REVIEW

Exocrine Drainage of the Transplanted Pancreas: A Review

Eliza W Beal[1,3], Ashraf M El-Hinnawi[1,3], Bryan A. Whitson[2,3], Elmahdi A. Elkhammas[1,3], Mitchell L. Henry[1,3], Sylvester M Black[1,3]

[1]The Department of General Surgery, Division of Transplantation, The Ohio State University Wexner Medical Center, 395 W. 12th Avenue, Suite 150, Columbus, OH 43210
[2]The Department of General Surgery, Division of CardioThoracic, The Ohio State University Wexner Medical Center, 410 W. 10th Avenue, N816 Doan Hall, Columbus, OH 43210
[3]The Comprehensive Transplant Center, The Ohio State University Wexner Medical Center, 395 W. 12th Avenue, Suite 150, Columbus, OH 43210

Corresponding Author: Dr. Sylvester M. Black Email: sylvester.black@osumc.edu
Published: 1 May 2017
Ibnosina J Med BS 2017;9(3):52-63
Received: 8 March 2017
Accepted: 11March 2017
This article is available from: http://www.ijmbs.org

Abstract
Pancreas transplant is an important treatment option for insulin dependent diabetic patients as it may result in physiologic euglycemia. Improvements in surgical technique, graft preservation, immunosuppression, diagnosis and management of rejection, and management of post-transplant complications have led to improved patient survival.

There are several technical variables to consider when performing a pancreas transplant. One is the type of exocrine drainage to be used. The most common types of exocrine drainage are enteric or bladder drainage. Gastric-exocrine drainage has also been recently introduced. The most commonly cited complications associated with bladder drainage include metabolic complications, urologic complications and the need for enteric conversion.

Many complications related to bladder drainage can be managed non-operatively with Foley catheter drainage. For those complications that cannot be managed in this manner, enteric conversion is an option. Complications associated with enteric drainage include anastomotic leak and intra-abdominal abscess, although at rates lower than cited in the early literature on the topic. Bladder drainage of exocrine secretions and enteric drainage of exocrine secretions, or a staged procedure with bladder drainage followed by indicated or elective enteric conversion are reasonable options for drainage of the exocrine secretions of the pancreas. Gastric-exocrine drainage is a promising therapy deserving of future exploration.

Keywords
Enteric drainage, Bladder drainage, Pancreas transplant, Simultaneous pancreas-kidney transplant, Pancreas after kidney transplant, Pancreas alone transplant, Enteric conversion

Introduction

The number of persons in the United States diagnosed with Diabetes Mellitus has tripled between 1980 and 2011 from 5.6 million to 20.9 million (1). It is believed that an additional 8.1 million people are living with diabetes without a diagnosis (2). Eighteen percent (18%) of diagnosed patients are insulin dependent, and 13% of them manage their diabetes with both pills and insulin (3).

Pancreas transplantation is an important treatment option for insulin dependent diabetics and the only option that allows resumption of euglycemia and normal physiology (4). Although initially limited to type I diabetic patients, pancreas transplantation is increasingly being used for the treatment of insulin-dependent type II diabetes as well (5,6).

As of December 2010, there were 35,000 pancreas transplants reported to the International Pancreas Transplant Registry (IPTR) (5), with 8,131 performed in the United States between January 1, 1988, and December 31, 2015 (7). Improvements in surgical technique, graft preservation, immunosuppression, diagnosis and management of rejection, and management of post-transplant complications have led to improved patient survival with one- and five-year patient survival of 95% and 83%, respectively (5).

An important consideration in performing a pancreas transplant is the method of exocrine drainage. The first vascularized pancreas transplant, performed in 1966, used a duct ligated segmental graft with no drainage of exocrine secretions (8). The second involved maintenance of a duodenal segment, which was brought out as a stoma to allow for drainage of exocrine secretions, and the third used a Roux-en-Y loop for enteric drainage of the exocrine secretions (8). Other techniques that have been used in pancreas transplantation to drain exocrine secretions include whole pancreaticoduodenal transplants with spleen attached, duct injection, and segmental grafts with main pancreatic duct anastomosed to the ureter, exocrine drainage, and bladder drainage (8,9).

There are two primary techniques in use for drainage of pancreas transplant graft exocrine sections: bladder drainage and enteric drainage. Bladder drainage was first described by Sollinger et al. in 1988 and involves the drainage of the duodenal segment to the bladder, or pancreaticoduodenocystostomy (10). This technique was designed with the intent of allowing closer monitoring of the health of the transplant graft through measurement of urine amylase and also allows cystoscopic access to the pancreas graft for biopsy to aid in the diagnosis of graft rejection (8,11). Several modifications of this technique were introduced around the same time (12).

Enteric drainage involves drainage of the duodenal segment to small bowel (4) and is the most common technique in use (5). The IPTR reported that between 2002 and 2003 there was 82% enteric drainage of the pancreas and in 2010, enteric drainage was used in 91% of simultaneous kidney-pancreas transplants, 89% of pancreas after kidney transplants and 85% of pancreas transplant alone (5). This transition from bladder drained procedures, which comprised >90% of procedure between 1988 and 1995, to enteric drainage, which comprised more than 50% of procedures by 1998, occurred in the mid-1990s. At this time studies showed that the risks previously shown to be associated with enteric drainage were not as significant as once thought (13).

