

Prevention of Diabetes for up to 13 Years by Autoislet Transplantation After Pancreatectomy for Chronic Pancreatitis

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Patients with chronic pancreatitis who undergo total pancreas resection inevitably become diabetic unless their islets are autotransplanted to prevent diabetes. We studied patients who underwent this procedure to assess its long-term efficacy in providing stable glucose regulation. Six patients were followed for up to 13 (6.2 ± 1.7) years after intrahepatic islet autotransplantation. From 290,000 to 678,000 islets were transplanted and no patients received drugs to control glucose levels postoperatively. Islet function was assessed by measurements of fasting plasma glucose (FPG), intravenous glucose disappearance rate (K_G), HbA_{1c}, insulin responses to intravenous glucose and to arginine, and insulin secretory reserve. Patients were studied two to four times each to obtain longitudinal data. Five of six patients remained free of insulin treatment and maintained FPG <126 mg/dl and HbA_{1c} levels <6.5%. As a group, they maintained stable insulin secretory reserve, but insulin responses to glucose tended to decrease over time in three patients. K_G values correlated significantly with the number of islets originally transplanted. These data indicate that intrahepatic autoislet transplantation can successfully maintain stable β -cell function and normal levels of blood glucose and HbA_{1c} for up to 13 years after total pancreatectomy as treatment for chronic painful pancreatitis. This usually overlooked procedure of intrahepatic islet transplantation designed to prevent diabetes in patients undergoing pancreatectomy for chronic pancreatitis should be considered more often. *Diabetes* 50:47–50, 2001

The association of chronic pancreatitis and diabetes has been known for more than 200 years and was instrumental in the discovery of insulin by Banting and Best (1). Although a major etiological factor leading to chronic pancreatitis is alcohol consumption, most alcoholics do not develop pancreatitis (2), and extensive lists of many other etiologies can be found in standard textbooks of medicine (3,4). Cardinal features of relapsing chronic pancreatitis include recurrent abdominal pain that is exacerbated

by ingestion of alcohol or a heavy meal, especially one rich in fat. This syndrome leads to weight loss, abnormal stools, and other signs or symptoms consistent with malabsorption. Treatment of chronic pancreatitis is directed toward the major problems of pain control and malabsorption. Pain often leads to frequent use of narcotics and a compromised lifestyle that interferes with child care and employment, and may require surgical intervention. Surgery is generally performed upon discovery of a pseudocyst or localized ductal obstruction. In the most extreme cases, total or near-total pancreatic resection is performed for relief of unrelenting pain.

Diabetes inevitably accompanies chronic pancreatitis once sufficient pancreatic tissue has been destroyed. It also occurs in nondiabetic pancreatitis patients who undergo 80–90% pancreatectomy for relief of pain. Uncommonly, islets isolated from the extirpated pancreas have been crudely isolated and autotransplanted into the liver without need for immunosuppression, in an attempt to prevent diabetes (5–7). Despite the success of this procedure, it surprisingly is not even mentioned in leading textbooks of internal medicine (3,4). On the other hand, the most recently published International Islet Transplant Registry (8) reports an overall 50% rate of diabetes prevention after pancreatectomy and immediate intrahepatic autotransplantation of the patient's own pancreatic islets. However, no data have been reported that address the stability of β -cell function and glycemic control over time after autotransplantation of islets in humans. Consequently, we conducted longitudinal studies in six patients for 1–13 years after transplantation.

RESEARCH DESIGN AND METHODS

Patients. Six successful recipients of intrahepatic autoislet transplantation were admitted on multiple occasions to the University of Minnesota General Clinical Research Center. After an overnight fast and at bed rest, intravenous catheters were placed into arm veins into which 0.45N saline was infused to maintain patency. One intravenous line was used for infusion of test substances; the other was used to draw samples of blood for determinations of glucose, HbA_{1c}, and insulin. All patients underwent total or at least 99% pancreatectomy for pain relief. While the patients were still in the operating room, their extirpated pancreata were taken to a laboratory where they were subjected to enzymatic digestion and partial separation of islets from exocrine tissue under sterile conditions (7). The islet/exocrine mixture was brought back to the operating room within 2 h and slowly infused into the recipient's portal venous system over 30 min with close monitoring of the portal venous pressure.

