

Transplanting islet cells can fix brittle diabetes. Why isn't it available in the U.S.?

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ABSTRACT

Type 1 diabetes, which affects 1.25 million American children and adults, and more than 20 million people around the world, is a challenging chronic disease caused by the body's inability to make insulin. Among its most severe forms is brittle diabetes. People with brittle diabetes frequently experience large swings in blood sugar that can quickly move from too high to too low or vice versa. Severely low blood sugar, called hypoglycemia, can cause sudden and unexpected seizures, coma, heart attacks, and even death. Insulin is the main treatment for this common disease. But it isn't a cure. A type of cell transplant that comes close to a cure for some people with type 1 diabetes, a technique pioneered and tested in the United States, is now available in many countries but is still deemed an experimental procedure in the U.S., making it almost impossible to get. More than a decade ago, the United Kingdom's National Health Service approved islet cell transplantation for type 1 diabetes — an approval based on an extensive review of the evidence generated by clinical trials conducted in the United States. Our federal dollars supported that research, and this treatment ought to be available to U.S. citizens. Islet cell transplantation is not a panacea for all forms of type 1 diabetes. And transplantation of any organ, including islet cells, requires the use of anti-rejection drugs that can have a range of adverse side effects. Nevertheless, individuals with severe brittle diabetes who are fully

informed of the risks and benefits should have the ability to access this lifesaving treatment option. We fully understand the FDA's efforts to rein in companies marketing unapproved stem cell products that have little or no evidence to support their use and that may put patients at risk. Yet the FDA should stay equally focused on its commitment to approving evidence-based transformative treatments for devastating diseases and conditions, including brittle diabetes.

The term "type 1 diabetes" generally conjures up images of insulin. That makes sense, because insulin is the main treatment for this common disease. But it isn't a cure. A type of cell transplant that comes close to a cure for some people with type 1 diabetes, a technique pioneered and tested in the United States, is now available in many countries but is still deemed an experimental procedure in the U.S., making it almost impossible to get.

That doesn't make sense to us.

Type 1 diabetes, which affects 1.25 million American children and adults, and more than 20 million people around the world, is a challenging chronic disease caused by the body's inability to make insulin. Among its most severe forms is brittle diabetes. People with brittle diabetes frequently experience large swings in blood sugar that can quickly move from too high to too low or vice versa. Severely low blood sugar, called hypoglycemia, can cause sudden and unexpected seizures, coma, heart attacks, and even death.

Insulin is made by specialized cells in the pancreas called islet cells. Transplanting these cells

from a donated pancreas to an individual with brittle diabetes can restore the recipient's ability to naturally produce insulin. The procedure has a record of effectiveness. A Phase 3 clinical trial sponsored by the National Institutes of Health, for which one of us (C.R.) was an investigator, showed that such transplants worked in 80% to 90% of the patients treated in eight centers in North America. The procedure virtually eliminated the risk of life-threatening hypoglycemia one and two years after the transplant. As with other types of transplant, the recipient must take anti-rejection drugs.

Individuals with brittle diabetes in Canada, Europe, Asia, and Australia can receive islet cell transplants, much the same way that individuals who need new hearts or livers can receive transplants. Islet cell transplants are even performed in China and Iran, whose doctors came to the U.S. to learn the technique and carried it back home. So why is this successful procedure, which can vastly improve the lives of those living with brittle diabetes, available in the U.S. only after a convoluted process that is often impossible to complete?

If a patient needed a pancreas transplant (which would include islet cells), he or she would be registered on the national organ transplant list and, once a pancreas became available, would receive the transplant, which is generally paid for by insurance.

But for a less-invasive islet cell transplant, an institution that wants to perform the procedure must file an investigational new drug application with the Food and Drug Administration, a very challenging process — and also figure out how to pay for the transplant.

That's due to the way the FDA interprets the code of federal regulations; specifically the criteria of minimal manipulation of human cells, tissues, and cellular and tissue-based products.

After islet cells are extracted from a donated pancreas, they need to sit in a culture medium at a temperature between 72 and 75 degrees Fahrenheit for two to three days. This gives the transplant team time to perform quality controls on the cells, and also to prepare the recipient for the transplant.

