,570	236	18
2018	6,266,066	25	250,643	253	20
2017	7,261,607	30	242,054	299	19
2016	10,116,793	36	281,022	411	20
2015	6,381,895	27	236,366	318	15
2014	4,854,582	25	194,183	208	17
2013	6,874,886	30	229,163	274	14
2012	8,367,646	34	246,107	251	12
2011	8,232,948	32	257,280	281	11
2010	9,220,793	35	263,451	186	7
2009	5,591,482	27	207,092	124	7
2008	4,248,236	23	184,706	94	8
2007	4,845,564	29	167,088	57	4
Mean	**6,607,443**	**28**	**232,994**	**230**	**14**
SD	**1,782,547**	**5**	**29,972**	**88**	**5**

IEQ; islet equivalent. IEQ/pancreas was calculated as IEQ distributed divided by the number of pancreases.

Figure 2 IEQ per shipment and frequency of shipment.

From the researcher's point of view, one of the disadvantages of using AIDP islets is the low purity of islets we prepare (Figure 3). Among 478 preparations distributed for research, 66.3% had purity ranging from 30 to 50%. Only 7.5% exhibited purity greater than 70%. The viability of islet

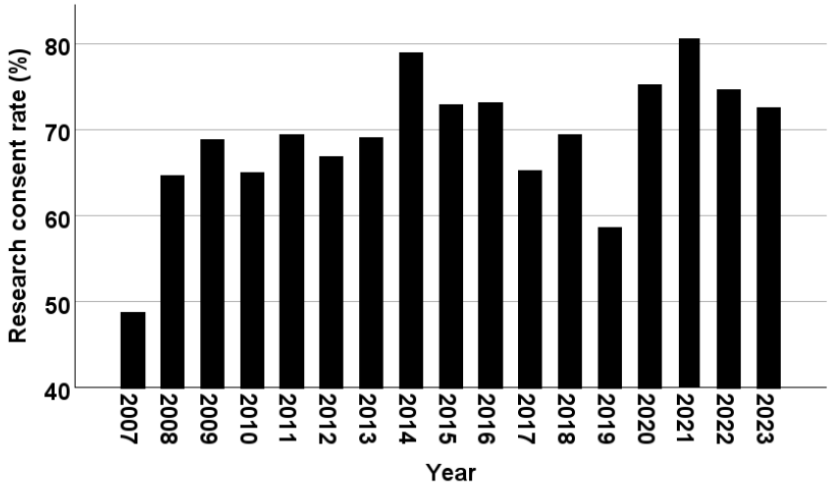
preparations was 85.1 ± 8.1%, which was comparable to our historical clinical transplantation data. Most islet preparations were shipped after culture preservation with a median period of 24 hours (Figure 3).



For islet purity and viability, data at post-purification are shown. Islet preparations shipped without culture (n=40) were excluded from culture duration data.

Figure 3 Islet purity, viability and culture duration.

Research consent is essential to basic researchers and AIDP. Figure 4 shows the percentages of research consent obtained from donors and/or their families by year. When we accept donor offers, the presence or absence of research consent is not taken into consideration. Therefore, we assume that our data are likely to reflect the general donor population in Canada. The consent rate was below 50% in 2007 (38.2% in 2006 and 63.6% in 2005). It increased over time and reached over 70% during the recent four years.



Black bars indicate research consent rate by year. Research consent rate was 38.2% in 2006 and 63.6% in 2005.

Figure 4 Changes in research consent rate.

Standard delivery time varies from 1 to 3 days depending on the region as stated in the Materials and Methods section. Islets have never arrived at distant sites before the expected day. Delay in delivery sometimes occurs due to a variety of reasons. We explored the frequency of delay in delivery and the utilization rate of islets for research among three continents. For obvious reasons, we excluded shipments to researchers at the University of Alberta campus. We also excluded shipments before 2010 when there were no researchers in Asia and only one in Europe. Delay in delivery for 1 day or more occurred in 6.8% (114/1682), 31.9% (201/631), and 30.8% (134/435) for North America, Asia, and Europe, respectively (Table 2). Researchers in Asia and Europe experienced a significantly higher frequency of delay than those in North America. There was no significant difference in the frequency of delay between Asia and Europe.

Table 2 Delayed delivery and utilization rate among three continents.

Continent	Delayed delivery rate (# Delayed deliveries/# Total shipments)	Utilization rate when delayed (# Used/# Delayed deliveries)
North America	6.8% (114/1682)	77.2% (88/114)
Asia	31.9%* (201/631)	91.5%** (184/201)
Europe	30.8%* (134/435)	83.6% (112/134)

* Bonferroni corrected p value < 0.0001 vs North America. ** Bonferroni corrected p value = 0.00036 vs North America.