The majority of these bladder and enteric drained pancreata have systemic venous delivery of insulin, although some centers use alternate drainage (13-15). The portal venous drainage approach was initially introduced by Gaber et al., with intraperitoneal portal venous drainage to the superior mesenteric vein (SMV) (16). A modified technique involving retroperitoneal placement of the pancreas graft was introduced by Boggi et al (17). Although other techniques have been described, portal venous drainage usually refers to the use of the recipient's superior mesenteric vein (18). No distinct physiologic advantages have been demonstrated in subsequent studies. Systemic venous drainage describes anastomoses of the graft to the recipient external iliac vein (19). The focus of this review will be on the drainage of exocrine secretions, but as many centers have compared systemic venous and bladder exocrine drainage to portal venous and enteric exocrine drainage it is worthwhile to mention the venous drainage options.

Enteric Drainage: Review, Advantages, Disadvantages, and Complications

The most common method of performing enteric drainage is to anastomose the duodenum to the jejunum with the pancreas graft placed in an intraperitoneal position. Other techniques that have been reported include: side-to-side duodenojejunostomy with the Roux-en-Y method with

graft placement in the retroperitoneum, side-to-side duodenoduodenostomy with pancreas graft in a retrocolic position, and gastric-exocrine drainage techniques (17,20). As noted previously, portal venous drainage and enteric exocrine drainage was pioneered by Gaber et al. in 1993 (16). Studies show a decrease in peripheral hyperinsulinemia with portal venous drainage (16). Reported advantages and disadvantages of exocrine drainage are detailed in table 1.

Table 1. Advantages and Disadvantages of Enteric Drainage

Advantages of Enteric Drainage
"More physiologic" (4)
Lower rates of urinary tract infection (4)
Lower rates of urologic complications (39)
Disadvantages of Enteric Drainage
Inability to directly monitor exocrine secretions (13)
Healing problems (13)
Leakage of pancreatic enzymes and sepsis (8,39)
Intra-abdominal abscesses (36,38,39)
Pancreas graft loss (36,38)
Diffuse peritonitis (39)
Anastomotic leak (38)

A single-center study by Reddy et al. of surgical complications after portal-enteric drainage reported 53 complications in 31 of 83 (37%) patients. A complication was defined as the need for re-laparotomy within 3 months of the original transplant or during the initial hospital stay for a variety of indications including vascular thrombosis, intra-abdominal bleeding, duodenal leak, culture-proven infection, and others (14). A similar incidence of complications was noted in comparing simultaneous kidney-pancreas transplant and solitary pancreas groups (p=NS). Most vascular graft thrombosis occurred early (55% within one week, 91% within one month), and were equally divided between arterial and venous thrombosis. All patients were treated with transplant pancreatectomy. Nine repeat laparotomies were performed for bleeding in seven patients. Of the remaining patients, two lost their pancreas grafts. Three patients developed duodenal segment leaks and underwent seven re-laparotomies, one of whom eventually lost their pancreas graft. Eight patients developed intraabdominal infections requiring thirteen re-laparotomies and five of these eventually lost their graft (14). This 37% complication rate is similar to complication rates reported for systemic-bladder drainage: Iowa group 28% reported in 1993 (21), Wisconsin group reported 24% in 1993 (22), Nebraska group 36% (23), and Minnesota group 32% (24).

This study also reports a rate of graft thrombosis of 13% (14). The incidence of this complication reported by other groups varies from 6% to 19% for systemic-bladder drainage ranges from 6-19% (21-25). In contrast, Bruce et al. from Chicago report a vascular thrombosis rate of only 1% in 500 simultaneous kidney-pancreas transplants, which included both systemic-bladder drained (n=388) and portal-enteric drained (n=112) for which there is no difference in rate (4% versus 8%) (26).

Enteric drainage and bladder drainage have similarly reported rates of intra-abdominal infection. Overall the reported rate of intra-abdominal infection in enteric drainage is 10-41% (14,24,27-30). The reported rate of intra-abdominal infections in bladder drainage is 14-30% (24,28,29,31).

Although Reddy reported a very low rate of duodenal leaks at just 4%, the overall the rate of duodenal leaks for enteric drainage is 4-16% (14,32-34). The rate of duodenal leaks for bladder drainage is 13-16% (29,32).

Regarding infectious complications, Berger et al. report on infectious complications following 72 consecutive enteric-drained pancreas transplants. They demonstrated an overall infection rate of 46%. The infections included 12 intra-abdominal infections, 7 wound infections, 13 cases of sepsis, 4 respiratory tract infections, 12 urinary tract infections, 5 HSV/HHV-6 infections, 7 CMV infection/disease, 3 PTLD, 4 invasive fungal/filamentous disease, 1 clostridial/rotavirus, and 1 endocarditis. In this series with a median follow-up of 23 months, there were four deaths, which were all related to infection and five graft losses which were not related to infection (30).

Walter et al. introduce the technique of retroperitoneal placement of the pancreatic graft to allow exocrine drainage directly via a duodenoduodenostomy and have performed this technique in 125 cases (20). Reported advantages of this technique include endoscopic access to the pancreas for biopsy for diagnosis of rejection and endoscopic access to the anastomotic site in case of bleeding at this site. A primary disadvantage, in this case,

is the difficulty of repairing a duodenal anastomotic leak. In a retrospective review, they compared this to 116 duodenojejunostomy cases with comparable patients and graft survival. They report a higher rate of graft thrombosis, anastomotic insufficiency, and re-laparotomy in the duodenojejunostomy group and a higher rate of gastrointestinal bleeding in the duodenoduodenostomy group (20).

Bonatti et al. report 112 enteric drained pancreas transplants with a 28% surgical complication rate and 40% rejection rate. There were 21 graft losses and causes are as follows: irreversible rejection (7), intraabdominal infection (8), arterial thrombosis (3) and death with a functioning graft (3). There were a total of 25 (22%) patients who developed intraabdominal infections. The authors report that midway through the study they changed to a stapling device and the rate went from 24% in the first 54 cases to 5.5% in the last 58 cases. The authors report a 6.5% technical failure rate in the first year after transplant (35).

