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Transplanting Islet Cells: How Do We Measure Success?

Announcer:
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Dr. Berney
Hello, everybody. My name is Thierry Berney. I'm a professor of surgery at the University of Geneva in Switzerland, and I've been involved in the islet transplantation program for more than 30 years. We're talking today about how to measure success of transplanted islet cells. So why do we need a definition for success? I will start by showing you these figures that are registry reports for islets on the left-hand side. And you see that islet function is reported both in terms of insulin dependence or graft function, which is circulating C-peptide. That's a measure of the intrinsically secreted insulin. You can see that roughly 25% of patients are off insulin after five years, but at the same times, up to 70% of patients have C-peptide. So what really matters? Is it insulin independence? Is it C-peptide secretion? We'll speak about that a little bit later.

On the right-hand side, you see that pancreas transplantation has been reported in terms of outcomes only as survival of the graft, and survival of the graft was defined more or less as patients being on or off insulin. So what can we say about that? Pancreas survival was reported without a uniform definition until the year 2022, where a new definition was decided. And graft loss was defined as either the need for a re-transplant, death of the patient, relisting for either an islet or a pancreas transplant, or need for insulin. And there is no metabolic outcome criteria in the definition of success or function of the pancreas graft. So what is the real meaning of insulin independence, you may ask. Is it insulin avoidance? Maybe some of these patients who are reported with a functioning graft are not on insulin but have a graft that does not function very well and would benefit from some insulin.

And what is the value of this definition of graft success? I'm talking about here the pancreas, when you don't have metabolic results that are integrated into the definition. To understand how we should better define outcomes, I think we need to look at what are the indications and the objectives of islet transplantation. Islet transplantation is done mostly in two modalities. The first is islet transplant alone, which is directed to patients with severe hypoglycemia. And of course, the goals are to prevent severe hypoglycemia, to restore hypoglycemia awareness, but also in the long run to prevent the progression of other secondary diabetic complications. In islet after kidney, it's a different ballgame. You need to protect the kidney graft primarily. But of course you also need to prevent the progression of other secondary diabetic complications in the long run. And in countries outside of the US where simultaneous islet kidney is also performed, this is the same objective.

So in this regard, what are the outcomes of interest? Of course, insulin independence or more refining insulin needs is an outcome of interest. But also what are the metabolic situations at this time? Fasting blood glucose is important. Functional parameters, and I'm talking here about C-peptide secretion, as we have told before, is also important. More specifically for islet transplant alone, the occurrence of severe hypoglycemic events is something that has to be known, because obviously it should be down to zero and the percent of time below the set range that can very easily be measured on a continuous glucose monitoring system is important. And of course the percentage ideally should be zero. In islet after kidney, HbA1c is also very important. This gives you an idea of the metabolic

stability of your graft, but also the percent of the time above range.

So, what I would like to show you here, and I'm presenting to you the latest data of the Edmonton series where they're reporting their results at 20 years after islet transplantation. The first on the upper left side, you can see insulin dependence, which is 8% at 20 years. This may seem very little, but when you look at graft function, you have almost 50% of graft survival at 20 years, which is extremely good in comparison to pancreas transplantation, for example. In terms of metabolic outcomes, you can see on the right-hand side upper panel, HbA1c in functioning grafts is 6% at 20 years. It means that it is normal. Half of the patients have a normal blood sugar control at 20 years. And below, the hypo score. This is a score designed to measure hypoglycemia, the importance of hypoglycemic events.

And you see that the score is zero. So it has a very long-lasting effect on preventing hypoglycemic events. So bearing this in mind that insulin independence is not a refined measure of function. A group of pancreas and islet transplant surgeons and physicians met in a consensus conference in Austria in 2015 and decided on what should be the criteria for function and for success. And we came with this definition that we call the Igls Criteria in which we integrated functional like C-peptide, the metabolic HbA1c, therapeutic insulin use, and clinical severe hypoglycemic events criteria to define function and success. And these criteria, which is interesting, are equally applicable to islet and pancreas transplant. And it allows comparisons between the two modalities. And you can see here that there are four categories of functional outcome, optimal, good, marginal and failure, based on diverse categories of HbA1c, hypoglycemia, insulin requirements, and C-peptide.

And the treatment was considered a success when it was in the first two categories, optimal or good, and a failure if it was in the marginal or failure category. Of course, since these criteria were devised and published, there has been a lot of progress with continuous glucose monitoring pumps and sensors for diabetic patients. And new criteria were defined incorporating the CGMS values. And this was published last year and we call that the Igls 2.0 Criteria. And basically, we integrated CGMS data in the definition, and this is roughly the timing range for stability and the time below range for hypoglycemia. And there is a differentiation of treatment outcome and beta cell graft function assessment, but the same categories of outcome and success are kept. So treatment outcome always optimal, good, marginal, failure. Beta cell function, optimal, good, marginal, failure. And treatment success is yes when the outcome is optimal or good.
So I'm not going to detail all these criteria, because it would be beside the point and I'm giving you here the reference that you can use and go and check. But you will see that these are extremely easy to utilize to define the outcome of your graft, and they are usable repeatedly as you follow up your patient. So to conclude, the Igls Criteria provide a reproducible definition of outcomes and success for islet cell transplantation. They are easy to use, they are a refined assessment outcome beyond the on off insulin criterion.

They are applicable to pancreas transplantation and allow direct comparison with a unified vocabulary. But what is very important, especially in these times of new development progress and breakthrough trials, they are applicable to the assessment of other form of beta cell replacement therapies and notably stem cell derived beta cell tissues, insulin-producing tissues. And the applicability to an artificial pancreas system should also be tested with these criteria, because of course, insulin is by definition what is used in an artificial pancreas. So I thank you for having listened to this and I hope you have learned a lot. And please feel free to get back to the references provided. Thank you.

Announcer:
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