

## REVIEW

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# Pancreas transplant for diabetes mellitus

## ABSTRACT

Pancreas transplant is an option for patients with type 1 diabetes and for some patients with type 2 diabetes and advanced diabetic kidney disease. The procedure has a high success rate, and performing it earlier in the course of diabetes could help prevent or reverse the long-term complications of diabetes.

## KEY POINTS

Current options are simultaneous pancreas-kidney transplant, pancreas-after-kidney transplant, and pancreas-alone transplant.

Simultaneous pancreas-kidney transplant provides a significant survival benefit over insulin- and dialysis-based therapies.

Isolated pancreas transplant for diabetic patients without uremia can prevent hypoglycemic unawareness.

**P**ANCREAS TRANSPLANT IS THE only long-term diabetes treatment that consistently results in normal hemoglobin A<sub>1c</sub> levels without the risk of severe hypoglycemia. Additionally, pancreas transplant may prevent, halt, or even reverse the complications of diabetes.

Here, we explore the indications, options, and outcomes of pancreas transplant as a treatment for diabetes mellitus.

## ■ DIABETES IS COMMON, AND OFTEN NOT WELL CONTROLLED

Diabetes mellitus affects more than 25 million people in the United States (8.3% of the population) and is the leading cause of kidney failure, nontraumatic lower-limb amputation, and adult-onset blindness. In 2007, nearly \$116 billion was spent on diabetes treatment, not counting another \$58 billion in indirect costs such as disability, work loss, and premature death.<sup>1</sup>

Despite the tremendous expenditure in human, material, and financial resources, only about 50% of patients achieve their diabetes treatment goals. In 2013, a large US population-based study<sup>2</sup> reported that 52.2% of patients were achieving the American Diabetes Association treatment goal of hemoglobin A<sub>1c</sub> lower than 7%. A similar study in South Korea<sup>3</sup> found that 45.6% were at this goal.

Most of the patients in these studies had type 2 diabetes, and the data suggested that attaining glycemic goals is more difficult in insulin-treated patients. Studies of patients with type 1 diabetes found hemoglobin A<sub>1c</sub> levels lower than 7% in only 8.1% of hospitalized patients with type 1 diabetes, and in only 13% in an outpatient diabetes clinic.<sup>4,5</sup>

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TABLE 1

**Pancreas transplant facts and figures, 2012**

	<b>Simultaneous pancreas-kidney transplant</b>	<b>Pancreas after kidney transplant</b>	<b>Pancreas transplant alone</b>
<b>Share of US pancreas transplants<sup>9</sup></b>	79%	12%	8%
<b>Indications</b>	Type 1 diabetes, advanced diabetic nephropathy (glomerular filtration rate < 20 mL/min)	Labile blood glucose control, prior well-functioning kidney transplant	Labile blood glucose control, normal or near-normal native renal function
<b>1-year graft survival<sup>8,9</sup></b>	89%	86%	84%
<b>5-year graft survival<sup>8,9</sup></b>	71%	65%	58%

### ■ YET RATES OF PANCREAS TRANSPLANT ARE DECLINING

Pancreas transplant was first performed more than 40 years ago at the University of Minnesota.<sup>6</sup> Since then, dramatic changes in immunosuppression, organ preservation, surgical technique, and donor and recipient selection have brought about significant progress.

Currently, more than 13,000 patients are alive with a functioning pancreas allograft. After reaching a peak in 2004, the annual number of pancreas transplants performed in the United States has declined steadily, whereas the procedure continues to increase in popularity outside North America.<sup>7</sup> The primary reason for the decline is recognition of donor factors that lead to success—surgeons are refusing to transplant organs they might have accepted previously, because experience suggests they would yield poor results. In the United States, 1,043 pancreas transplants were performed in 2012, and more than 3,100 patients were on the waiting list.<sup>8</sup>

Islet cell transplant—a different procedure involving harvesting, encapsulating, and implanting insulin-producing beta cells—has not gained widespread application due to very low long-term success rates.

### ■ THREE CATEGORIES OF PANCREAS TRANSPLANT

Pancreas transplant can be categorized according to whether the patient is also receiving or has already received a kidney graft (Table 1).