Bladder Drainage: Review, Advantages, Disadvantages, and Complications

Bladder drainage with a duodenal segment conduit was the preferred technique among all centers in the United States until the mid- to the late-1990's (5,13,36). The procedure is safe, sterile and convenient. However, it does provide a non-physiologic connection between the pancreas, duodenal conduit, and bladder. This results in fluid and bicarbonate loss into the urine and changes in the flora of the lower genitourinary tract (20,37).

Commonly cited advantages and disadvantages of bladder drainage are listed in Table 2. Recognized advantages of bladder drainage include ease of monitoring for rejection with measurement of urinary amylase, easy access for cystoscopic biopsies, easy control of anastomotic problems with prolonged catheter drainage and avoidance of complications associated with enteric drainage (4,8,13, 38). Notable disadvantages of bladder drainage include risk of enteric conversion, which requires another operative procedure; higher risk of and/or more frequent urinary tract infections; metabolic complications, most commonly hyperchloremic metabolic acidosis secondary to bicarbonate loss through the urine; dehydration; reflux pancreatitis; and more frequent urologic complications including dysuria secondary to cystitis and/or urethritis,

Table 2. Advantages and Disadvantages of Bladder Drainage

Advantages of Bladder Drainage
Monitor for rejection with urine amylase levels (8,38)
Avoids contamination seen with leaks of enteric drained pancreata (4,38)
Easy control of anastomotic problems with prolonged catheter drainage (13)
Access for cystoscopic biopsies (13)
Disadvantages of Bladder Drainage
Risk of enteric conversion (8)
Higher risk of infection (8,27,37,39)
Metabolic complications (8,27,38)
Hyperchloremia metabolic acidosis secondary to bicarbonate loss (4,8,39)
Dysuria (4,8,39)
Dehydration (4,38,39)
Recurrent urinary tract infections (UTI) (4,8,37,39)
Hematuria (4,8,37,39)
Reflux pancreatitis (4, 8,37,39)
Urologic Complications (36,37,39)
Ureteral stricture and disruption (37)

hematuria and urethral stricture or disruption (4,8,27,36,39).

Patients who undergo simultaneous kidney-pancreas transplant are usually diabetic patients who often have pre-existing diabetes-related bladder dysfunction and may develop urological complications secondary to this, surgically altered anatomy, pancreatic enzymes, and high urinary pH levels (38). Sollinger et al. reported on urological complications in 210 consecutive simultaneous pancreas-kidney (SPK) transplant patients. They reported that the most frequent urologic complications were as follows: hematuria (15.7%), leak from the duodenal segment (14.2%), recurrent urinary tract infections, urethritis (3.3%), and ureteral stricture and disruption (2.8%). Urologic complications related to the kidney graft included: ureteral stricture, ureteral leak and lymphocele (37).

Stratta et al. report duodenal segment complications including duodenal segment leak, duodenal segment bleeding requiring cystoscopy and duodenal segment bleeding requiring open repair, cytomegalovirus duodenitis, ampullary obstruction, rejection of the

duodenal segment, stone formation of the duodenal staple line, enteric conversion. They report that for those patients experiencing a duodenal segment complication patient survival is 84% and pancreas graft survival is 68% after a mean follow-up of 44 months (40). An additional consideration for bladder drained patients is that a certain percentage will be unable to tolerate the complications of bladder drainage and will require enteric conversion. Reported rates of enteric conversion range from less than 10% to 20% (20,32,33,41).

Enteric Conversion

Bladder drainage of exocrine pancreatic secretions is accompanied by some complications that are best resolved with enteric conversion, reported rates of which are 10-31% (8,16,20,32,33,41). Indications for enteric conversion are reported in table 3 and table 4. Using a prospective database, 32 (24.6%) simultaneous kidney-pancreas transplant patients who underwent enteric conversion were identified with a mean interval between simultaneous pancreas-kidney transplant and enteric conversion of 5 years.

Table 3. Indications for Enteric Conversion
Acidosis (excessive sodium bicarbonate loss) (38,39,42,52)
Urinary tract infections (38, 39)
Pancreatitis (38,39,42,52)
Urologic complications (38,39,42)
Hematuria (27,38)
Bladder dysfunction (38)
Dysuria (27,38,52)
Pyelonephritis (38)
Urethritis (27,38)
Prostatitis (38)
Discomfort of oral sodium bicarbonate intake (38)
Excessive sodium bicarbonate intake and hypotension (38)
Vesicocutaneous fistula (38)
Urethral disruption (38)

Table 4. Indications for enteric conversion and rates reported by Sollinger et al. (27), Van der Werf et al. (33), and West et al. (41)

	Sollinger et al. (10)	Van der Werf (33)	West (41)
	n=138	n=95	n=80
Confirmed enzyme leak	46 (29%)	42 (44%)	-
Persistent hematuria	38 (24%)	18 (19%)	12 (15%)
Recurrent urinary tract infection	33 (21%)	-	16 (20%)
Multiple indications	17 (11%)	-	14 (18%)
Urethral disruption	10 (6%)	-	-
Neurogenic bladder and reflux	5 (3%)	-	-
Urethral stricture	3 (2%)	-	-
Suspected leak, not confirmed	2 (1%)	-	-
Dysuria	1 (0.7%)	-	-
Urethritis	1 (0.7%)	22 (23%)	5 (6%)
Infected bladder suture	1 (0.7%)	-	-
Pancreatitis	1 (0.7%)	1	15 (19%)
Persistent metabolic acidosis	1 (0.7%)	1	26 (33%)
Duodenal perforation	-	-	3 (4%)
Anastomotic leak	-	-	2 (2.5%)
Pancreatic fistula	-	-	1 (1%)
Total rate of enteric conversion	-	21%	14.80%

Reported indications included: genitourinary symptoms (62.5%), duodenal complications (15.6%), graft pancreatitis (12.5%), pyelonephritis (6.3%) and metabolic acidosis (3.1%) (40). The authors report that 31.3% (10) of patients experienced surgical complications after their enteric conversion procedure including anastomotic leak (4,12.5%), peritonitis (3, 9.4%), pancreatic graft loss (2, 6.3%), fascial dehiscence/deep wound infection (2,6.3%). Reoperations were required in 25% of patients. Early graft loss occurred in 6.3% of patients and thirty-day mortality was 3.1% (42).

