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Towards a New Surgical Standard for the Treatment of Chronic Pancreatitis

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Chronic pancreatitis is an inflammatory process leading to progressive destruction of pancreatic parenchyma and ductal structures, with subsequent formation of fibrosis and atrophy. The disease is progressive and irreversible. The time between diagnosis and development of end-stage pancreatic disease differs greatly among patients and is influenced by multiple factors. Varying degrees of exocrine and endocrine pancreatic dysfunction are common, chronic, and frequently intractable, but persistent and unrelenting pain is the predominant symptom. Because of the pain, patients with chronic pancreatitis are frequently totally disabled and depend on chronic use of (high-dose) narcotics. Most therapeutic efforts are, therefore, directed toward pain control. Medical and endoscopic management usually fails over time; as a result, patients and their physicians end up pursuing surgical procedures.

Currently, no single surgical treatment option is considered the therapy of choice for patients with chronic pancreatitis. The large variety of resective and drainage operations illustrates the lack of consensus, to date, about the ideal procedure. Unfortunately, partial pancreatic resections, drainage procedures, and combinations thereof leave diseased tissue behind and usually do not improve patients' intractable pain. And total pancreatic resections typically resorted to after partial resections and drainage procedures have failed to eradicate patients' chronic pain lead to the development of brittle diabetes mellitus, with a low quality of life, and considerable morbidity and mortality due to hypoglycemia. The annual mortality rate due to hypoglycemia is substantial, ranging from 4% to 10%.

Because exocrine deficiency is much easier to manage than endocrine deficiency, many surgeons still prefer partial resections, drainage procedures, and combinations thereof over total resections in hopes of disease cessation and/or prevention of brittle diabetes mellitus. Many surgeons still consider a total pancreatectomy for patients with chronic pancreatitis to be a radical therapy for a "benign" disease, especially since pain persistence or recurrence is not uncommon postoperatively. For endocrinologists and diabetologists alike, pancreatic patients are particularly challenging: they are very sensitive to insulin and prone to hypoglycemic episodes (or even unawareness) because of their postoperative lack of glucagon and other glucose regulatory hormones After a total pancreatectomy, emergency department visits and hospitalizations due to hypoglycemia, ketoacidosis, and failure to thrive are common, all contributing operation's considerable mortality rate.

In the past, pain relief has been the primary, and frequently only, goal of surgery for patients with chronic pancreatitis. A total pancreatectomy usually achieves better pain relief than a partial pancreatectomy or drainage procedure. However, it is not for everyone. Relative contraindications include: a history of alcohol abuse and a likelihood of non-compliance adhering to the postoperative medication regimen. To decrease the relatively high morbidity and mortality that is associated with a total pancreatectomy, the ensuing endocrine deficiency in previously nondiabetic patients has to be alleviated. In already diabetic patients, a total pancreatectomy should only be performed by an interprofessional team that combines integrates approaches to pain management and psychological treatments; above

all, an endocrinologist must be on board who is committed to long-term follow-up. The reality is that, even in already diabetic patients, a total pancreatectomy makes their diabetes much more difficult to control than before the surgery.

But there is a solution, already available at select medical centers. In nondiabetic patients who are candidates for a total pancreatectomy, beta-cell preservation through auto grafting offers the opportunity to either maintain insulin independence or at least better manage the surgery-induced diabetes.

Admittedly, the first clinical attempt at beta-cell preservation, in the late 1970s, was unsuccessful. It took the form of heterotopic autotransplants of the segmental pancreas; however, the, technical complication rate was high, and the pain recurrence rate was higher than after a total pancreatectomy alone.

Another concept, also introduced in the late 1970s, has proved to be more promising, namely, islet autotransplants into the native liver via the portal vein. Early on, the limiting factor was known to be the islet isolation process: in order to achieve insulin independence in at least 70% of islet autotransplant recipients, an islet yield of at least 300,000 islet equivalents per kilogram is required Yet even though lower islet yields usually do not lead to insulin independence, they such transplants can still prevent the development of brittle diabetes mellitus with its wide fluctuations in blood sugar levels and therefore can still improve the recipient's physical and mental health.

Given the strict technical requirements for islet processing facilities (and the high costs associated with facility construction), only a handful of medical centers in the United States offer a total pancreatectomy combined with a simultaneous islet autotransplant (TP-IAT). The prospect of either insulin independence or development of only a mild form of diabetes after a TP-IAT should be major incentivefor physicians to refer their patients with chronic pancreatitis to the few centers that offer the combined operation, rather than settling for the imperfect solution of a total pancreatectomy alone.

The key to a successful metabolic outcome after a TP-IAT lies in early referral. Yet all too often nowadays, patients with chronic pancreatitis are still subjected to a series of inadequate endoscopic and surgical procedures that do not relieve their chronic pain but do cause further deterioration of their endocrine function. Early referral of

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patients with normal hemoglobin A1C levels, and with normal or only slightly abnormal continuous glucose monitoring results, provides the best outcomes after a TP-IAT.

Of note, in children with chronic pancreatitis, outcomes after a TP-IAT also appear to be promising. Short-term outcomes include a decrease in postoperative narcotic requirements, stable glycemic control, and improved quality of life, but more long-term follow-up is required. Nonetheless, we already know that delaying surgery until early adulthood needlessly erodes quality of life during childhood and adolescence, causing psychosocial and learning issues not only for the patient but also for the entire family.

When it comes to the treatment of patients with chronic pancreatitis, surgeons and gastroenterologists must become bolder: yes, a TP-IAT is a radical therapy but the disease is not benign and not reversible. A TP-IAT should be the definitive treatment option early in the disease process, i.e., before the patient develops abnormal glucose metabolism and becomes dependent on pain medications. Once the diagnosis of chronic pancreatitis is established, the numerous endoscopic and inadequate surgical procedures that patients typically undergo are unnecessary and utterly ignore the irreversibility of their disease. Only an early referral to a TP-IAT center will improve metabolic outcome and quality of life. As physicians, we must realize that, with chronic pancreatitis, the most radical surgical option is in the best interest of our patients.