ADVICE ON POLICY PROPOSITION 1670: TOTAL PANCREATECTOMY WITH ISLET CELL AUTO TRANSPLANTATION

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Background

The draft policy proposition 'total pancreatectomy with islet cell auto transplantation' has been in development for some time. It has been considered by The Specialised Services Commissioning Clinical Panel and whilst the benefits in terms of pain reduction are described in the research evidence available, the effectiveness of islet cell auto transplant was less clear, with the available research evidence limited. Given the limited evidence, the potential risks associated with major surgery and the need to understand the overall benefit to inform future prioritisation decisions it was determined to seek expert advice from Professor Jonathan Valabhji National Clinical Director for Obesity and Diabetes, NHS England. Registry data from NHS Blood and Transplant regarding islet cell allograft transplants was also identified and is summarised below.

Data available from allograft (donor) islet cell transplants patients

The Annual Report on Pancreas and Islet Transplantation 2016/17, NHS Blood and Transplant reports that a little over 200 donor transplants are commissioned each year in the UK. These are made up of (approximate numbers per year in the UK) simultaneous pancreas and kidney (SPK) (165) pancreas only (20) and islet cells (30). The indications for these allograft 'allo' transplants may include the improvement of diabetic control. In the islet cell transplant group (all performed to improve diabetic control) the annual rate of severe hypoglycaemic events, glycated haemoglobin (HbA1c – reflects the average blood glucose levels over the previous 2-3 months), and insulin dose have been reported at one-year post routine islet transplant. This registry data should be treated with caution because; it is not adjusted; reports data at one year post transplant only, includes patients transplanted across a number of years and does not include data for all patients. The reported median annual rate of severe hypoglycaemic events prior to transplant (reported as number of events between registration and transplant) was 7 events per year (Interquartile range 0-34). Of the 91 patients where the number of severe hypoglycaemic events at one-year post-transplant was available, 71 (78%) experienced no severe hypoglycaemic events, 13 (14%) experienced one or two events and 7 (8%) experienced three or more events. Median HbA1c for routine islet transplants dropped from 64mmol/mol prior to transplant to 51mmol/mol at one-year post-transplant and median insulin dose per kg body weight dropped by about 50%.

Advice from Professor Jonathan Valabhji

Professor Valabhji considered specific questions raised by Clinical Panel, consulted with colleagues at Imperial College (Professor Nick Oliver, Wynn Professor of Diabetes, Imperial College London and Honorary Consultant, Imperial College Healthcare NHS Trust and Dr Shivani Misra, Consultant, Imperial College Healthcare NHS Trust and Honorary Senior Lecturer, Imperial College London) and took into account information provided by the Policy Working Group which has been developing the policy. Imperial college is a tertiary referral Type 1 diabetes centre providing services for people with challenging glucose variability and hypoglycaemia, including provision of all available technologies and intraperitoneal insulin. This includes experience caring for people with Type 1 diabetes who have undergone whole pancreas transplantation, but not experience caring for those with islet cell transplantation. Professor Valabhji, with advice from colleague, based the answers to the questions raised by using the evidence review completed to inform the policy, through further exploration of the evidence, and from clinical experiences managing those with diabetes and those pancreatectomised early in life for congenital hyperinsulinism.

Questions Raised By Clinical Panel

What is the nature of the diabetes experienced after total pancreatectomy? A description of the clinical picture would assist clinical panel understand the problem. What proportion of patients experience diabetes that is difficult to manage? How different is the clinical picture from other patients with type 1 diabetes?

There are data in those with both Type 1 and Type 2 diabetes to suggest that achievement of good glycaemic control, without causing hypoglycaemia that interferes with quality of life, is increasingly difficult as endogenous insulin production (measured by C-peptide levels) falls below the detectable limit (1,2), and in those with Type 1 diabetes, evidence to suggest that in those with low/undetectable C-peptide microvascular outcomes are worse (1). For individuals who have undergone total pancreatectomy, endogenous insulin production will be zero, so that glycaemic control will be challenging. There are however additional factors that will make glycaemic control more challenging following total pancreatectomy:

1. Total pancreatectomy also results in loss of the pancreatic islet alpha cells, which produce glucagon, an important counter-regulatory hormone that deals with hypoglycaemia, so this contributes significantly to greater risk of severe, disabling hypoglycaemia in those following total pancreatectomy. While one can see loss of pancreatic alpha cell function in autoimmune Type 1 diabetes, this is usually seen in those many years following diagnosis.
2. Malabsorption related to pancreatic exocrine insufficiency will pose additional challenges for glucose control.

In this regard, the concept of maintaining some endogenous insulin production following total pancreatectomy, through islet auto-transplantation, is attractive.

What are the options for the management of 'brittle diabetes' that patients may experience after total loss of islet cell function (such as after total pancreatectomy without islet cell auto transplant)? How effective are they?