Metabolic studies. Intravenous glucose disappearance rate (K_G) and acute insulin response to intravenous glucose (AIR_g) were determined by drawing samples of blood 5 and 0 min before and 3, 4, 5, 7, 10, 15, 20, 25, and 30 min after a 20-g intravenous injection of glucose. AIR_g was calculated as the mean of the 3, 4, and 5 min values from which was subtracted the mean of the –5 and 0 min values. K_G was calculated as the slope of time in minutes and the natural log of glucose concentration using the data collected between 10 and 30 min after the glucose injection. The acute insulin response to arginine (AIR_a) was determined by drawing samples of blood 15, 5, and 0 min before

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AIR_a , acute insulin response to arginine; AIR_{aMAX} , insulin secretory reserve; AIR_g , acute insulin response to glucose; FPG, fasting plasma glucose; K_G , glucose disappearance rate.

TABLE 1
Clinical profile of autoislet recipients

Patient	Islet equivalents (n)	Sex	Age at ITx (years)	Years since ITx	% PancX	Cause of pancreatitis
A	290,000	F	42	4	100	Pancreas divisum
B	337,000	F	50	5	100	Idiopathic
C	420,000	F	39	13	99	Idiopathic
D	470,000	M	47	3	100	Idiopathic
E	652,000	F	34	8	100	Idiopathic
F	678,000	M	32	4	100	Idiopathic

ITx, islet transplantation; PancX, pancreatectomy.

and 2, 3, 4, and 5 min after a 5-g intravenous injection of arginine. AIR_a was calculated as the mean of the 2, 3, and 4 min values, from which was subtracted the mean of the -10, -5, and 0 min values. β-Cell insulin secretory reserve (AIR_aMAX) was determined by the method of glucose potentiation of arginine-induced insulin responses. This method uses an infusion of intravenous glucose at a rate of 900 mg/min by intravenous pump, a rate that results in maximal potentiation of arginine-induced insulin secretion (9).

Statistics. Statistical comparisons were performed by Student's paired *t* tests and linear correlation analysis was performed by Pearson product moment.

RESULTS

Patients. Of the six recipients, four were female (Table 1). None of the patients was diabetic before pancreatectomy and all patients underwent at least 99% pancreatectomy. The number of islets transplanted varied from 290,000 to 678,000 islet equivalents. None of the etiologies involved chronic alcoholism.

Metabolic studies. None of the patients was treated with insulin at the time of study. Patients were studied from two to four times each at yearly intervals ranging from 1 to 13 years after pancreatectomy and intrahepatic autoislet transplantation. Of 16 fasting plasma glucose (FPG) levels, 14 were <126 mg/dl; the two higher values were obtained from the same patient 2 and 4 years after transplantation (Fig. 1). This patient received the fewest islets (290,000). HbA_{1c} values were <6% in 13 of the 16 samples measured; 2 of the elevated samples were in the same patient who also had elevated FPG levels and low glucose disappearance rates (Fig. 2). AIR_g tended to decrease over time in three of the six patients

(Fig. 3). Intravenous glucose disappearance rates were >1.0%/min in 6 of the 16 studies (Fig. 4). K_G correlated significantly with the number of islets transplanted (Fig. 5). The AIR_a values (Fig. 6) and insulin secretory reserve, assessed by measuring AIR_aMAX (Fig. 7), were generally stable in all recipients throughout the study.

DISCUSSION

We studied six patients two to four times at yearly intervals who had undergone near-total or total pancreatectomy because of chronic, unrelentingly painful pancreatitis. They would have become diabetic had they not been autotransplanted with a crude preparation of their own islets within hours of pancreatectomy. Only one of the six patients developed clinical diabetes with mild fasting hyperglycemia. This patient used small amounts of NPH insulin to maintain HbA_{1c} levels as close to 7% as possible, but no other patient used insulin or other treatment for hyperglycemia. HbA_{1c} values were generally within the normal range with two exceptions—but even these two were in the range that would be considered excellent glycemic control in diabetic patients receiving treatment. The patient who became frankly diabetic received the fewest islets (290,000), whereas the patient who received 337,000 islets has maintained normal fasting glucose and HbA_{1c} levels. Insulin responses to glucose appear to have deteriorated over the course of the study, whereas insulin responses to arginine and insulin-secretory reserve

