Clinical Islet Transplantation Covered by Health Insurance in Japan

Hirofumi Noguchi

Pancreatic islet transplantation is a treatment option for patients with type 1 diabetes mellitus and has been performed in various countries [1–5]. Islet transplantation is a minimally invasive approach for β-cell replacement compared with pancreas transplantation. In Japan, clinical islet transplantation (CIT) has received national health insurance (NHI) coverage since April 2020 [6]. The NHI coverage of CIT is very beneficial to patients with type 1 diabetes who experience hypoglycemic unawareness despite maximal care.

In Japan, a severe donor shortage has been a serious issue. Until 1997, there was no legislation for donation after brain death (DBD) in Japan and, therefore, fewer than 200 cases of kidney transplantation from fewer than 100 donations after circulatory death (DCD) per year were performed [7,8]. In 1997, a law on organ transplantation from DBD donors was enacted, and organ transplantation with DBD started under this law [9]. However, from 1997 to 2009, only a few cases of DBD organ transplantation per year were performed because DBD required the person to make their intention clear before BD.

In 1997, the working group of islet transplantation in the Japanese Pancreas and Islet Transplantation Association (JPITA) officially held a meeting [6]. The working group in JPITA conducted feasibility studies for the implementation of CIT in Japan and defined and standardized the donor criteria for CIT, the recipient criteria, and the facility criteria for islet isolation and CIT [6]. In 2004, we performed the first case of CIT in Japan [10]. The pancreatic graft for the CIT was derived from DCD, without the withdrawal of life-sustaining therapies. CIT has been performed 34 times in 18 cases from 2004 to 2007 in Japan [11,12]; we performed 17 CITs (50% of those in Japan) in this era [5]. Although DBD for CIT was not prohibited in Japan, all transplanted cases were performed with DCD because there were only a few DBD per year from 1997 to 2009 and pancreata with DBD were mainly used for pancreas transplantation at this time. We also performed the first case of CIT using a partial pancreatic graft from a living donor due to the absolute donor shortage in Japan and the patient became insulin-independent [13].

However, the shortage of DBD from 1997 to 2009 remained serious. Therefore, the law on organ transplantation with DBD was amended in 2009 and came into effect in 2010. The main modification of the law was that the declaration of a person’s intent to donate before brain death was no longer required for DBD [6]. After the law was amended, the number of DBD has gradually increased, reaching a record high of 98 cases in 2019 [14], although the number of DBD is still low compared with that in the United States and Europe. As DBD in Japan has increased, the rate of pancreas transplants per DBD has gradually decreased and some pancreata with DBD have been used for CIT from 2013 [14].

In 2007, CIT in Japan was interrupted because it was discovered that bovine brain component was used in the manufacturing process of collagenase for islet isolation [15]. In 2013, CIT in Japan was reopened using pancreata with DBD because of the increase in DBD from 2010. We performed the first case of CIT with DBD in Japan [6]. CIT has been performed 18 times in nine cases from 2013 to 2020 in Japan [6]; we performed CIT 15 times in this period (83% of such transplantations in Japan). The proportion of patients with HbA1c of <7.4% without severe hypoglycemic attacks from 90 days to 365 days after the
first CIT made up 75% of cases. Islet graft survival (C-peptide level: >0.3 ng/mL) at 4 years after the first islet infusion was achieved in 80% of the cases [6]. Based on these results, CIT has received NHI coverage from April 2020 [6].

In Japan, we performed 21 clinical islet isolations and 17 CITs with DCD from 2004 to 2007 and 16 clinical islet isolations and 15 CITs with DBD from 2013 to 2020. The high success rate of CIT with not only DBD (94%) but also DCD (81%) is due to our modifications of the Ricordi/Edmonton islet isolation methods. These modifications included pancreatic ductal injection of a preservation solution [16,17], pancreas preservation with MK solution [18], and the use of an iodixanol-based purification solution [17,19–21] and islet culture/preservation [22–24]. The islet isolation technique also enabled us to perform successful single-donor CITs with DBD from 2007 to 2010 in the United States [25].