**Simultaneous kidney and pancreas transplant** is performed in patients who have type 1 diabetes with advanced chronic kidney disease due to diabetic nephropathy. This remains the most commonly performed type, accounting for 79% of all pancreas transplants in 2012.<sup>8</sup>

**Pancreas-after-kidney transplant** is most often done after a living-donor kidney transplant. This procedure accounted for most of the increase in pancreas transplants during the first decade of the 2000s. However, the number of these procedures has steadily decreased since 2004, and in 2012 accounted for only 12% of pancreas transplants.<sup>8</sup>

**Pancreas transplant alone** is performed in nonuremic diabetic patients who have labile blood sugar control. Performed in patients with preserved renal function but severe complications of “brittle” diabetes, such as hypoglycemic unawareness, this type accounts for 8% of pancreas transplants.<sup>9</sup>

#### Indications for pancreas transplant

A small number of these procedures are done for indications unrelated to diabetes mellitus. In most of these cases, the pancreas is transplanted as part of a multivisceral transplant to facilitate the technical (surgical) aspect of the procedure—the pancreas, liver, stomach, gallbladder, and part of the intestines are transplanted en bloc to maintain the native vasculature. Very infrequently, pancreas transplant is done to replace exocrine pancreatic function.

A small, select group of patients with type 2 diabetes and low body mass index (BMI)

**Only about half of patients achieve hemoglobin A<sub>1c</sub> < 7% with medical therapy**

## Preparing and implanting the graft

Once a donor pancreas is determined to be suitable, procurement must be coordinated with liver procurement because of the shared vasculature between these two organs.

During procurement, the common arterial circulation and venous drainage are divided preferentially for the liver, and considerable time must be spent in “back-table” or “bench” preparation of the pancreas allograft. The allograft is procured with its vasculature, the donor spleen, and a variable length of donor duodenum. The arterial supply to the pancreas allograft, which includes the splenic and superior mesenteric arteries, must be reconstructed. This is most often done by anastomosis of the splenic and superior mesenteric arteries to a segment of donor iliac artery (iliac Y-graft), to facilitate a single arterial anastomosis in the recipient. Additional steps during bench preparation include removal of excess peripancreatic tissue, splenectomy, and mobilization of the donor bowel and portal vein.

### IMPLANTING THE GRAFT

The allograft is usually implanted along the recipient’s right common iliac or external iliac vessels.

Over 90% of pancreas transplants are done with systemic venous drainage, through anastomosis of the donor portal vein to the inferior vena cava or iliac

vein of the recipient (**Figure 1**).<sup>12</sup> In the remainder of cases, the donor portal vein is drained into the recipient’s portal venous circulation, duplicating the normal physiologic relationship. The supposed metabolic and immunologic benefits of portal drainage have not been realized in clinical practice, and interest in portal venous drainage has waned over the past decade.

Management of pancreatic exocrine secretions, initially the Achilles heel of pancreas transplant, is done with either enteric or bladder drainage. Currently, over 80% of pancreas transplants are performed with enteric drainage, in which the segment of donor duodenum is anastomosed to a segment of recipient bowel, most often the jejunum. In addition to standard duodenojejunostomy, we have also utilized a technique of duodenoduodenostomy, which may provide easier endoscopic access to the allograft, both for biopsy and for management of exocrine complications.<sup>13</sup>

The remaining 20% of pancreas transplants are performed with bladder drainage, ie, anastomosis of the donor duodenum to the recipient bladder.<sup>12</sup> Initially developed as a means to avoid significant enteric complications, the nonphysiologic nature of bladder drainage is associated with numerous urologic and metabolic complications, prompting up to 50% of patients to undergo subsequent conversion to enteric drainage.<sup>14</sup>

may be eligible for pancreas transplant, and they accounted for 8.2% of active candidates in 2012.<sup>8</sup> However, most pancreas transplants are performed in patients with type 1 diabetes.