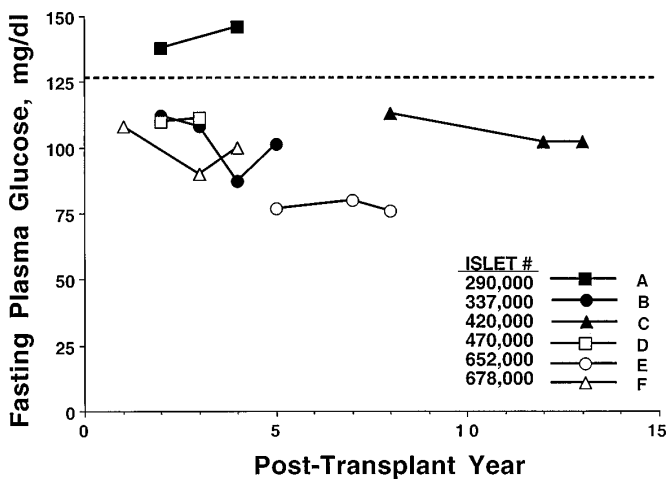


FIG. 1. FPG levels in six recipients (A–F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Dashed line represents upper limit of normal values. Numbers of islets transplanted are given next to initials A–F.

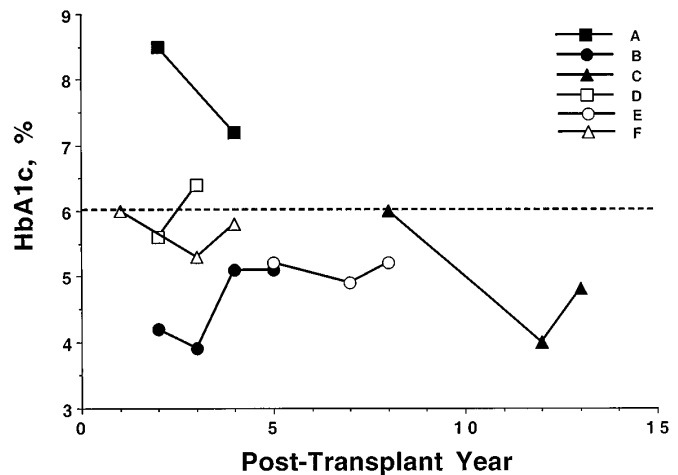


FIG. 2. HbA_{1c} levels in the six recipients (A–F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Dashed line represents upper limit of normal values. Number of islets transplanted: ■, 290,000; ●, 337,000; ▲, 420,000; □, 470,000; ○, 652,000; △, 678,000.

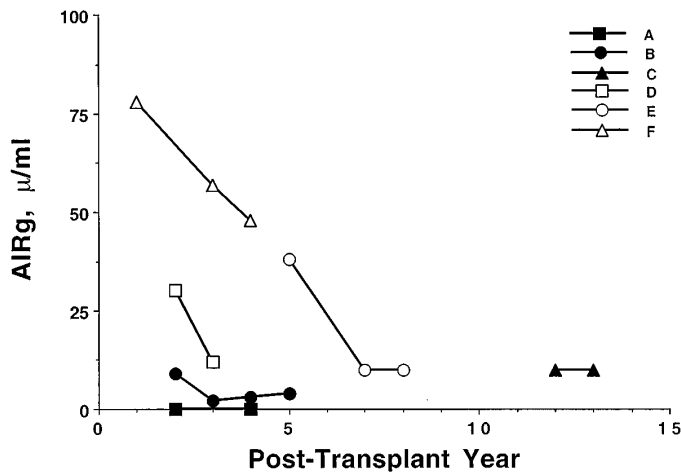


FIG. 3. Acute insulin responses to 20-g intravenous injection of glucose (AIRg) in six recipients (A-F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Number of islets transplanted: ■, 290,000; ●, 337,000; ▲, 420,000; □, 470,000; ○, 652,000; △, 678,000.

remained stable for as long as 13 years. However, as we have reported previously (9), these insulin responses are generally of a smaller magnitude than normal and the magnitude of the responses correlates significantly with the numbers of islets transplanted. Intravenous glucose disappearance rates correlated significantly with the number of islets transplanted. This correlation suggests that ~500,000 islets should be sufficient to normalize glucose tolerance.