Researchers may hesitate to use islets when delivered with a few days delay. The overall utilization rate within delayed deliveries was 85.5% (384/449). Interestingly, the utilization rate was highest in researchers in Asia (91.5%, 184/201) followed by Europe (83.6%, 112/134) and North America (77.2%, 88/114) (Table 2).

4. Discussion

AIDP, with a 17-year track record, has been actively distributing human islets to basic researchers. Our activity has been stable without any disruptions except for a 22-week hiatus related to COVID-19. We have not faced any financial issues because AIDP does not rely on any external funding agencies. Our volunteer spirit is the primary driver for AIDP operation.

A unique aspect of the AIDP is that we provide access to human islets without any cost to researchers. This may be advantageous to researchers. However, some limitations exist in the AIDP from the researchers' perspective. First, islet purity is relatively low in our preparations. This is inherent for islet isolation aiming for clinical transplantation. There is a trade-off between islet purity and islet recovery rate in the purification procedure [8]. We always aim to maximize islet recovery by sacrificing islet purity with hope of introducing the beneficial effects of non-islet fraction [9] because our primary objective is to obtain adequate amounts of islet for transplantation. On the other hand, for centers whose aim is only research islet distribution, not transplantation, it is not difficult to obtain a higher purity of islets. Secondly, we use an "opt-out" system, meaning that we do not ask researchers to accept or decline to receive islets prior to shipment. Researchers have to inform us in advance when they cannot accept islets for a certain period. It takes 3 to 4 hours for our staff to collect islets from tissue culture flasks, to prepare materials including packaging and labelling, and to fill out shipping documentation for all available researchers. This task has to be

completed by around noon to meet requirements of our courier. As mentioned before, our priority is clinical transplantation, which sometimes prevents scheduling shipping activity. For logistical and operational reasons, we may have to extend a culture preservation period for a few days [10] or distribute islets only to local researchers. Third, we use only one particular courier service. In the past, some researchers requested us to use an alternative courier but we cannot accommodate such requests due to organizational agreement. Finally, islets from donors with diabetes are not available from us as our policies exclude such pancreas for islet isolation for transplantation and we are mandated to not perform islet isolation with the primary objective of islet distribution for research.

There are few publications describing research consent rate in the context of organ donation [11]. It is fortunate to have research consent rates above 70% during the recent four years. Thanks to widespread public awareness of importance of research and to the efforts of organ donation coordinators in obtaining research consent, the AIDP can continue to be active. We encountered several cases where research consent was given only to islets among other organs. This is not likely to happen unless donation coordinators explain to donor families that we do not always obtain enough islets for transplant.

Longer delivery time is likely deleterious to islets. Standard delivery to Europe or Asia takes at least 2 days whereas researchers in North America receive islets the next day. On top of this fact, we found that delayed delivery occurred more often in Europe and Asia than in North America. Thus, researchers in Europe and Asia had an extra disadvantage. For researchers in North America who usually receive islets the next day, it may be a significant concern to use 2-day-old islets. However, researchers in North America should realize that researchers in other continents consistently use islets following at least 2 days of travel time. It should be noted, on the other hand, that researchers in North America have disadvantages in terms of time constraint. Because of our opt-out system, they have only one day to schedule experiments with the use of coming islets.

Researchers in Asia, especially in Japan, appear to be suffering from limited access to human islets for research. Organ donation rate has been extremely low in Japan in the recent past although current trends indicate increasing rates of donation [12]. Therefore, islet isolation activities are limited in Japan [13]. Another significant deterrent in Asia, is the absence of centers or programs publicly distributing islets for research [14]. On the other hand, such distribution activity is high in Europe [3, 5] and North America [2, 4, 6]. Although Japan is trying to build a framework to distribute research islets within the country [15], limited supply and uncertainty of research consent rate are potential limitations. Our findings that researchers in Asia had the highest utilization rate of islets despite longer delivery time can be partially attributed to aforementioned circumstances in Asian countries. However, it should be noted that our data solely relied on self-reported feedback forms from researchers regarding the usability of islets.