The number of islets from one donor pancreas is usually insufficient to achieve insulin independence [1,26–28], although we achieved it from a single donor in the United States [25]. The islet isolation procedure destroys the cellular and non-cellular components of the pancreas and the activation of some components, including resident neutrophils, macrophages, and T cells, probably plays an important role in the impairment of islet survival [26–30]. Although the NHI coverage of allogeneic CIT in Japan is a turning point, the donor shortage in Japan is still serious. The improvement of the islet isolation technique as well as an increase in DBD are key factors of successful CIT in Japan.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Shapiro, A.M.; Lakey, J.R.; Ryan, E.A.; Korbutt, G.S.; Toth, E.; Warnock, G.L.; Kneteman, N.M.; Rajotte, R.V. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N. Engl. J. Med. 2000, 343, 230–238. [CrossRef] [PubMed]
2. Shapiro, A.M.; Ricordi, C.; Hering, B.J.; Auchincloss, H.; Lindblad, R.; Robertson, R.P.; Secchi, A.; Brendel, M.D.; Berney, T.; Brennan, D.C.; et al. International trial of the Edmonton protocol for islet transplantation. N. Engl. J. Med. 2006, 355, 1318–1330. [CrossRef] [PubMed]
3. Hering, B.J.; Kandaswamy, R.; Harmon, J.V.; Ansite, J.D.; Clemmings, S.M.; Sakai, T.; Paraskevas, S.; Eckman, P.M.; Sageshima, J.; Nakano, M.; et al. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. Am. J. Transpl. 2004, 4, 390–401. [CrossRef] [PubMed]
4. Froud, T.; Ricordi, C.; Baidal, D.A.; Hafiz, M.M.; Ponte, G.; Cure, P.; Pileggi, A.; Poggioli, R.; Ichii, H.; Khan, A.; et al. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. Am. J. Transpl. 2005, 5, 2037–2046. [CrossRef]
5. Noguchi, H.; Iwanaga, Y.; Okitsu, T.; Nagata, H.; Yonekawa, Y.; Matsumoto, S. Evaluation of islet transplantation from non-heart beating donors. Am. J. Transplant. 2006, 6, 2476–2482. [CrossRef]
6. Ito, T.; Kenmochi, T.; Kurihara, K.; Aida, N. The History of Clinical Islet Transplantation in Japan. J. Clin. Med. 2022, 11, 1645. [CrossRef]
7. Nakagawa, Y.; Ikeda, M.; Ando, T.; Tasaki, M.; Saito, K.; Takahashi, K.; Aikawa, A.; Kikuchi, M.; Akazawa, K.; Tomita, Y. Re-evaluating Cut-off Points for the Expansion of Deceased Donor Criteria for Kidney Transplantation in Japan. Transplant. Proc. 2017, 49, 10–15. [CrossRef]
8. Aida, N.; Ito, T.; Kurihara, K.; Naka Mieno, M.; Nakagawa, Y.; Kenmochi, T. Analysis of risk factors for donation after circulatory death kidney transplantation in Japan. Clin. Exp. Nephrol. 2022, 26, 86–94. [CrossRef]
9. Soyama, A.; Eguchi, S. The current status and future perspectives of organ donation in Japan: Learning from the systems in other countries. Surg. Today 2016, 46, 387–392. [CrossRef]
10. Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Yamada, Y.; Fukuda, K.; Shibata, T.; Kasai, Y.; et al. Successful islet transplantation from nonheartbeating donor pancreata using modified Ricordi islet isolation method. Transplantation 2006, 82, 460–465. [CrossRef]
11. Anazawa, T.; Saito, T.; Goto, M.; Kenmochi, T.; Uemoto, S.; Itoh, T.; Yasunami, Y.; Kenjo, A.; Kimura, T.; Ise, K.; et al. Long-term outcomes of clinical transplantation of pancreatic islets with uncontrolled donors after cardiac death: A multicenter experience in Japan. Transplant. Proc. 2014, 46, 1980–1984. [CrossRef] [PubMed]
12. Kenmochi, T.; Asano, T.; Maruyama, M.; Saigo, K.; Akutsu, N.; Iwahashi, C.; Ohbuki, K.; Ito, T. Clinical islet transplantation in Japan. J. Hepatobiliary Pancreat. Surg. 2009, 16, 124–130. [CrossRef]
13. Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Yamada, Y.; Fukuda, K.; Tsukiyama, K.; Suzuki, H.; et al. Insulin independence after living-donor distal pancreatectomy and islet allotransplantation. Lancet 2005, 365, 1642–1644. [CrossRef]
14. Ito, T.; Kenmochi, T.; Aida, N.; Kurihara, K.; Tomimaru, Y.; Ito, T. Impact of the revision of the law on pancreatic transplants in Japan-An analysis of the Japanese Pancreas Transplants Registry. *J. Hepatobiliary Pancreat. Sci.* 2021, 28, 353–364. [CrossRef]

15. Saito, T.; Anazawa, T.; Gotoh, M.; Uemoto, S.; Kenmochi, T.; Kuroda, Y.; Satomi, S.; Itoh, T.; Yasunami, Y.; Kitamoto, T.; et al. Actions of the Japanese Pancreas and Islet Transplantation Association regarding transplanted human islets isolated using Liberase HI. *J. Transplant. Proc.* 2010, 42, 4213–4216. [CrossRef] [PubMed]

16. Noguchi, H.; Ueda, M.; Hayashi, S.; Kobayashi, N.; Okitsu, T.; Iwanaga, Y.; Nagata, H.; Nakai, Y.; Matsumoto, S. Ductal injection of preservation solution increases islet yields in islet isolation and improves islet graft function. *Cell Transplant.* 2008, 17, 69–81. [CrossRef] [PubMed]

17. Kuwae, K.; Miyagi-Shiohira, C.; Hamada, E.; Tamaki, Y.; Nishime, K.; Sakai, M.; Yonaha, T.; Makishi, E.; Saitoh, I.; Watanabe, M.; et al. Excellent Islet Yield after 18-h Porcine Pancreas Preservation by Ductal Injection, Pancreas Preservation with MK Solution, Bottle Purification, and Islet Purification Using Iodixanol with UW Solution and Iodixanol with MK Solution. *J. Clin. Med.* 2019, 8, 1561. [CrossRef] [PubMed]