Table 5. Complications of Enteric Conversion Procedures
Urinary tract infection (38)
Low-grade superficial wound infection (38,42)
Minor bleeding (38)
Phlebitis (38)
Paralytic ileus (38)
Relaparotomy (38)
Leak (38)
Incisional hernia (33)
Intraabdominal abscess (33)
Small bowel obstruction (33)
Negative re-exploration (33)
Dehiscence (33,42)
Postoperative hemorrhage (33)
Enterovesical fistula (33,41)
Anastomotic leak (33,42)
Duodenal perforation (41)
Peritonitis (42)
Pancreatic graft loss (42)

In a single-center study of 540 pancreas transplants with bladder drainage, 80 underwent enteric conversion (14.8%). 12 of these (15%) had surgical complications after enteric conversion and 2 of the 12 lost their grafts. The majority of complications were treated with primary repair and external drainage and the authors concluded that enteric conversion is safe for intractable complications of bladder drainage (41). Kukla et al. analyzed the risk for enteric conversion in 312 bladder-drained solitary pancreas transplants was 31% with median follow-up time of 184.6 months. The majority (84.5%) of these were primary transplants (8).

Enteric conversion procedures are not without complications. These complications are detailed in Table 5. Complications of enteric conversion include urinary tract infection, superficial wound infection, minor bleeding, phlebitis, paralytic ileus, intra-abdominal abscess, small bowel obstruction, negative re-exploration, dehiscence, postoperative hemorrhage and enterovesical fistula (33,38,41,42).

Two-Stage Procedures: Bladder Drainage Followed by Enteric Drainage

A two-step approach to simultaneous kidney-pancreas transplants has also been proposed, beginning with bladder drainage and then following up with an elective enteric conversion (36,38). Proponents argue that this approach avoids the short-term complications of enteric drainage and the long-term complications of bladder drainage (36,38). Patients were generally converted between 6 and 12 months. Indications for earlier conversion included: excessive loss of sodium bicarbonate, recurrent and persistent urinary tract infections, abscesses around the bladder, leakage of anastomosis and abscess, persistent bleeding from the anastomosis, ureter obstruction, suspicion of vesico-cutaneous fistula after suprapubic catheter (36). Disadvantages of this two-step approach include cost to the patient and hospital requires and additional hospitalization (36) and the risk the patient undertakes in undergoing a second surgery.

Van de Linde et al. report on their experience with 51 patients who underwent this two-step procedure for simultaneous pancreas-kidney (SPK) patients. Primary indications for enteric conversion included urological problems (n=39), metabolic complications (excessive sodium bicarbonate loss and hypotension, n=3; need for large amounts of oral sodium bicarbonate, n=20), reflux-pancreatitis (n=2), and suspicion of a vesico-cutaneous fistula. Twelve patients had multiple indications. The median interval between transplantation and enteric conversion was twelve months (range 2-40). The authors report that they performed enteric conversion for less strict and severe indications over time as they observed a low complication rate. In 51 patients they observed seven urinary tract infections (UTIs), two superficial wound infections, one minor bleeding, one phlebitis, one paralytic ileus, and two re-laparotomies. They report

decreased intake of oral sodium bicarbonate (p<0.0005), significantly decreased urinary protein loss (p<0.0005) and significantly decreased urinary sodium loss (p<0.005). There were no instances of graft rejection in their cohort. They report one-year and three-year survival of patient, kidney, and pancreas as 100%, 98%, 100% and 93%, 97%, 93%. In nearly all of the included patients (96%) their pre-conversion symptoms resolved, although two with persistent urinary tract infections continued to have persistent urinary tract infections. They concluded that "enteric conversion is a safe and effective procedure," and recommend a two-stage approach (38). The authors report that several months after their original simultaneous kidney-pancreas or pancreas-alone transplant patients are generally in better health, are taking reduced doses of immunosuppressive medications and are further out from induction therapy (38). Additionally, there has been time for any preservation or reperfusion injury of the duodenal graft to have resolved (38).

Comparative Studies: Retrospective

In a single-center retrospective study comparing 66 patients who underwent bladder drainage and 52 patients who underwent enteric drainage, the authors concluded that enteric drainage is a good alternative to bladder drainage with similar patient and graft survival (39). They found higher rates of urinary tract infections in patients with bladder drainage (48.5%, 32 versus none, p <0.001), similar rates of intra-abdominal infections (24.2%, 16 versus 29.4%, 15, p = NS), similar rates of reoperations (33.9%, 40 versus 32.7, 17, p = NS), similar rates of pancreas graft loss (31.8%, 21 versus 17.3%, 9, p = 0.055), similar rates of graft pancreatectomy (22.7%, 15 versus 11.5%, 6, p = 0.09) and similar rates of acute rejection (15.2%, 10 versus 9.8%, 5, p = NS). There was also similar actuarial patient and graft survival between the two groups. Five-year patient survival was 97% in the bladder drainage group and 91.2% in the enteric drainage group (p=NS). Five-year graft survival was 70% in the bladder drainage group and 83.6% in the enteric drainage group (p=NS). The group performed enteric conversion in 12.1% of bladder-drained patients for the following indications: UTI recurrence, reflux pancreatitis and one case of duodenal-bladder fistula (39).

