COMMENTARY

Islet Transplantation for Hypoglycemia Unawareness/ Severe Hypoglycemia: Caveat Emptor

David M. Harlan

Diabetes Care 2016;39:1072–1074 | DOI: 10.2337/dci16-0008

Current estimates are that 1.25 million Americans have type 1 diabetes (T1D) (1) caused by the gradual loss of nearly all pancreatic insulin-producing β-cells via a presumed T cell–mediated autoimmune process (2). Eventually, all with T1D display severely impaired endogenous insulin production (3) and are dependent upon injected insulin for survival. Because subcutaneously administered insulin displays sluggish "on" and delayed "off" kinetics compared with that from pancreatic β-cells, the glycemic control patients achieve using subcutaneous insulin is suboptimal. For too many individuals, chronic episodic hypoglycemia dulls the typical compensatory responses, leading to impaired hypoglycemia awareness. Absent the usual warning symptoms of a blood glucose too low to sustain higher cognitive functions, such individuals are susceptible to severe hypoglycemic events defined as those requiring assistance from others to recover. Some die as a result of severe and prolonged hypoglycemia (4). Severe hypoglycemia occurs with alarming frequency among patients with T1D (5).

Scientists have long dreamed of restoring endogenous insulin production for those with T1D. One approach has been allogeneic pancreas transplantation. However, most pancreatic tissue makes digestive enzymes, and any damage to the organ can lead to leakage and potentially serious complications. In the 1970s, investigators reasoned that isolated pancreatic islets (only about 2% of the pancreatic mass) might be transplanted via a percutaneous cannula avoiding surgical and other complications associated with pancreas transplantation (6).

Early clinical islet transplantation results, however, were disappointing (7). Then in 2000, Shapiro et al. (8) reported seven consecutive T1D patients achieving 1-year insulin independence following islet transplantation, but serious issues remained. For instance, the only currently viable islet source is cadaveric donors. In 2015, the U.S. had only ∼9,000 such donors, of which ∼1,300 were deemed suitable for pancreas transplantation (9). Also, islets suitable for transplant are successfully isolated from approximately one-half of the donated organs, and many individuals with T1D receive islets from two or more donors. Even if all cadaveric pancreata were assigned for islet transplantation, on the basis of organ donor supply and other limitations, the procedure might benefit ∼2.000 U.S. patients each year. Moreover, islets are highly vascularized. With whole-pancreas transplantation, the donor organ is immediately revascularized, whereas isolated islets are separated from their vascular supply and take weeks to revascularize after transplantation (10). These and probably other factors (11,12) result in many transplanted isolated islets dying shortly after their infusion such that the recipient's glycemic control is neither as robust or as long lasting as that achieved by pancreas transplantation. Last, recipients with T1D require immunosuppression to prevent both allograft rejection and recurrent anti–β-cell autoimmunity. The current standard treatment uses calcineurin phosphatase inhibitors with associated toxicities, e.g., an increased risk for infections and some cancers and too often progressive renal dysfunction (13). The critical question then is, "Can a cohort with T1D and recurrent severe hypoglycemia be identified with sufficiently high morbidity and mortality to justify the known risks associated with a transplant-based approach?" One large study evaluating whether pancreas transplantation improved survival for patients with T1D found a very

Diabetes Center of Excellence, Department of Medicine, University of Massachusetts Medical School, Worcester, MA

Corresponding author: David M. Harlan, david.harlan@umassmemorial.org.

See accompanying article, p. 1230.

significant survival benefit for individuals receiving a simultaneous kidney and pancreas transplants but found increased mortality associated with solitary (i.e., patients did not need a kidney transplant) pancreas transplantation (14). Thus, although T1D with recurrent severe hypoglycemia is associated with significant morbidity and increased mortality, the absolute mortality risk is quite low. Whether transplantation-based approaches improve survival for such individuals is far from certain.

Hering et al. (15) in this issue of *Diabetes Care* now report long-awaited results from a Clinical Islet Transplantation (CIT) Consortium trial (CIT-07) testing whether islet transplantation achieves good but not normal glycemic control (HbA_{1c} of $<7.0\%$) without severe hypoglycemia from day 28 to day 365 following the procedure. The study enrolled 48 individuals with T1D $\geq$5 years and recurrent severe hypoglycemia in the preceding 12 months despite expert medical management. All islet preparations were done at one of the eight expert centers using standardized approaches and release criteria. Enrollees received islets from 75 different donors. At 1 and 2 years, respectively, the primary end point was achieved by 87.5% (42 of the 48) and 71% (34 of the 48) of individuals. The study also describes complications and several other outcomes such as insulin independence. Only 20 of the 48 individuals remained "insulin independent" at 2 years. The required calcineurin-based immunosuppression caused a significant decline in kidney function (glomerular filtration rate decreased from 102 mL/min/1.73 m^2 at baseline to 82 mL/min/1.73 m^2 at 2 years). Two enrollees developed donor-specific antibodies influencing their eligibility should they need a future transplant. The study's strengths were that it included some of the world's best centers working to develop islet transplantation for clinical applicability, that it was a multicenter trial, and that it used standardized procedures. The study's limitations include its quite understandable inability to keep up with the rapidly developing technology-based improvements to manage T1D.