Diabetes is not an infrequent complication of chronic pancreatitis. Larsen (2) reported that in unselected patients with chronic pancreatitis, roughly one-third developed type 1 diabetes and another third developed type 2 diabetes or glucose intolerance. Total or near-total pancreatectomy inevitably leads to insulin-dependent diabetes, because at least 20–30% of the normal complement of pancreatic islets must be functioning to maintain normal glucose levels. Wahoff et al. (7) reported

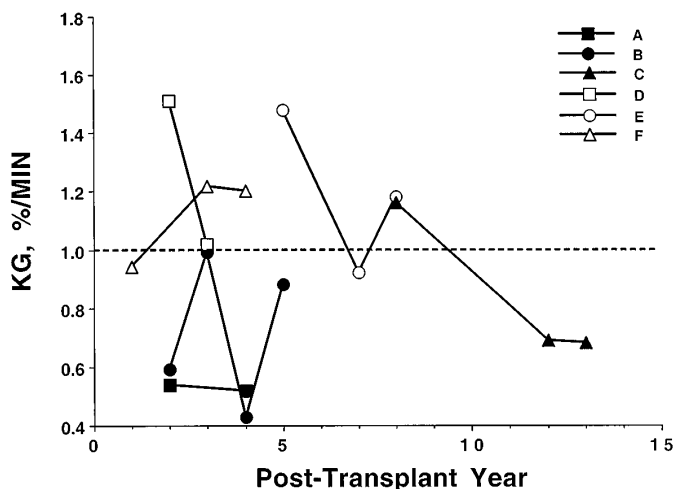


FIG. 4. Glucose disappearance rates after 20-g intravenous injection of glucose (KG) in the six recipients (A-F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Dashed line represents lower limit of normal values. Number of islets transplanted: ■, 290,000; ●, 337,000; ▲, 420,000; □, 470,000; ○, 652,000; △, 678,000.

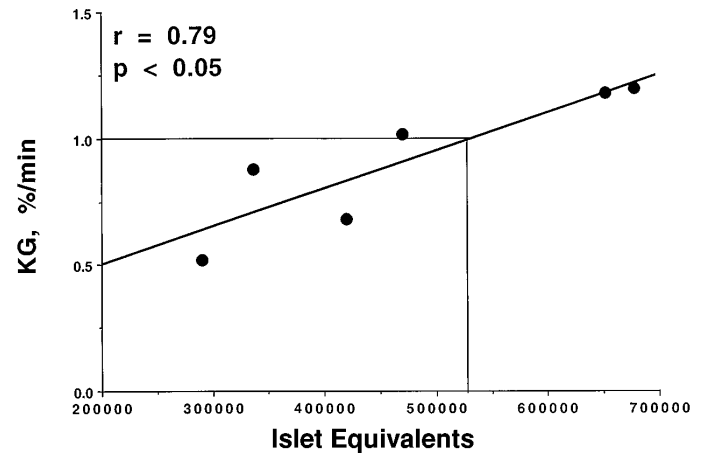


FIG. 5. Correlation between the number of islet equivalents transplanted and K_G (KG). K_G of 1.0%/min correlated to ~500,000 islets.

cross-sectional data indicating that the success rate for insulin independence for >2 years was 74% for 14 patients who received >300,000 autotransplanted islets. In this series of 48 patients, the surgical complication rate was 25%, the rate of significant pain relief was 80%, and one perioperative death (colon perforation and sepsis) occurred. The six patients reported herein are a subset of this series, but they are the only ones with functioning islets whom we have been able to study longitudinally. These findings overall underscore the need to evaluate early in the course of chronic pancreatitis whether and when the patient is likely to develop diabetes. Factors such as family history of diabetes and the extent of pancreatic injury and previous surgery are likely to be important variables. Earlier pancreatectomy and maximal recovery of islets are two important variables that favor successful prevention of hyperglycemia after autoislet transplantation. The difficult clinical choice is when to discontinue temporizing procedures such as removal of pseudocysts or use of stents as opposed to removing the diseased organ and autotransplant-