The FDA has interpreted the brief hiatus for islet cells as going beyond minimal manipulation, a concept based on the premise that processing cells does not alter their relevant biological characteristics. The hibernation process for islet cells does not change the cells' characteristics or increase their

number, both of which occur with the manipulation of advanced stem cell therapies, which reasonably need extra scrutiny.

The European Medicines Agency has determined that transplanting pancreatic islet cells should just follow the standard rules of organ transplantation, even though the cells require a brief hibernation period. This recommendation is based in part on its view that transplanting a pancreas, with islet cells intact, is an organ transplant, so there is no reason to treat transplantation of just the islet cells as anything different.

Because of the benefits to the thousands of Americans with brittle diabetes, there is a strong incentive to harmonize the FDA's approach to islet cell transplantation with the EMA's approach.

More than a decade ago, the United Kingdom's National Health Service approved islet cell transplantation for type 1 diabetes — an approval based on an extensive review of the evidence generated by clinical trials conducted in the United States. Our federal dollars supported that research, and this treatment ought to be available to U.S. citizens.

Islet cell transplantation is not a panacea for all forms of type 1 diabetes. And transplantation of any organ, including islet cells, requires the use of anti-rejection drugs that can have a range of adverse side effects. That said, individuals with severe brittle diabetes who are fully informed of the risks and benefits should have the ability to access this lifesaving treatment option.

We fully understand the FDA's efforts to rein in companies marketing unapproved stem cell products that have little or no evidence to support their use and that may put patients at risk. Yet the FDA should stay equally focused on its commitment to approving evidence-based transformative treatments for devastating diseases and conditions, including brittle diabetes.

About the Authors

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Commentaries

AM: I have been a type 1 diabetic for 43 years, my mom and dad both passed waiting for a cure. I can't believe we paid for the research and the side in the United Kingdom after they came over here to learn about it but it can't be done here, that's wrong. Too many of us need it and have lived long enough without it. It's about helping save people, not big pharma collecting until we die!!!!

LL: Please find a cure our daughter was diagnosed at age 5 she is now 6 this is the worse disease ever super high super lows so fast when everyone is playing she dropping and keeps asking why why cant they find a cure our hearts are breaking

Debbie: My 44 year old son was diagnosed with type 1 two years ago. Now his daughter who is 7 was just diagnosed 3 months ago with type 1. Praying for a cure and praying for the scientists to find a cure. This is life changing to all of us in our family. Please find a cure soon. My son and Granddaughter are counting on it as our whole family is.

Reply

Camillo Ricordi: Please contact me, as there may be a clinical trial you may want to consider for your son and especially for his 7 year old daughter. <https://www.cellr4.org/wp-content/uploads/sites/2/2018/04/2018-03-POSEIDON-Protocol-Consent-Assent-2.pdf>

RC: I have a dear friend who has had great success after her islet cell transplant. She has gone from huge swings in blood sugar (despite being otherwise healthy and conscientious) to requiring no insulin at all. In fact, she has been completely insulin free for years now. Before her transplant she had several pretty significant scares. Her life has been drastically changed, and likely saved, due to this procedure. The thought of delays due to policy is disheartening. It is my opinion that this option should be open and available for patients who meet the criteria and whose doctors feel it would benefit.

Erin Sowards: A good friend of mine was fortunate enough to receive islet cell transplantation and it has truly changed her life. Diagnosed type 1 from a teenager, she faced serious health complications every day. This procedure has the potential to transform so many lives if only we can get it properly labeled.