Compared with the 36 subjects in a 2006 CIT study (16), the subjects in the current study received islets from fewer donors (1.6 vs. 2.1 donors per recipient), had better glycemic control (e.g., 42% were insulin independent at 2 years compared with 14%), and had fewer complications (e.g., 10% suffered intraperitoneal bleeds vs. 19% in 2006). Clearly, through research, progress is being made.

Do these results justify the U.S. Food and Drug Administration (FDA) licensing isolated islets for transplantation to individuals with T1D and recurrent severe hypoglycemia? The study suggests that islet transplantation could help ~70% of individuals for 2 years, but all previous experience suggests that islet allograft function will continue to deteriorate over time. Further, although a criterion for study entry was failed medical management, 11 subjects never used an insulin pump, 27 (more than half) never used a continuous glucose monitor, and 2 were later determined to be medically nonadherent and ideally should not have been enrolled. Thus, identifying suitable individuals for the expensive transplant approach can be most difficult and FDA licensure may open Pandora's box.

The FDA licensing decision should weigh other concerns. Should this country's limited cadaveric pancreata be allocated for islet isolation and potential transplantation? Modern islet isolation procedures yield islets suitable for transplant about 60% of the time. Thus, one can calculate that ~125 cadaveric pancreata were "invested" toward this trial that infused 75 donor islets into the 48 enrollees, with 20 individuals achieving 2-year "insulin independence," albeit using relaxed glycemic targets for that definition. Had those same 125 donor organs been allocated for pancreas transplantation, even if surgical teams transplanted only half those organs, ~50–60 patients would have achieved 2-year insulin-independent euglycemia using standard criteria. Perhaps only donor pancreata rejected for solid organ transplant should be taken for islet isolation.

Last, the FDA licensing decision should weigh that kidney function predictably and significantly worsens following islet transplant when using currently available immunosuppressive regimens. The various pros and cons associated clinical islet transplantation in its present state of development are depicted in Fig. 1. The net long-term benefit achieved by the temporarily improved but not normal glycemia with decreased severe hypoglycemic episodes must be weighed against the harm caused by the procedure and subsequent immunosuppression. This study does not deliver that critical verdict.

Isolated human islets are invaluable for research, and the future of islet transplantation remains bright. In particular, studies coordinated by the JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD) (17) and the Integrated Islet Distribution Program (IIDP) (18) are shedding light on the T1D pathologic process. Research is overcoming the biggest hurdles limiting islet transplantation, i.e., islet supply and immunosuppression

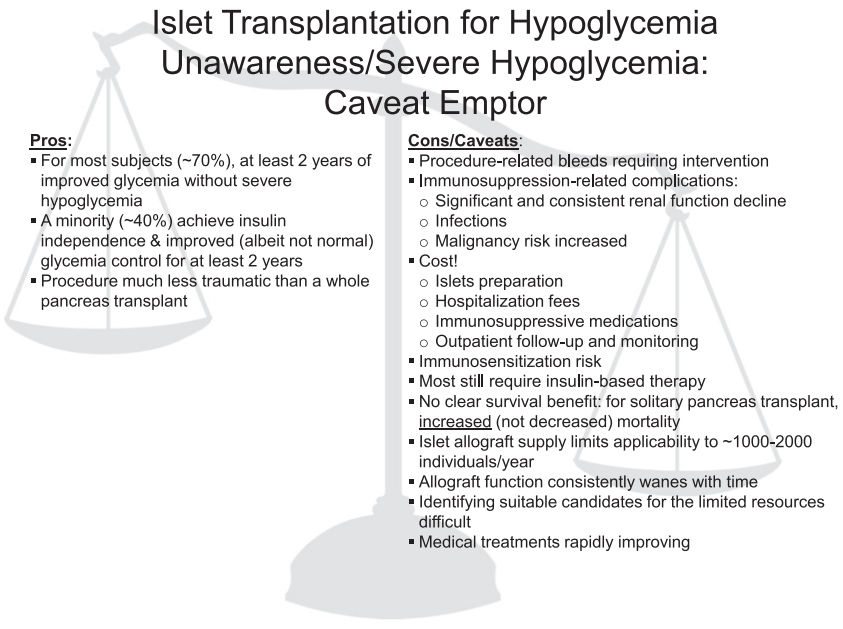

Figure 1—The multiple factors to weigh when considering therapeutic islet transplantation.