The AIDP's objective is to support basic and applied diabetes research globally. Distribution of human islets for research contributes to advancing knowledge and capacity building to conduct innovative and impactful studies to improve understanding of islet biology. The AIDP has been a successful endeavor, but there are a few challenges we have been constantly trying to address. As our findings show that shipments to Europe and Asia were frequently delayed, we have been exploring to include additional couriers who might have better availability and connectivity in certain geographical areas. In addition, we proactively contact with our researchers to discuss about hiatus periods, especially holiday seasons, where they may have difficulty in using the islets for experiments. This is important because researchers may not recognize that our program operates

365 days a year. We also take public holidays in each country into consideration in relation to timing of shipping. These would help us in avoiding unnecessary shipments and mitigate the non-utilization considerably. The pricing system may affect the performance of researchers. If we start charging a fee for the islets to researchers, the non-utilization rate may decrease. However, we will not do so because we believe that the benefits of no fee for islets outweigh the disadvantage of less utilization rate.

Our research islet distribution program is small in terms of the number of researchers compared to other centers consisting of multiple islet isolation facilities [2]. However, our effort to respect the wishes of donors and their families made it possible to continue our program to be successful.

Acknowledgments

We would like to express our sincere thanks to donors and their families for their generosity in donating organs, and to organ donor coordinators and organ donation organizations across Canada for their efforts in obtaining research consent. We thank and acknowledge past staff of the Clinical Islet Laboratory at the University of Alberta Hospital, including Brad Richer and late Adam Schroeder.

Author Contributions

TK performed data collection and analysis, and drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, read and approved the final manuscript.

Funding

The authors did not receive funding for this manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Hart NJ, Powers AC. Use of human islets to understand islet biology and diabetes: Progress, challenges and suggestions. Diabetologia. 2019; 62: 212-222.
2. Kaddis JS, Hanson MS, Cravens J, Qian D, Olack B, Antler M, et al. Standardized transportation of human islets: An islet cell resource center study of more than 2,000 shipments. Cells Transplant. 2013; 22: 1101-1111.
3. Nano R, Bosco D, Kerr-Conte JA, Karlsson M, Charvier S, Melzi R, et al. Human islet distribution programme for basic research: Activity over the last 5 years. Diabetologia. 2015; 58: 1138-1140.
4. Lyon J, Manning Fox JE, Spigelman AF, Kim R, Smith N, O'Gorman D, et al. Research-focused isolation of human islets from donors with and without diabetes at the Alberta diabetes institute IsletCore. Endocrinology. 2016; 157: 560-569.
5. Asplund O, Storm P, Chandra V, Hatem G, Ottosson-Laakso E, Mansour-Aly D, et al. Islet gene view-a tool to facilitate islet research. Life Sci Alliance. 2022; 5. doi: 10.26508/lsa.202201376.

6. Kin T, O'Gorman D, Schroeder A, Onderka C, Richer B, Rosichuk S, et al. Human islet distribution program for basic research at a single center. Transplant Proc. 2011; 43: 3195-3197.
7. Barnett MJ, McGhee-Wilson D, Shapiro AM, Lakey JR. Variation in human islet viability based on different membrane integrity stains. Cell Transplant. 2004; 13: 481-488.
8. Kin T. Islet isolation for clinical transplantation. In: The islets of Langerhans. Dordrecht, Netherlands: Springer; 2010. pp. 683-710.
9. Benomar K, Chetboun M, Espiard S, Jannin A, Le Mapihan K, Gmyr V, et al. Purity of islet preparations and 5-year metabolic outcome of allogenic islet transplantation. Am J Transplant. 2018; 18: 945-951.
10. Olack BJ, Alexander M, Swanson CJ, Kilburn J, Corrales N, Flores A, et al. Optimal time to ship human islets post tissue culture to maximize islet recovery. Cell Transplant. 2020; 29. doi: 10.1177/0963689720974582.
11. Lentine KL, Jones C, Cheungpasitporn W, Rothweiler R, Xiao H, Marklin G, et al. Disparities in deceased organ donor research authorization: Experience at one organ procurement organization and call for national conversations. Kidney Int Rep. 2021; 6: 2331-2337.
12. Tomimaru Y, Eguchi H, Doki Y, Ito T, Kenmochi T. Current state of pancreas transplantation in Japan based on the nationwide registry. Ann Gastroenterol Surg. 2021; 5: 494-501.
13. Ito T, Kenmochi T, Kurihara K, Aida N. The history of clinical islet transplantation in Japan. J Clin Med. 2022; 11: 1645.
14. Ng N, Tan WX, Koh Y, Teo A. Human islet isolation and distribution efforts for clinical and basic research. OBM Transplant. 2019; 3: 068.
15. Shirakawa J. Translational research on human pancreatic β-cell mass expansion for the treatment of diabetes. Diabetol Int. 2021; 12: 349-355.