SW: This past week I celebrated 5 years of not only being insulin-free but being alive because of an islet cell transplant! I found myself being defeated by this disease and NOTHING I did controlled the bouncing from 20-400+. My A1C was decent, I'm a dietitian by education so it seemed like I had everything under control. Not so if you asked my husband who would regularly find me unresponsive or my friends to whom I appeared severely intoxicated (though without any alcohol!) or my 3 beautiful babies at the time whose mother wasn't able to be there for them. With any medical procedure there are bumps and processes of balancing meds etc. An islet cell transplant is TRULY minimally invasive. No one I describe it to can comprehend the difference it makes without having a giant scar to show off for it! As for the immunosuppressive meds – I have taken consistent amounts for a few years now and daily notice no side effects. When asked if I would do the transplant again – 100x YES! I hurt daily for those I am close to who are type 1s and are not offered the opportunity to get their lives back: my husband, my brother-in-law, a couple of friends, my daughter's friend's mom. Type 1 truly is all consuming. Every decision of every day is gauged by "how will my blood sugar respond" or "how do I need to adjust my insulin to balance this out". It's something you cannot comprehend unless you have the disease. In addition to bringing back my health, the transplant saves my family thousands of dollars a year – as my husband and I compare insurance/medical spending. Please continue to educate on this matter. Aside from being near and dear to my heart...it just makes sense for it to be available.

Piotr Witkowski: I cannot agree more! Thank you, Camillo, for your very important article pointing out fatal consequences of over-regulation of islet transplantation by FDA, which has been precluding the introduction of this therapy in the US for nearly a decade despite safety and efficacy proven in NIH funded multicenter clinical trials.

As a director of the islet transplantation program at the University of Chicago, I have experienced it first-hand. I have been able to treat only 18 patients over the last 10 years due to limited research funding. What is important, none of my patients have regretted participation in the study:

- all our patients benefited from the treatment, improved their glucose control,
- all but one was able to stop insulin completely.
- nearly half (8) patients have been enjoying insulin freedom already for more than 5 years,
- other 4 patients- for more than 2-4 years insulin-free so far.
- oey, our very first patient has been off insulin for over 14 years, since 2005.

In fact, all of our patients feel like they won a lottery ticket. Their lives were transformed from fearful existence in anxiety into fully independent personal, professional and social activities. They found new love, got engaged, married, pregnant, started new jobs, sports, traveling, running in election for an office. They eager to share their experience so we put their stories on our website: <https://www.pwitkowski.org/islet-diabetes-patient-stories>

Today, we celebrated 5 years off insulin with Stacy, who came to us from Tennessee. Her visit and outcome stimulated me to write my commentary.

All our patients consistently ask one important question- when islet transplantation will be available to more diabetic patients in the US? why their sacrifices and participation in the clinical study have not allowed for wide implementation of the procedure? The answer is frustrating for all of us. It did help, but in Europe, Asia, and Australia, unfortunately not yet in the US only due to old and unadjusted regulation by the FDA. In fact, over-regulation, which unnecessarily inflates the requirements, the cost and logistic efforts related to the procedure.

For over last 19 years regulation of islet transplantation as an organ transplant instead as a drug has been proven safe and effective not only in countries in Europe, Asia, and Australia, and in Canada but also in setting of clinical trials in the US. Over 2,000 islet transplant procedures have been already safely performed all over the world without BLA and drug regulation. Do we really think that after such extensive experience,

we should upgrade our islet isolation processing to standards for drug production in order to meet BLA requirements? Shouldn't we instead adjust regulation promptly and exempt human islets like other cell therapies (reproductive cell/tissue), which have been already exempt for a long time and continue islet processing as we have been doing for last 19 years? It would solve the legal obstacle and allow for quick implementation of islet transplantation in the US hospitals for the benefit of our patients. I think, it should be done, the sooner the better.

Additionally, none of the university hospitals involved in the trials are capable of meeting all the requirements related to the regulation of pharmaceutical drug production, invest a large amount of money to build the infrastructure, run costly operation and take risks of the related liability. We should not wait for that any longer. In contrast, transplant programs have the infrastructure and required personnel to prepare islets as any other organ for clinical transplantation meeting related requirements as in other countries.

Joey: I received my islet cell transplant 14 years ago. I was that brittle diabetic that everyone wanted to toss aside. They said I was not in good control. Please listen to my story... I was the person who did everything possible to control my diabetes. My insulin ratio was 1:100 and under stress, it was 1:125. As you can imagine, any miscalculation, and I was unconscious. I had a prescription for 2 glucagon a week! Paramedics knew me by name! Family and friends were always at my house "dropping by" or calling. Everyone was afraid to leave me alone. My job was at risk. My life was in shambles. The islet cell transplant absolutely changed my life! Conventional treatments did not, nor would they ever, be able to stabilize the crazy rollercoaster that I was on. We have learned to think of autism as a spectrum. Why can we not think of diabetes as a spectrum also? Yes, there are some that may be treated easily. But there are others that struggle with much more unforgiving circumstances. To those of us in this brittle category, I would implore for this procedure to move forward. It is not a matter of taking the easy route. It is a matter of life and death to those so affected!