toxicity. Human β-like cells can now be created from stem cell precursors in vitro to enable an essentially limitless supply (19), and such cells lend themselves to genetic engineering to resist allo- and autoimmunity. Progress is also being made with encapsulation strategies to eliminate the need for immunosuppression (20), and newer immunosuppressive agents more favorable to preserving kidney function are being reported to prevent allograft rejection (21) and T1D autoimmunity (22–25).

With ever-evolving technologies and medications for glycemia management, whether the results now reported support the FDA licensing islet transplantation for patients with T1D and severe hypoglycemia remains a difficult question. Current evidence suggests that more cost-effective medical treatments (continuous subcutaneous insulin infusion, continuous glucose monitoring, psychological assessment, education, behavioral counseling, etc.) be exhausted before considering a transplant approach that may help a vanishingly small, properly informed and consented population, e.g., individuals with T1D and recurrent severe hypoglycemia who have already received a kidney transplant and therefore are already taking immunosuppressive agents.

Acknowledgments. The author thanks Drs. Dale L. Greiner and Kavita Seetharaman (University of Massachusetts Medical School) for their reading of this commentary. The author also thanks Dr. Leonard D. Shultz (The Jackson Laboratory) for his help in creating Figure 1.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Centers for Disease Control and Prevention. National diabetes statistics report, 2014: estimates of diabetes and its burden in the United States. Atlanta, GA, U.S. Department of Health and Human Services, 2014.
2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383:69–82
3. Lachin JM, McGee P, Palmer JP, Group DER; DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014;63: 739–748
4. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999;22(Suppl. 2):B40–B42
5. Fiallo-Scharer R, Cheng J, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset. Diabetes Care 2011;34:586–590
6. Lacy PE. Transplantation of islet cells–isografts and allografts. Monogr Pathol 1980; 21:156–165
7. Oberholzer J, Triponez F, Lou J, Morel P. Clinical islet transplantation: a review. Ann N Y Acad Sci 1999;875:189–199
8. 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
9. Organ Procurement and Transplant Network (OPTN) statistics. Available from http://optn.transplant.hrsa.gov. Accessed 9 May 2016
10. Henriksnäs J, Lau J, Zang G, Berggren PO, Köhler M, Carlsson PO. Markedly decreased blood perfusion of pancreatic islets transplanted intraportally into the liver: disruption of islet integrity necessary for islet revascularization. Diabetes 2012;61:665–673
11. Johansson H, Lukinius A, Moberg L, et al. Tissue factor produced by the endocrine cells of the islets of Langerhans is associated with a negative outcome of clinical islet transplantation. Diabetes 2005;54:1755–1762
12. Harlan DM, Kenyon NS, Korsgren O, Roep BO; Immunology of Diabetes Society. Current advances and travails in islet transplantation. Diabetes 2009;58:2175–2184
13. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931–940
14. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003;290:2817–2823
15. Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care 2016;39:1230–1240
16. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355: 1318–1330
17. Campbell-Thompson M, Fu A, Kaddis JS, et al. Insulitis and β-cell mass in the natural history of type 1 diabetes. Diabetes 2016;65: 719–731
18. Kaddis JS, Hanson MS, Cravens J, et al. Standardized transportation of human islets: an islet cell resource center study of more than 2,000 shipments. Cell Transplant 2013;22:1101–1111
19. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. Cell 2014;159:428–439
20. Vegas AJ, Veiseh O, Doloff JC, et al. Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nat Biotechnol 2016;34: 345–352
21. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med 2016;374:333–343
22. Orban T, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Abatacept Study Group. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. Diabetes Care 2014;37:1069–1075
23. Rigby MR, Harris KM, Pinckney A, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. J Clin Invest 2015;125: 3285–3296
24. Pescovitz MD, Greenbaum CJ, Bundy B, et al.; Type 1 Diabetes TrialNet Anti-CD20 Study Group. B-lymphocyte depletion with rituximab and β-cell function: two-year results. Diabetes Care 2014;37:453–459
25. Herold KC, Gitelman SE, Ehlers MR, et al.; AbATE Study Team. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes 2013;62: 3766–3774