### ■ WHAT MAKES A GOOD ALLOGRAFT?

Pancreas allografts are procured as whole organs from brain-dead organ donors. Relatively few pancreas allografts (3.1% in 2012) are from cardiac-death donors, because of concern about warm ischemic injury during the period of circulatory arrest.<sup>8</sup>

Proper donor selection is critical to the success of pancreas transplant, as donor factors including medical history, age, BMI, and cause of death can significantly affect the outcome. In general, transplant of a pancreas allograft from a young donor (age < 30) with excellent

organ function, low BMI, and traumatic cause of death provides the best chance of success.

The Pancreas Donor Risk Index (PDRI)<sup>10</sup> was developed after analysis of objective donor criteria, transplant type, and ischemic time in grafts transplanted between 2000 and 2006. One-year graft survival was directly related to the PDRI and ranged between 77% and 87% in recipients of “standard” pancreas allografts (PDRI score of 1.0). Use of grafts from the highest (worst) three quintiles of PDRI (PDRI score > 1.16) was associated with 1-year graft survival rates of 67% to 82%, significantly inferior to that seen with “higher-quality” grafts, again emphasizing the need for rigorous donor selection.<sup>10</sup>

In addition to these objective measures, visual assessment of pancreas quality at the

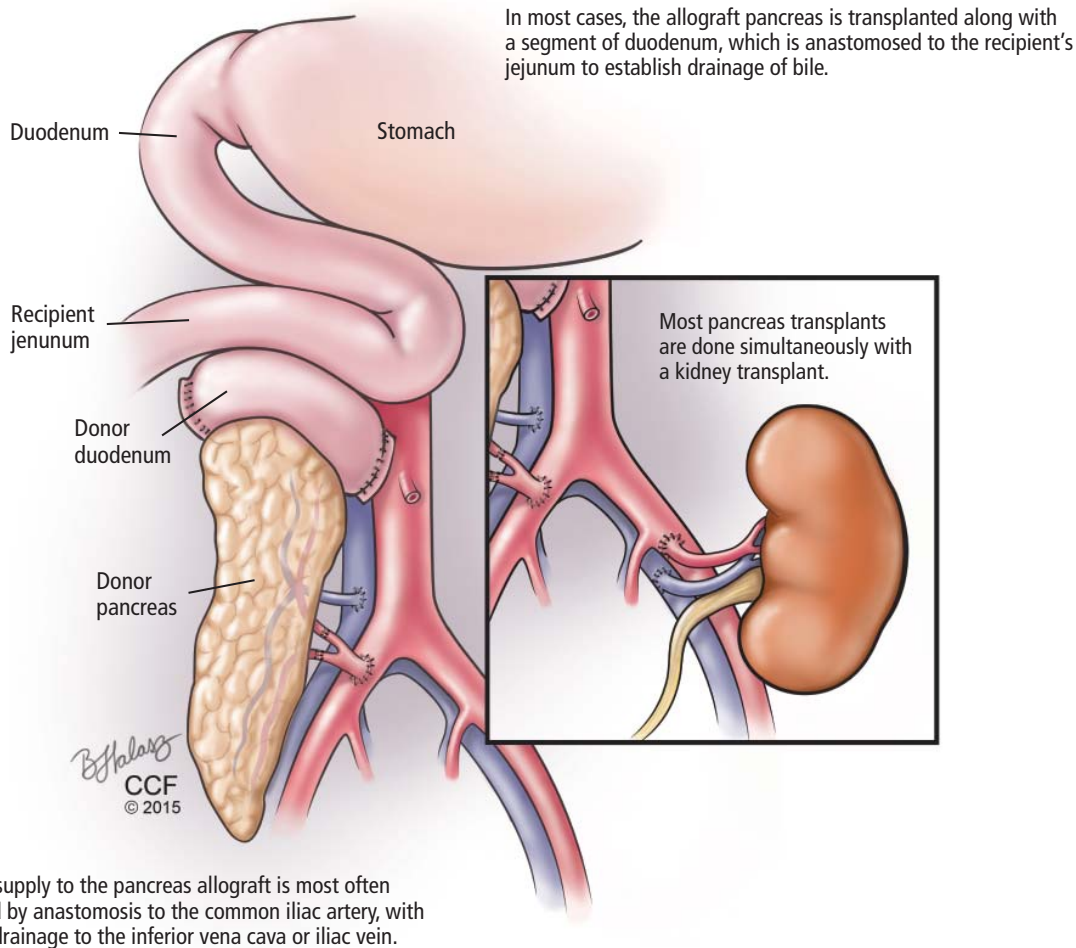


FIGURE 1

time of procurement remains an equally important predictor of success. Determination of subjective features, such as fatty infiltration and glandular fibrosis, requires surgical experience developed over several years. In a 2010 analysis, dissatisfaction with the quality of the donor graft on inspection accounted for more than 80% of refusals of potential pancreas donors.<sup>11</sup> These studies illustrate an ill-defined aspect of pancreas transplant, ie, even when the pancreas donor is perceived to be suitable, the outcome may be markedly different.

**■ SURGICAL COMPLICATIONS**

Surgical complications have long been considered a limiting factor in the growth of pancreas transplant. Technical failure or loss of the graft within 90 days is most commonly due to graft

thrombosis, leakage of the enteric anastomosis, or severe peripancreatic infection. The rate of technical failure has declined across all recipient categories and is currently about 9%.<sup>8</sup>

**■ DO RECIPIENT FACTORS AFFECT OUTCOMES?**

As mentioned above, the PDRI identifies donor factors that influence the 1-year graft survival rate. Recipient factors are also thought to play a role, although the influence of these factors has not been consistently demonstrated.