18. Noguchi, H.; Ueda, M.; Nakai, Y.; Iwanaga, Y.; Okitsu, T.; Nagata, H.; Yonekawa, Y.; Kobayashi, N.; Nakamura, T.; Wada, H.; et al. Modified two-layer preservation method (M-Kyoto/PFC) improves islet yields in islet isolation. *Am. J. Transpl.* 2006, 6, 496–504. [CrossRef]

19. Noguchi, H.; Ikemoto, T.; Naziruddin, B.; Jackson, A.; Shimoda, M.; Fujita, Y.; Chujo, D.; Takita, M.; Kobayashi, N.; Onaca, N.; et al. Iodixanol-controlled density gradient during islet purification improves recovery rate in human islet isolation. *Transplantation 2009*, 87, 1629–1635. [CrossRef]

20. Noguchi, H.; Naziruddin, B.; Shimoda, M.; Fujita, Y.; Chujo, D.; Takita, M.; Peng, H.; Sugimoto, K.; Itoh, T.; Kobayashi, N.; et al. Evaluation of osmolality of density gradient for human islet purification. *Cell Transplant.* 2012, 21, 493–500. [CrossRef] [PubMed]

21. Noguchi, H. Pancreatic Islet Purification from Large Mammals and Humans Using a COBE 2991 Cell Processor versus Large Plastic Bottles. *J. Clin. Med.* 2020, 10, 10. [CrossRef] [PubMed]

22. Noguchi, H.; Naziruddin, B.; Jackson, A.; Shimoda, M.; Ikemoto, T.; Fujita, Y.; Chujo, D.; Takita, M.; Kobayashi, N.; Onaca, N.; et al. Low-temperature preservation of isolated islets is superior to conventional islet culture before islet transplantation. *Transplantation 2010*, 89, 47–54. [CrossRef] [PubMed]

23. Noguchi, H.; Miyagi-Shiohira, C.; Nakashima, Y.; Saitoh, I.; Watanabe, M. Novel cell-permeable p38-MAPK inhibitor efficiently prevents porcine islet apoptosis and improves islet graft function. *Am. J. Transplant.* 2020, 20, 1296–1308. [CrossRef] [PubMed]

24. Noguchi, H.; Naziruddin, B.; Jackson, A.; Shimoda, M.; Ikemoto, T.; Fujita, Y.; Chujo, D.; Takita, M.; Peng, H.; Sugimoto, K.; et al. Fresh islets are more effective for islet transplantation than cultured islets. *Cell Transplant.* 2012, 21, 517–523. [CrossRef]

25. Matsumoto, S.; Takita, M.; Chausabel, D.; Noguchi, H.; Shimoda, M.; Sugimoto, K.; Itoh, T.; Chujo, D.; SoRelle, J.; Onaca, N.; et al. Improving efficacy of clinical islet transplantation with iodixanol-based islet purification, thymoglobin induction, and blockage of IL-1β and TNF-α. *Cell Transplant.* 2011, 20, 1641–1647. [CrossRef]

26. Abdelli, S.; Ansie, J.; Roduit, R.; Borsello, T.; Matsumoto, I.; Sawada, T.; Allaman-Pillet, N.; Henry, H.; Beckmann, J.S.; Hering, B.J.; et al. Intracellular stress signaling pathways activated during human islet preparation and following acute cytokine exposure. *Diabetes 2004*, 53, 2815–2823. [CrossRef]

27. Paraskesas, S.; Maysinger, D.; Wang, R.; Duguid, T.P.; Rosenberg, L. Cell loss in isolated human islets occurs by apoptosis. *Pancreas 2000*, 20, 270–276. [CrossRef]

28. Nishime, K.; Miyagi-Shiohira, C.; Kuwae, K.; Tamaki, Y.; Yonaha, T.; Sakai-Yonaha, M.; Saitoh, I.; Watanabe, M.; Noguchi, H. Preservation of pancreas in the University of Wisconsin solution supplemented with AP39 reduces reactive oxygen species production and improves islet graft function. *Am. J. Transplant.* 2021, 21, 2698–2708. [CrossRef]

29. Bottino, R.; Balamurugan, A.N.; Tse, H.; Thirunavukkarasu, C.; Ge, X.; Profiozich, J.; Milton, M.; Ziegenfuss, A.; Trucco, M.; Piganelli, J.D. Response of human islets to isolation stress and the effect of antioxidant treatment. *Diabetes 2004*, 53, 2559–2568. [CrossRef]

30. Yonaha, T.; Miyagi-Shiohira, C.; Kuwae, K.; Tamaki, Y.; Nishime, K.; Sakai-Yonaha, M.; Saitoh, I.; Watanabe, M.; Noguchi, H. Pancreas preservation in extracellular-type p38 inhibitor-containing solution improves islet yield for porcine islet isolation. *Xenotransplantation 2021*, 28, e12661. [CrossRef]