In a single-center study of 1000 simultaneous pancreas-kidney transplants the first 390 of these were performed using the bladder drainage technique, and the following 610 were using the enteric drainage technique. There was no difference in survival between the two groups, but a decreased quality of life was demonstrated in patients with bladder drained allografts in compared to those with enteric drained grafts (16). In terms of complications there was a 5-year rate of enteric conversion of 30% and a 5-year enteric conversion rate of 50%. There were more complications requiring reoperation in the enteric drained group, but more late reoperations in the bladder drained group given the need for enteric conversion. Bladder drained patients were more likely to have leaks (bladder drained 89/390 versus enteric drained 35/610, p<0.0001). The authors report anastomotic leak as the most common technical complication in the bladder drained group, but comment that non-operative management with Foley catheter was sometimes successful. The most common cause of pancreas graft loss in both groups was death with a functioning graft (bladder drained group 77, 19.7%; enteric drained group 48, 7.9%). These authors concluded that enteric drainage is superior to bladder drainage. They report a very high rate of enteric conversion (>50%). They also argue that there is a high incidence of urinary tract infections and frequent urological complications in the bladder drainage group and that enteric drainage eliminates the need for enteric conversion (27).

In a single-center retrospective study of 1,194 pancreas transplants performed between 1996 and 2000 it was noted that graft survival rates in era 3 (1994 – 1998) and era 4 (1998-2000) were significantly higher for bladder drainage (n=136) than for enteric drainage (n=70) in simultaneous pancreas-kidney transplant patients with one-year graft survival of 82% versus 74% (p = 0.03). Patient survival was not significantly different between the two groups. The authors report that in their hands there was a, "technical penalty," for using enteric drainage. They report the incidence of conversion of technically successful simultaneous pancreas-kidney bladder drainage (n=126) to enteric drainage to be 3% at 6 months, 8% at one year and 14% at two-years. For pancreas after kidney grafts (n=140) the rates were 6% by one year and 16% by two years. For pancreas transplant alone grafts (n=66) the rates were 6% at one year and 19% at two years (43).

In a single-center retrospective study of 243 patients transplanted between 1994 and 2000 it was demonstrated that 1-year and 2-year survival were 85% and 81% for enteric-drainage and 74% and 71% for bladder drainage (p=0.1). For patients with pancreas after kidney and pancreas transplant alone the survival curves were

reversed with one-year survival for the bladder drainage group at 77% and one-year survival for the enteric drainage group at 69%. The complication rate was reported to be 26% (n=51) for the enteric drainage group and 41% (n=18) for the bladder drainage group (p=0.04). There was a rate of 16% for enteric drainage and 24% for bladder drainage of re-laparotomy (p=0.02). There was a rate of 6% for enteric drainage and 14% for bladder drainage of fistula (p=0.10) (44).

In a single-center retrospective study of 71 patients transplanted between 1988 and 1996 there were 37 bladder drained and 34 enteric drained grafts. They had five early graft losses in each group. The incidence of volume depletion, acidosis, pancreatitis and urinary tract infections were all significantly lower in enteric drainage patients. ($p<0.005$). Initial hospital length of stay was equivalent, but the number of admissions and in-hospital days/year/patient were higher in the bladder drainage group ($p<0.05$). Patient and allograft survival was similar between groups. The authors concluded that the two groups had equivalent perioperative morbidity, enteric drainage was associated with fewer complications and not associated with long term graft failure (32).

In a single-center study of the incidence of post-transplant infectious complications for 78 enteric drained versus 48 bladder drained simultaneous pancreas-kidney transplants performed between 1995 and 1997 there was no difference in one year survival, time to first infection or first abdominal infection between the two groups. Enteric drained patients acquired fewer opportunistic infections (p=0.002) and fewer urinary tract infections (p=0.0001) (45).

In a retrospective cohort study of 23 consecutive simultaneous pancreas-kidney transplants with enteric drainage performed between July and November of 1995 compared to a group of 23 age and sex matched patients with bladder drainage transplanted between November 1994 and June 1995 there was equivalent one year actuarial patient (Enteric drainage 100%, bladder drainage 95.7%) and graft survival (Enteric drainage 87.5%, bladder drainage 91.5%) as well as equivalent hospital charges, length of stay, readmissions, rejection, sepsis-related procedures. Enteric drainage patients experienced significantly fewer urinary tract infections and other urologic complications (28).

A recent meta-analysis was performed with the goal of analyzing the question: "In patients undergoing pancreatic transplantation alone, does enteric drainage or bladder drainage of exocrine secretions provide the best graft survival?" This study included analysis of the results of four retrospective cohort studies – three of the four reported equivalent graft survival at 6-months and at 1-year. The fourth reported decreased graft survival in the exocrine drainage population secondary to technical failure. The authors concluded that more robust studies were needed (46).

Comparative Studies: Prospective

In a prospective study of systemic-bladder drainage including a total of 32 patients it was noted that there was similar patient, kidney graft and pancreas graft survival rates between the two groups with no immunologic graft losses. They also found similar cost and length of stay between the two groups. They noted that the systemic-bladder group had a slightly higher rate of readmissions, urinary tract infections, urologic complications, metabolic acidosis and dehydration. They demonstrated that portal-enteric drainage can be performed with similar short-term results to those with systemic-bladder drainage. Additionally the authors suggest that both methods should be included in the armamentarium of the pancreas transplant surgeon (13).