Humar et al<sup>15</sup> found that recipient obesity (defined in this study as BMI > 25 kg/m<sup>2</sup>) and donor age over 40 were risk factors for early laparotomy after pancreas transplant.<sup>15</sup> Moreover, patients undergoing early laparotomy had poorer graft survival outcomes.

**Patient survival 1 year after pancreas-alone transplant is > 96%**

This finding was reinforced by an analysis of 5,725 primary simultaneous pancreas-kidney recipients between 2000 and 2007. Obesity (BMI  $30 \geq \text{kg/m}^2$ ) was associated with increased rates of patient death, pancreas graft loss, and kidney graft loss at 3 years.<sup>16</sup>

More recently, Finger et al<sup>17</sup> did not find a statistically significant association between recipient BMI and technical failure, but they did notice a trend toward increased graft loss with a BMI greater than  $25 \text{ kg/m}^2$ . Similarly, others have not found a clear adverse association between recipient BMI and pancreas graft survival.

Intuitively, obesity and other recipient factors such as age, vascular disease, duration of diabetes, and dialysis should influence pancreas graft survival but have not been shown in analyses to carry an adverse effect.<sup>18</sup> The inability to consistently find adverse effects of recipient characteristics is most likely due to the relative similarity between the vast majority of pancreas transplant recipients and the relatively small numbers of adverse events. In 98 consecutive pancreas transplants at our center between 2009 and 2014, the technical loss rate was 1.8% (unpublished data).

Acute rejection most commonly occurs during the first year and is usually reversible. More than 1 year after transplant, graft loss is due to chronic rejection, and death is usually from underlying cardiovascular disease.

The immunosuppressive regimens used in pancreas transplant are similar to those in kidney transplant. Since the pancreas is considered to be more immunogenic than other organs, most centers employ a strategy of induction immunosuppression with T-cell-depleting or interleukin 2-receptor antibodies. Maintenance immunosuppression consists of a calcineurin inhibitor (tacrolimus or cyclosporine), an antimetabolite (mycophenolate), and a corticosteroid.<sup>8</sup>

Immunosuppressive complications occur at a rate similar to that seen in other solid-organ transplants and include an increased risk of opportunistic infection and malignancy. The risk of these complications must be balanced against the patient's risk of health decline with dialysis and insulin-based therapies.