AS: I used to have brittle diabetes and I received an islet transplant with Dr. Ricordi method over 14

years ago. I have been free from insulin injections for all this years with perfect glucose control and I don't believe I would be alive without this procedure that changed my life. I hope that patients in the USA will be able to benefit from this treatment like patients Canada, Europe and Australia already do. Thank you for dedicating your life to improve ours. If you need more info you can contact Dr. Ricordi, Dr. Bertuzzi or me, Antonella.

Reply

Camillo Ricordi: Thank you Antonella. Helping one patient at a time while trying to develop a cure for all is what keeps us focused on our mission. Seeing how this treatment has improved and changed the life of patients like you is what keeps us focused on a biological cure.

JE: I am a patient at the diabetes research institute in Miami, Florida. I received two Islet cell transplant's at the Diabetes Research Institute in 2005. Today, my body continues to produce insulin on its own from the islet cells I received from my two donors. I was one of the "Brittle" diabetics that Dr. Ricordi has referred to in this article. Although I am aware that other terms are used today to me the brittle term is most accurate for what I experienced pre-transplant. To no longer worry about low blood sugars (I was completely hypoglycemic unaware), as well as no longer experiencing high blood sugars has been a gift and a blessing. Yes, I take immunosuppressive medications each day and I am aware that there is a possibility of long term problems from these meds. However, for me, because I could not feel any low blood sugar symptoms, I lived in constant fear of killing someone or myself because of a low blood sugar while driving. Today that fear is gone and the health I have because of receiving the islet cell transplants outweighs the risk of something that may or may not happen in the future because of the immunosuppressive medication. I am so grateful for Dr Ricordi, as well as all of the Drs, researchers and scientists that have made the life I now live possible. Someone asked me if I would do it again and without hesitation I said YES. My only regret is that this treatment is not available in the US for the many patients that need it.

Reply

Anthony Japour, MD: Dear JE – thank you for your comment on our Op-Ed. Testimonials like

these from real individuals are incredibly important to assist decision makers in making innovative treatments available particularly when the research supports it.

AS: Yes, me too ... always YES and Yes and Yes.....

KK: I'm quite surprised Dr. Ricordi is using the term "brittle diabetes" Most experts in Endocrinology see this as an antiquated term – "Patients and their providers use it as a fall back or an excuse to stop looking for answers," said Gary Scheiner, a diabetes educator and the owner and clinical director of Integrated Diabetes Services, based in Pennsylvania. "They think there's nothing they can do, but that's not the case." Depending on the circumstances, clinicians and educators now prefer terms such as labile diabetes, glucose variability or, simply, uncontrolled diabetes.

Reply

Piotr Witkowski: Dear KK, your comment is excellent since it perfectly highlights the reason of miscommunications and a growing gap between diabetologists and transplant community. We all want the best for our patients. Diabetologists eliminate the word "brittle" to stimulate endocrinology community to work harder on optimization of patient education, insulin therapy instead of just giving up and labeling patient "brittle" and saying "nothing more can be done, he is just brittle". And we agree this is a great approach. However, we on the transplantation side, see group of patients who struggle, lives in fear of sudden death despite the best, optimized therapy offered by university endocrinologists, and we still call those patients "brittle". I can reassure that the risk of death is real. It was devastating experience for us to lose one patient on the waiting list for islet transplant in car accident despite best care we could provided. The most experienced endocrinologist at UPenn lost one patient on islet waiting list due to hypoglycemic episode too (one of his twenty patients). In recent multicenter trial in France one of 25 patients in the group of those with the best insulin treatment died due to severe hypoglycemic episode. Another almost died and was expedited to islet transplant group (Labalche et al Lancet...Diabetes & Endocrinology, 2018). Endocrinologists at Kovler Diabetes Center at

University of Chicago from time to time identify those patients who are in danger and refer them to us for islet transplant. I am proposing that we leave a name of brittle for those type 1 diabetic patients who remain in danger of sudden death despite the best optimal insulin treatment. Piotr Witkowski MD PhD, Director of Pancreatic Islet Transplantation Program at University of Chicago.