In a prospective study of 40 consecutive simultaneous kidney-pancreas transplants undergoing either bladder (n=20) or enteric (n=20) drainage of exocrine sections there was similar 1-year patient, kidney and graft survival. There was no significant difference in surgical complications, hospital length of stay, incidence of acute rejection, major infections or CMV disease. There was a higher rate of urologic complications, metabolic acidosis and dehydration in the bladder-drainage group. The authors conclude that patients have excellent patient and graft survival irrespective of the chosen drainage technique (9).

In a prospective study of 20 consecutive patients undergoing systemic-bladder drainage followed by 20 consecutive patients undergoing portal-enteric drainage there was similar patient survival, graft survival and mean initial hospital stay. There were an increased number of visits for dehydration and metabolic acidosis in the systemic-bladder group and these patients required bicarbonate replacement. Patients in the systemic-bladder

group required more outpatient visits than those in the portal-enteric group (4.9 vs. 0.3 per patient, $p < 0.0001$). There was no significant difference in the cumulative incidence of rejection. There were significantly fewer cases of cytomegalovirus infection in the portal-enteric group. There was no significant difference in the number of urinary tract and other infections. The authors concluded that portal-enteric drainage could be performed with good outcomes (16)

Animal Studies

Salahi et al. compared the early outcomes and histologic findings of enteric drainage with bladder drainage in pancreas transplantation in a canine model. They performed diabetizaiton of 16 dogs and randomly assigned them to either the bladder drainage or enteric drainage group. There was not a significant difference in mean survival time, pre-operative fasting blood sugar values and two-week post-operative fasting blood sugar values. There were no cases of early leakage in canines with bladder drainage. There was early leakage in 37.5% of the enteric drainage canines ($p<0.05$). There was not a significant difference in the number of canines in each group demonstrating clinical and pathologic evidence of pancreatic necrosis. They concluded that there were similar early outcomes, but dogs undergoing enteric drainage experienced more complications (47).

New Techniques

New techniques for exocrine drainage have been proposed including gastric-exocrine drainage of the pancreatic allograft. A 34year-old female presented for re-transplantation of her pancreas 2 years status-post pancreas transplantation. Both iliac arteries were affected by perivascular fibrosis and could not be used for arterial anastomosis. The decision was made to proceed with arterial implant in the infra-renal aorta, venous drainage to the SMV and exocrine drainage to the gastric antrum. The patient recovered from her surgery uneventfully. The authors concluded that the duodenum-stomach anastomosis is an option for exocrine drainage of the pancreas (48). In a single-center retrospective study of 38 patients who underwent pancreas transplant with gastric-exocrine drainage there was good one-, three- and five-year patient and graft survival (patient: 94%, 87%, 70% and graft: 83%, 65%, 49%). The authors concluded that the technique provides easy access for biopsy in the case of suspected pancreatic allograft dysfunction. Reported complications in this cohort of 38 patients included nine episodes of acute rejection in eight patients and seven episodes of CMV in six patients (49).

Conclusions

Early reports on bladder and enteric drainage reported that enteric drainage had significantly more associated complications. Prieto et al. in 1987 reported increased one-year graft survival for patients with bladder drainage was 90% versus 47% compared to enteric drainage, despite the fact that patients with bladder drainage had more episodes of rejection. Although they report that bladder drainage is associated with metabolic acidosis, they concluded that bladder drainage was the preferred procedure secondary to the ability to monitor exocrine function allowing for early recognition and treatment of rejection (50). Sutherland et al. reported in 1988 that graft survival rates were higher in bladder drainage than enteric drainage, 58% versus 29% at one year. Patient survival rates were similar (51). As cited above, the groups reporting since that time show similar graft and patient survival between enteric drainage and bladder drainage. There are few prospective studies evaluating this topic. Of the several analyzed here, Stratta et al. and Adamec et al. both conclude that both enteric drainage and bladder drainage are valuable techniques.

In conclusion, enteric exocrine drainage of the pancreas allograft is the most commonly used technique presently. Bladder drainage may have some utility in some situations. Pancreas transplant surgeons should have both available to offer to their patients. Additionally, a bladder drainage procedure followed by indicated or elective enteric conversion is also a valid option given the advantages of avoiding long-term urologic complications of bladder drainage. Gastric-exocrine drainage requires further study to determine long-term outcomes.

Abbreviations

SPK or SKP = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant, PTA = pancreas transplant alone, SPT = solitary pancreas transplant, include PAK and PTA, BD = bladder drainage, ED = enteric drainage, UTI = urinary tract infection, NS = non-significant, IPTR = International Pancreas Transplant Registry

Disclosures

Author contributions: EWB and SMB contributed equally to the design of the study and analysis. AME, MLH, EAE and BAW provided expertise and manuscript review and editing.

Conflict of interest: All authors declare that they do not have any competing commercial, personal, political, intellectual or religious interests in relation to the submitted work.