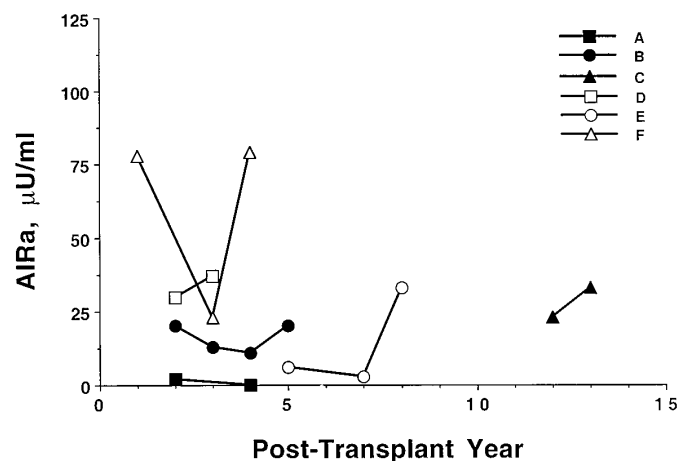


FIG. 6. Acute insulin responses to 5-g intravenous injection of arginine (AIRa) in the six recipients (A-F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Number of islets transplanted: ■, 290,000; ●, 337,000; ▲, 420,000; □, 470,000; ○, 652,000; △, 678,000.

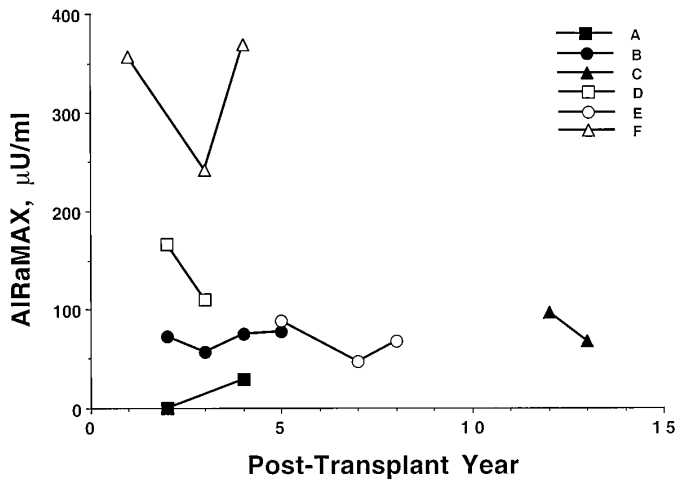


FIG. 7. Insulin secretory reserve (AIRaMAX) in six recipients (A–F) of intrahepatic autoislet transplantation over 1–13 years after transplantation. Number of islets transplanted: ■, 290,000; ●, 337,000; ▲, 420,000; □, 470,000; ○, 652,000; △, 678,000.

ing islets with the intent of relieving abdominal pain and preventing the eventual development of diabetes. It would seem that the standard practice in the U.S. probably errs on waiting too long, since the concept of autotransplantation of pancreatic islets after pancreatectomy is not even mentioned in standard textbooks of internal medicine (3,4). Although the success rate is very encouraging, the potential lethality of this procedure was underscored by Froberg et al. (10), who published a case report of fatal disseminated intravascular coagulation immediately after autoislet transplantation.

The success of autotransplantation of pancreatic islets stands in stark contrast to the success rates of alloislet transplantation in type 1 diabetic patients. The most recently published edition of the International Islet Transplant Registry reports an 8% success rate of islet allografts in type 1 diabetic patients, defined as insulin independence for >1 year after transplantation (8). The longest instance of success appears to have been the case reported by Ferreira et al. (11), who reported normalization or near-normalization of HbA_{1c} levels without insulin treatment in two type 1 diabetic patients for 9 years. It remains an enigma why the same immunosuppressive drugs that are effective in protecting whole-organ pancreas allografts (12) are not nearly as effective in protecting islets after allotransplantation, although most of these drugs have been known for years to adversely affect β -cells (13–21). Another potentially important variable is that patients receiving intrahepatic islet transplants usually have type 1 diabetes, whereas patients with chronic pancreatitis have had no such previous autoimmune-directed pressure on their pancreatic islets. The adverse effect of glucocorticoids used for immunosuppression on β -cell survival may be a very important factor, as recently reported by Shapiro et al. (21), who reported 100% success for an average of 1 year in seven allotransplant recipients treated with a steroid-free regimen.

In conclusion, our data indicate that long-term function of autotransplanted islets and prevention of diabetes is possible in patients who have undergone pancreas resection because of chronic pancreatitis. This procedure should be routinely con-

sidered when patients with chronic pancreatitis are scheduled to undergo pancreatectomy.

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