■ **OVERALL OUTCOMES ARE GOOD**

The success rate of pancreas transplant is currently at its highest since the inception of the procedure. The unadjusted patient survival rate for all groups is over 96% at 1 year, and over 80% at 5 years.<sup>8</sup> One-year patient survival after pancreas transplant alone, at better than 96%, is the highest of all organ transplant procedures.<sup>9</sup>

Several recently published single-center reviews of pancreas transplant since 2000 report patient survival rates of 96% to 100% at 1 year and 88% to 100% at 5 years.<sup>19-22</sup> This variability is likely closely linked to donor and recipient selection, as centers performing smaller numbers of transplants tend to be more selective and, in turn, report higher patient survival rates.<sup>19,21</sup>

Long-term patient survival outcomes can be gathered from larger, registry-based reviews, accepting limitations in assessing causes of patient death. Siskind et al<sup>23</sup> analyzed the outcomes of 20,854 US pancreas transplants done between 1996 and 2012 and found the 10-year patient survival rate ranged from 43% to 77% and was highly dependent on patient age at the time of the procedure.<sup>23</sup> Patient survival after transplant must be balanced against the generally poor long-term survival prospects of diabetic patients on dialysis.

**By type of transplant,** pancreas graft survival rates at 1 year are 89% for simultaneous pancreas-kidney transplant, 86% for pancreas-after-kidney transplant, and 84% for pancreas-alone transplant. Graft survival rates at 5 years are 71% for simultaneous pancreas-kidney transplant, 65% for pancreas-after-kidney transplant, and 58% for pancreas-alone transplant.<sup>8,9</sup>

Simultaneous pancreas-kidney transplant has been shown to improve the survival rate compared with cadaveric kidney transplant alone in patients with type 1 diabetes and chronic kidney disease.<sup>24,25</sup> The survival benefit of isolated pancreas transplant (after kidney transplant and alone) is not evident at 4-year follow-up compared with patients on the waiting list. However, the benefit for the individual patient must be considered by weighing the incapacities experienced with insulin-based treatments against the risks of surgery and immunosuppression.<sup>26,27</sup> For patients who have

experienced frequent and significant hypoglycemic episodes, particularly those requiring third-party assistance, pancreas transplant can be a lifesaving procedure.

### Effects on secondary diabetic complications

Notwithstanding the effect on the patient's life span, data from several studies of long-term pancreas transplant recipients suggest that secondary diabetic complications can be halted or even improved. Most of these studies examined the effect of restoring euglycemia in nephropathy and the subsequent influence on renal function.

**Effect on renal function.** Kleinclauss et al.<sup>28</sup> examined renal allograft function in type 1 diabetic recipients of living-donor kidney transplants. Comparing kidney allograft survival and function in patients who received a subsequent pancreas-after-kidney transplant vs those who did not, graft survival was superior after 5 years, and the estimated glomerular filtration rate was 10 mL/min higher in pancreas-after-kidney recipients.<sup>28</sup> This improvement in renal function was not seen immediately after the pancreas transplant but became evident more than 4 years after establishment of normoglycemia. Somewhat similarly, reversal of diabetic changes in native kidney biopsies has been seen 10 years after pancreas transplant.<sup>29</sup>

**Effect on neuropathy.** In other studies, reversal of autonomic neuropathy and hypoglycemic unawareness and improvements in peripheral sensory-motor neuropathy have also

been observed.<sup>30–32</sup>

**Effect on retinopathy.** Improvements in early-stage nonproliferative diabetic retinopathy and laser-treated proliferative lesions have been seen, even within short periods of follow-up.<sup>33</sup> Other groups have shown a significantly higher proportion of improvement or stability of advanced diabetic retinopathy at 3 years after simultaneous pancreas-kidney transplant, compared with kidney transplant alone in patients with type 1 diabetes.<sup>34</sup>

**Effect on heart disease.** Salutary effects on cardiovascular risk factors and amelioration of cardiac morphology and functional cardiac indices have been seen within the first posttransplant year.<sup>35</sup> Moreover, with longer follow-up (nearly 4 years), simultaneous pancreas-kidney recipients with functioning pancreas grafts were found to have less progression of coronary atherosclerosis than simultaneous pancreas-kidney recipients with early pancreas graft loss.<sup>36</sup> These data provide a potential pathophysiologic mechanism for the long-term survival advantage seen in uremic type 1 diabetic patients undergoing simultaneous pancreas-kidney transplant.

In the aggregate, these findings suggest that, in the absence of surgical and immunosuppression-related complications, a functioning pancreas allograft can alter the progress of diabetic complications. As an extension of these results, pancreas transplant done earlier in the course of diabetes may have an even greater impact. ■

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