Ethical approval: Not applicable (Review)

References

1. Prevention., C.f.D.C.a. Number (in Millions) of Civilian, Noninstitutionalized Persons with Diagnosed Diabetes, United States, 1980-2011. 2013. (cited 2015. October 21, 2015.); Available from: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm.
2. Health., N.I.o. National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics Report. 2014. (cited 2015. June 21, 2015.); Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
3. Prevention., C.f.D.C.a. Age-Adjusted Percentage of Adults with Diabetes, Using Diabetes Medication, by Type of Medication, United States, 1997-2011. 2013. (cited 2015. October 21, 2015.); Available from: http://www.cdc.gov/diabetes/statistics/meduse/fig2.htm.
4. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol, 2013;9(9):555-62.
5. Gruessner AC. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). Rev Diabet Stud 2011; 8(1):6-16.
6. Weems P, Cooper M. Pancreas transplantation in type II diabetes mellitus. World J Transplant 2014;4(4):216-21.
7. OPTN. Transplants in the U.S. by Recipient ABO. U.S. Transplant Performed: January 1, 1988 - December 31, 2015. (cited 2015. March 31, 2016.); Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
8. Kukla A, Radosevich DM, Finger EB, Kandaswamy R. High urine amylase level and the risk of enteric conversion in solitary pancreas transplant recipients. Transplant Proc 2014;46(6):1938-41.
9. Adamec M, Janousek L, Lipár K, Hampl F, Saudek F, Koznarová R et al. A prospective comparison of bladder versus enteric drainage in vascularized pancreas transplantation. Transplant Proc 2004;36(4):1093-4.
10. Sollinger HW, Stratta RJ, D'Alessandro AM, Kalayoglu M, Pirsch JD, Belzer FO.Experience with simultaneous pancreas-kidney transplantation. Ann Surg 1988;208(4):475-83.
11. Larsen JL. Pancreas transplantation: indications and consequences. Endocr Rev 2004;25(6):919-46.
12. Corry RJ, Nghiem DD, Schulak JA, Beutel WD, Gonwa TA. Surgical treatment of diabetic nephropathy with simultaneous pancreatic duodenal and renal transplantation. Surg Gynecol Obstet 1986;162(6):547-55.
13. Stratta RJ, Gaber AO, Shokouh-Amiri MH, Reddy KS, Egidi MF, Grewal HP, Gaber LW. A prospective comparison of systemic-bladder versus portal-enteric drainage in vascularized pancreas transplantation. Surgery 2000;127(2):217-26.
14. Reddy KS, Stratta RJ, Shokouh-Amiri MH, Alloway R, Egidi MF, Gaber AO. Surgical complications after pancreas transplantation with portal-enteric drainage. J Am Coll Surg 1999;189(3):305-13.
15. Havrdova T, Boucek P, Jedinakova T, Lipar K, Kocik M, Skibova J, et al. Portal versus systemic venous drainage of the pancreatic graft: the effect on glucose metabolism in pancreas and kidney transplant recipients. Transplant Proc 2014;46(6):1910-2.
16. Cattral MS, Bigam DL, Hemming AW, Carpentier A, Greig PD, Wright E, et al. Portal venous and enteric exocrine drainage versus systemic venous and bladder exocrine drainage of pancreas grafts: clinical outcome of 40 consecutive transplant recipients. Ann Surg 2000;232(5):688-95.

17. Boggi U, Vistoli F, Signori S, Del Chiaro M, Amorese G, Vanadia Bartolo T, et al. Outcome of 118 pancreas transplants with retroperitoneal portal-enteric drainage. Transplant Proc 2005;37(6):2648-50.
18. Rogers J, Farney AC, Orlando G, Farooq U, Al-Shraideh Y, Stratta RJ. Pancreas transplantation with portal venous drainage with an emphasis on technical aspects. Clin Transplant 2014;28(1):16-26.
19. Mulholland MW, Lillemoe KD, Doherty GD, Maier RV, Simeone DM, Upchurch GR Jr. (Eds). Greenfield's Surgery: Scientific Principles and Practice, 5e. Lippincott Wiliams and Wilkins. 2010
20. Walter M, Jazra M, Kykalos S, Kuehn P, Michalski S, Klein T. 125 Cases of duodenoduodenostomy in pancreas transplantation: a single-centre experience of an alternative enteric drainage. Transpl Int 2014;27(8):805-15.
21. Douzdjian V, Abecassis MM, Cooper JL, Smith JL, Corry RJ. Incidence, management and significance of surgical complications after pancreatic transplantation. Surg Gynecol Obstet 1993; 177(5):451-6.
22. Eckhoff DE, Sollinger HW. Surgical complications after simultaneous pancreas-kidney transplant with bladder drainage. Clin Transpl;1993:185-91.
23. Ozaki CF, Stratta RJ, Taylor RJ, Langnas AN, Bynon JS, Shaw BW Jr . Surgical complications in solitary pancreas and combined pancreas-kidney transplantations. Am J Surg 1992;164(5):546-51.
24. Gruessner RW, Sutherland DE, Troppmann C, Benedetti E, Hakim N, Dunn DL, et al., The surgical risk of pancreas transplantation in the cyclosporine era: an overview. J Am Coll Surg 1997;185(2):128-44.
25. Sugitani, A, Gritsch HA, Shapiro R, Bonham CA, Egidi MF, Corry RJ. Surgical complications in 123 consecutive pancreas transplant recipients: comparison of bladder and enteric drainage. Transplant Proc 1998;30(2):293-4.
26. Bruce DS, Newell KA, Woodle ES, Cronin DC, Grewal HP, Millis JM, et al. Synchronous pancreas-kidney transplantation with portal venous and enteric exocrine drainage: outcome in 70 consecutive cases. Transplant Proc 1998;30(2):270-1.
27. Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. Ann Surg 2009;250(4):618-30.
28. Kuo PC1, Johnson LB, Schweitzer EJ, Bartlett ST. Simultaneous pancreas/kidney transplantation--a comparison of enteric and bladder drainage of exocrine pancreatic secretions. Transplantation 1997;63(2):238-43.
29. Sollinger HW, Odorico JS, Knechtle SJ, D'Alessandro AM, Kalayoglu M, Pirsch JD. Experience with 500 simultaneous pancreas-kidney transplants. Ann Surg 1998;228(3): 284-96.
30. Berger N, Wirmsberger R, Kafka R, Margreiter C, Ebenbichler C, Stelzmueller I, et al. Infectious complications following 72 consecutive enteric-drained pancreas transplants. Transpl Int 2006;19(7):549-57.
31. Abecassis M, Bridges ND, Clancy CJ, Dew MA, Eldadah B, Englesbe MJ, Flessner MF et al. Solid-organ transplantation in older adults: current status and future research. Am J Transplant 2012;12(10):2608-22.
32. Bloom RD, Olivares M, Rehman L, Raja RM, Yang S, Badosa F. Long-term pancreas allograft outcome in simultaneous pancreas-kidney transplantation: a comparison of enteric and bladder drainage. Transplantation 1997;64(12):1689-95.
33. Van der Werf WJ, Odorico JS, D'Alessandro AM, Knechtle SJ, Pirsch JD, Kalayoglu M, et al. Enteric conversion of bladder-drained pancreas allografts: experience in 95 patients. Transplant Proc 1998;30(2):441-2.
34. Heredia EN, Ricart MJ, Astudillo E, Lopez-Boado M, Delgado S, Amador A, et al. Pancreas transplantation with enteric drainage: duodenal segment leak. Transplant Proc 2002;34(1):215.
35. Bonatti H, Berger N, Kafka R, Tabbi MG, Königsrainer A, Margreiter R, et al. Experience with ATG short course high dose induction therapy in a series of 112 enteric drained pancreatic transplants. Ann Transplant 2002;7(3):22-7.

