Editorial

Total pancreatectomy with islet cell auto-transplantation for chronic pancreatitis: sustaining long-term glycemic health with or without graft function

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Chronic pancreatitis is an inflammatory disease of the pancreas that causes significant challenges to both patients and providers. The combination of excruciating pain often requires narcotic pain medications and leads to dependency; exocrine and endocrine insufficiencies lead to an extremely poor quality of life for these patients (1). The heightened sensitivity often makes management more complicated from the provider's perspective. Medical management has limited options, primarily involving narcotic pain medications, antioxidants, fluid therapies, and pancreatic enzyme replacement. While there have been advancements in endoscopic therapies, which offer some progress in treatment, failure of endoscopic interventions often leads to the consideration of surgical options (2). In some cases, early surgical intervention can significantly improve the patient's quality of life, as supported by studies like the Dutch Pancreatitis Study Group (3).

When a patient is referred to a surgeon, the decision-making process is complex and multifaceted. Surgery for chronic pancreatitis has evolved over the period of time with different options, beliefs, and availability. Selecting the appropriate surgical approach is crucial and usually based on the parameters such as the extent of pancreatic involvement in the head, body, or tail; the presence of ductal dilation, factors like genetic mutations and glycemic control (4). Total pancreatectomy (TP) for benign diseases such as chronic pancreatitis is often perceived as a radical procedure, mainly due to concerns over diabetes management. However, the addition of islet cell auto-transplantation (IAT) after TP, known as TPIAT, has shown benefits in mitigating the onset of brittle diabetes, avoidance of severe hypoglycemic episodes, and tremendous improvement in quality of life in both adult and pediatric patients (5-7).

The study by the Leicester group, published in this journal, brings out several key points (8). Having 10-year follow-up data on such patients is rare, and while the sample size is small and only 28% of patients have long-term follow-up post-surgery, the glycemic outcomes are encouraging with some distinctive findings like the minimal hypoglycemic episodes and improvements in hemoglobin A1c (HbA1c) levels are worth noting in this cohort. One of the standout points is the modification of the Igls criteria which were originally generated for the evaluation of allogenic islet graft function. The Minnesota group had adopted it for autologous islet cell graft functions modifying variables such as insulin doses and c peptide (9) and The

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Leicester group further simplified eliminating HbA1c and severe hypoglycemia episodes (SHE) adopting to a non-weight-based insulin dosage (8). Both kept C-peptide requirement for classification at the similar level. Although the C-peptide level is a good marker of graft function, it can be argued that achieving the best possible euglycemic level with the avoidance of the most feared problems of type 3c diabetes such as severe variation in glucose risking end organ damage and hypoglycemic episodes threatening life, at whatever extent of insulin dose, should be of paramount importance. One of the benefits of IAT coupling with TP is to avoid brittleness of diabetes and C-peptide would suggest the function of beta cells but not explain all the success towards this goal contributed by other cells for which surrogate markers are better glycemic control on continuous glucose monitoring (CGM) and taking into consideration avoiding SHE. With advancements in insulin pump, CGM and hybrid pumps technologies over the last decade, many patients are managed very well from an endocrine perspective, raising the question of whether TP, with or without islet auto-transplantation, should be considered more liberally in patients with chronic pancreatitis disregarding the evaluation for the prediction of graft function (10,11).

The long-term outcomes of islet graft function in this cohort did not correlate with islet yield, a finding that contrasts with other studies. Though findings may be discrepant, it is well known that the long-term survival of autograft is limited due to the multifactorial nature of islet loss, issues with engraftment in the variable host environment and the limited ability of transplanted islets to regenerate to the same extent as native pancreatic islets (12,13). There has been some progress in the field over the period of years from the standpoint of improving all these aspects but none has changed field drastically, and yet increasing utility of TPIAT as a treatment tool for chronic pancreatitis emphasize and underscore the common acceptance of the principle behind providing this treatment being the improvement in the quality of life and eliminating the pain as the primary goal point over insulin independence. There has been lack of any significant comparative data as regarding the long-term glycemic outcomes between the parenchyma-preserving surgeries (PPS) and TPIAT for chronic pancreatitis patients. Our group has initial data leaning towards the better outcomes with PPS in shorter to intermediate term (4). The long-term glycemic outcomes and quality of life comparative data between the PPS and TP with or without IAT needs to be further studied in multicenter setting making a case for more of algorithmic approach for surgery selection rather than one size fit all approach.

One interesting observation in the study is that three patients underwent partial pancreatectomy with islet auto-transplantation. It would be important to assess which category these patients fall into: good, partial or poor responders. If three out of five patients were good responders, this supports the argument for considering islet auto-transplantation even in patients with partial pancreatic resections, particularly those with severe fibrosis in the tail of the pancreas in cases like disconnected pancreatic duct. Considering as high as up to around 40% patients become diabetic after distal pancreatectomy, highlighting the role of IAT after distal or subtotal pancreatectomy is very meaningful (14).

Despite long-term challenges with exocrine and endocrine insufficiencies, recently published data suggested 93% to 85% patient survival at 10 and 15 years, respectively (15). Older age at TPIAT, extremes of weight, preexisting diabetes mellitus and daily opioid requirement before surgery were some of the high-risk factors whereas longer pancreatitis duration, later years of receiving TPIAT within disease process and genetic mutation were deemed lower risk of mortality. Risk of death attributed to diabetes was evaluated to be 0.5% at 10 years and 2.4% at 15 years. Though only 8.3% were so called good responder, overall survival was good in the published study. These findings challenge the notion of offering early TPIAT to these patients for obtaining higher islet yield for insulin independence, and probably delaying surgeries later in the disease course may be more beneficial for long-term patient survival. The Leicester group reported mortality rate of around 26% in the cohort, with most cases attributed to alcohol-related causes or unknown etiologies. The authors note that alcoholic chronic pancreatitis has limited outcomes after TPIAT, a finding supported by other research in the field making a strong argument for good case selection.

In conclusion, TP remains a valuable option for patients with chronic pancreatitis. Outcomes are generally better when IAT is included with TP. Good graft function always helps; however, the success should be evaluated by euglycemic status, prevention of long-term end organ damage, good quality of life and long-term survival in these patients. With advancement in other technologies like sophisticated insulin pumps, CGM technologies, artificial pancreas, etc., future for the role of TP as a treatment option for chronic pancreatitis looks promising with the goal of

persistent euglycemia achievable at variable graft function.

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