We would suggest avoiding use of the term “brittle diabetes”, which in more recent years has been interpreted by some to align with behavioural and psychological disorders that impact diabetes self-care.

There are more recent developments and innovations that are indicated for use in certain situations in those with Type 1 diabetes: insulin pump therapy, continuous glucose monitoring, flash monitoring, and closed loop systems/artificial pancreata. All can be used to improve overall glycaemic control (quantified by a reduction in HbA1c) and all except flash monitoring can be used to tackle severe disabling hypoglycaemia. It is probably fair to say that for those with absolute insulin deficiency, these technologies can prove helpful. Artificial pancreas technology is still at a very early stage of development. However, endogenous insulin production, which confers intrinsic autoregulation of insulin output, as might be achieved following islet auto-transplantation, is likely to achieve greater benefit than the technologies listed.

What is the relevance of c-peptide biologically? Does it make a difference clinically, independent of insulin? Is there any clinical benefit for maintaining c-peptide production? Are c-peptide and insulin production produced in proportion to each other and does loss of islet cells result in loss of both at a similar rate?

Insulin is produced by the pancreas as a larger pro-insulin molecule, which is cleaved to produce the therapeutic insulin molecule, and C-peptide, in a ratio of 1 to 1. Unlike insulin, c-peptide does not undergo first pass hepatic metabolism, making it an ideal measure of endogenous insulin production in those treated with insulin injections. However, the evidence of a therapeutic effect of C-peptide per se is weak. There is no role for C-peptide as an adjunct treatment for those with Type 1 diabetes.

What is the durability of islet cell functioning following islet cell auto transplant? (Some patients, particularly with inherited disorders, may be young with many years of life ahead.) Is there any evidence on the metabolic outcomes and complications that occur despite islet cell auto transplant?

The survival of islet auto-transplantation, as far as we can gather, is as yet unknown. The lack of future immune insult (as the transplantation is from self) and the lack of immunosuppression therapy toxicity, are major advantages, that could in theory see auto-transplanted islets last longer than allo-transplanted islets. However, this will be dependent on how much damage there has already been to the endogenous islets due to the pancreatitis prior to auto-transplantation. The earlier the total pancreatectomy, one might assume the more successful the harvest of functioning beta cells for auto-transplantation, and the better the outcome in terms of extent and duration of endogenous insulin production.

On this last point, the genetic causes of recurrent pancreatitis are rather distinct from other disease processes that lead to chronic pancreatitis; they are likely to present earlier, in childhood and the risk of recurrence is high. It may therefore be prudent to separate clinical pathways for these two groups as the intervention may be beneficial at an earlier time point in the hereditary cases. (Mutations in the PRSS (cationic trypsinogen) and SPINK-1 (serine protease inhibitor, Kazal type 1) genes may result in hereditary pancreatitis; the CFTR (cystic fibrosis transmembrane regulator) gene has also been implicated in cases of idiopathic pancreatitis (3)).

We are not aware of studies with sufficient duration of follow up for there to be sufficient evidence of complications and outcomes following islet auto-transplantation – in terms of whether islet auto-transplantation at the time of total pancreatectomy will reduce long term microvascular and cardiovascular complications of the resulting diabetes compared to total pancreatectomy alone.

Given the difficulty managing diabetes post-pancreatectomy, and the fact that there is only a once in a lifetime opportunity for islet auto-transplantation for those that require total pancreatectomy for their chronic pancreatitis, it would seem reasonable to perform islet auto-transplantation at the same time as total pancreatectomy. However, we would suggest a contractual requirement for completion of a minimum dataset for each individual operated on, including pre- and post-operative metabolic assessment data. For some, it will not be possible to harvest islets for auto-transplantation, providing a comparator group of those undergoing total pancreatectomy without islet auto-transplantation. This will facilitate generation of further evidence prospectively of the relative benefit of islet auto-transplantation at the time of total pancreatectomy.

Incidentally, Insulin independence is a crude marker of effectiveness of islet transplantation. The majority with type 1 diabetes who have islet allo-transplantation do so as a treatment for severe, disabling hypoglycaemia, which is more likely to complicate those with absolute insulin deficiency. Islet transplantation can prove a highly effective treatment in this regard, whether or not individuals remain independent of insulin injections following islet transplantation. Such individuals with Type 1 diabetes are likely to already have long duration of diabetes, and so will also have microvascular complications, including autonomic neuropathy, which blunts some of the physiological responses to hypoglycaemia, putting them more at risk of such disabling, severe hypoglycaemia. In the early years, people with diabetes due to total pancreatectomy will not yet have the microvascular complications, such as autonomic neuropathy, but there is significant risk that they will develop the microvascular complications in the future.

References

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3. Rosendahl J et al. Hereditary chronic pancreatitis. Orphanet J Rare Dis 2007;2:1.

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