36. Marang-van de Mheen PJ, Nijhof HW, Khairoun M, Haasnoot A, van der Boog PJ, Baranski AG. Pancreas-kidney transplantations with primary bladder drainage followed by enteric conversion: graft survival and outcomes. Transplantation 2008;85(4):517-23.
37. Sollinger HW1, Messing EM, Eckhoff DE, Pirsch JD, D'Alessandro AM, Kalayoglu M, et al., Urological complications in 210 consecutive simultaneous pancreas-kidney transplants with bladder drainage. Ann Surg 1993;218(4):561-8; discussion 568-70.
38. van de Linde P1, van der Boog PJ, Baranski AG, de Fijter JW, Ringers J, Schaapherder AF. Pancreas transplantation: advantages of both enteric and bladder drainage combined in a two-step approach. Clin Transplant 2006;20(2):253-7.
39. Jiménez-Romero C, Manrique A, Meneu JC, Cambra F, Andrés A, Morales JM, et al. Compative study of bladder versus enteric drainage in pancreas transplantation. Transplant Proc 2009; 41(6):2466-8.
40. Stratta RJ, Sindhi R, Sudan D, Jerius JT, Radio SJ. Duodenal segment complications in vascularized pancreas transplantation. J Gastrointest Surg 1997;1(6):534-44.
41. West M, Gruessner AC, Metrakos P, Sutherland DE, Gruessner RW. Conversion from bladder to enteric drainage after pancreaticoduodenal transplantations. Surgery 1998;124(5):883-93.
42. Kleespies A, Mikhailov M, Khalil PN, Preissler G, Rentsch M, Arbogast H, et al, Enteric conversion after pancreatic transplantation: resolution of symptoms and long-term results. Clin Transplant 2011;25(4):549-60.
43. Sutherland DE, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R, et al, Lessons learned from more than 1,000 pancreas transplants at a single institution. Ann Surg 2001;233(4):463-501.
44. Corry RJ1, Chakrabarti P, Shapiro R, Jordan ML, Scantlebury VP, Vivas CA. Comparison of enteric versus bladder drainage in pancreas transplantation. Transplant Proc 2001;33(1-2):1647-51.
45. Pirsch JD, Odorico JS, D'Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Posttransplant infection in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. Transplantation 1998;66(12):1746-50.
46. Senaratne NV, Norris JM. Bladder vs enteric drainage following pancreatic transplantation: How best to support graft survival? A best evidence topic. Int J Surg 2015;22:149-52.
47. Salahi H, Nikeghbalian S, Shamsaee AR, Kheradmand E, Sabet B, Jalaeian H, et al., Comparison of early outcome and histologic findings of enteric drainage with bladder drainage in pancreas transplantation of dogs. Transplant Proc 2007;39(4):1255-6.
48. Linhares MM, Beron RI, Gonzalez AM, Tarazona C, Salzedas A, Rangel EB, et al., Duodenum-stomach anastomosis: a new technique for exocrine drainage in pancreas transplantation. J Gastrointest Surg 2012;16(5):1072-5.
49. Zibari GB, Fallahzadeh MK, Hamidian Jahromi A, Zakhary J, Dies D, Wellman G, et al., Portal-endocrine and gastric-exocrine drainage technique of pancreas transplantation provides an easy access for evaluation of pancreatic allograft dysfunction: six-year experience at a single center. J La State Med Soc 2014;166(5):207-12.
50. Prieto M, Sutherland DE, Goetz FC, Rosenberg ME, Najarian JS. Pancreas transplant results according to the technique of duct management: bladder versus enteric drainage. Surgery 1987;102(4):680-91.
51. Sutherland DE, Goetz FC, Moudry KC, Najarian JS. Pancreas transplantation: the Minnesota experience. J Diabet Complications 1988;2(3):125-9.
52. Stephanian E, , Gruessner RW, Brayman KL, Gores P, Dunn DL, Najarian JS, et al., Conversion of exocrine secretions from bladder to enteric drainage in recipients of whole pancreaticoduodenal transplants. Ann Surg 1992;216(6):663-72.

Reviewers
NA (Invited Submission).

Editor
Salem A Beshyah (Abu Dhabi, UAE).