Ana: And what about xenotransplant? Dont need immunosuppressive drugs and the font of islets are actually very well controled. Human pancreas donators are insuficients. There are some avance about this therapy in US?

Reply

Anthony Japour, MD: Dear Ana - Innovations in medicine are built one advance at a time. Each advance brings greater knowledge that can be used to get us to the next step. Eventually, I'm confident we will have a cure for diabetes that will not require immunosuppressive drugs.

Donna Shalala: Your brilliant research ought not to be kept from US patients

Reply

Camillo Ricordi: Thank you Rep. Donna E. Shalala, coming from the longest-serving Secretary of Health and Human Services in American history, and one of America's foremost experts on health care, it means a lot to all of us dedicating our lives to finding a cure. The first randomized controlled trial comparing islet transplantation with insulin therapy indicated superiority of islet transplantation on all variables considered, from quality of life to metabolic control. New data on two decades patient survival following islet transplant recipients will soon be published and will help understand why long term islet transplant recipients consider receiving the transplant like "winning a lottery". There is still a lot of work to be done, but the significant progress in the field has been unquestionable, and clearly apparent to all of those following open access, peer reviewed literature. It is because of our collective progress that the procedure is now approved and reimbursed in several other countries, ironically even based on the promising results obtained in US clinical trials . I hope that the FDA will consider our comments.

Ron: The amount of cadaver islet cells available at any given time will only treat 1/10 of 1% of all Type I's in the US. The other issue is of course the life time commitment of immunosuppressive drugs. I am with Tony, I have heard of "breakthroughs" in Type I diabetes for over 30 years now with zero clinical application. Type I's are treating their disease the same as they have since the discovery of insulin in 1921, with subcutaneous insulin injections. I can't think of any other disease who's treatment progress has been so lacking. It is truly a crime.

Reply

SW: Tony & Ron – I agree with your statement "It is truly a crime". When I was diagnosed I was told I wouldn't be able to have kids, I wouldn't see a cure in my lifetime and I would always be on insulin. 2/3 of those we've proven wrong – I have 3 kids and off insulin 5 years! Progress definetely won't be made if we halt research or make current options (like islets) impossible for others to receive. Please read other posts above. Though we are few in number – islets are life changing if not life-saving.

Tony: Over the last decade I've read, one after the other, of "breakthroughs" in the Big D. Stem Cells, Gene Therapy etc. all Big Headlines, all Big Claims – ZIP has advanced in to actual curative treatments available for patients. Billions of dollars, over generations... and always 5yrs off! Enough, it's time for the patient community to just say enough... hard metrics next to claims... and clear focus on clinical delivery... no more generations to wait!

Reply

Leslie Wilson: I am a UCSF professor conducting an on-line survey to measure people's preferences for islet cell transplants. If you have T1D, are over 18 years, and have hard to control T1Diabetes with severe hypoglycemic episodes and would like to take this 30 minute survey please email me at Leslie.Wilson@ucsf.edu. Thanks

Camillo Ricordi: I am not sure you read this opinion paper. It is all about clinical delivery, already available in other countries based on our clinical results in the US, with over ten year-long FDA Phase 3 trials completed at 8 North American institutions (<https://care.diabetesjournals.org/content/39/7/1230.full-text.pdf>), and the first ran-

domized prospective clinical trial comparing islet transplantation to intensive insulin treatment (with insulin pumps and continuous glucose monitoring) already published and available to all. Incidentally, the randomized trial results indicated superiority of

islet transplantation, compared to intensive insulin therapy, on all counts, from quality of life variables, to metabolic control, HbA1c <7, incidence of severe hypoglycemic episode, etc. (<https://www.ncbi.nlm.nih.gov/pubmed/29776895>).