Orthostatic Hypotension in Kidney Pancreas Transplant Patients and its Relation to Preexisting Autonomic Neuropathy

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Abstract

Objectives: **Orthostatic hypotension is a known complication of pancreas transplant. This retrospective study of 25 kidney-pancreas transplant patients at our center was done to determine the incidence and course of postoperative orthostatic hypotension.**

Materials and Methods: **A chart review was done for all patients who received a kidney-pancreas transplant between January 1997 and December 2005. Patients with orthostatic hypotension after surgery were selected and compared with patients without orthostatic hypotension for preexisting autonomic and peripheral neuropathy status. The kidney-pancreas transplant group was then compared with a group of diabetic kidney-only transplant recipients to assess the contribution of the renal transplant in this process.**

Results: **Seven kidney-pancreas transplant patients (28%) developed orthostatic hypotension after the transplant. It occurred with much higher frequency in kidney-pancreas transplant patients than it did in kidney transplant patients (*P* = .002). The onset of orthostatic hypotension was between 8 and 20 days after transplant. Six patients required midodrine for symptomatic relief. Orthostasis resolved completely within 3 weeks to 9 months in all but 1 patient. There was no correlation between postoperative orthostasis and preoperative history of orthostatic hypotension, gastroparesis, or peripheral neuropathy. Orthostasis was related to posttransplant polyuria in only 1 patient. In the remaining patients, orthostasis seemed to be related to the presence of the pancreas transplant. The exact pathogenesis of orthostasis is unclear but may be related to hyperinsulinemia after transplant or neuropeptides involved in the regenerative process.**

Conclusions: **Orthostatic hypotension is common after kidney-pancreas transplant. It is unrelated to preexisting autonomic neuropathy or post-transplant polyuria in most patients. This complication requires further study.**

Key words: *Autonomic neuropathy, Diabetic complications, Orthostasis*

Introduction

Kidney-pancreas transplant, when available, is the treatment of choice for patients with type 1 diabetes mellitus. Pancreas transplant restores euglycemia and improves the peripheral sensorimotor neuropathy (1-3). Data on objective improvement of autonomic function parameters have been variable (1, 4-9). Orthostatic hypotension has been observed postoperatively in patients who have undergone a pancreas transplant, but its frequency and characteristics have not been well documented (10). Orthostatic hypotension is generally felt to be a manifestation of preexisting autonomic neuropathy. The aim of our study was to determine the incidence of orthostatic hypotension in our kidney-pancreatic transplant patients and correlate it with the presence of autonomic neuropathy preoperatively.

Materials and Methods

This retrospective study involved 25 kidney-pancreatic transplant patients operated on between

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January 1997 and December 2005 at our institution. Demographic data, duration of diabetes, and date of transplant were obtained from a chart review. We reviewed the operative notes for surgical anastomosis, perioperative blood loss, episodes of hypotension, and postoperative fluid balance. Any episodes of pancreatic transplant rejection (as determined by an elevation of pancreatic enzymes) and/or thrombosis (as determined by ultrasound or magnetic resonance imaging) were noted. The patients' postoperative course was reviewed for the presence of orthostatic hypotension, its onset, and duration. The use of midodrine and the duration of drug use also were noted.

The status of patients' preexisting neuropathy was judged by presence of orthostatic hypotension, gastroparesis, and peripheral sensorimotor neuropathy. The incidence of orthostatic hypotension was obtained by examining the chart history of documented incidents of symptomatic orthostasis (which was defined as a drop in systolic blood pressure of > 20 mm Hg when standing or a history of presyncope or syncope in the upright position with systolic blood pressure < 100 mm Hg). Patients were considered as having gastroparesis if they had evidence of delayed gastric emptying on gastric emptying study, or if there was a presence of metoclopramide in the patient's pretransplant medication list. Documentation of peripheral neuropathy was obtained from the notes, if there was a history of symptoms of numbness or paresthesias in a glove-and-stocking distribution or if there was pretransplant use of gabapentin for neuropathic pain. An objective assessment of the neuropathy was not available in this retrospective analysis. The characteristics of patients with orthostasis were compared with patients without orthostasis. To assess any contribution of the renal transplant in the process, we selected all the diabetic kidney-only transplant recipients at our center during this time and reviewed their charts for postoperative orthostatic hypotension. The Fisher exact test was used to compare group characteristics.

Results

Twenty-five kidney-pancreas patients were included for analysis. The mean age of patients was 38 years (range, 25-53 years; 56% men). The average duration of diabetes for the whole group was 26 years. The surgical procedure in all cases involved draining pancreatic secretions into the small intestine (jejunum or ileum). The transplanted pancreas received its vascular supply from the iliac vessels.

Seven patients (28%) developed orthostatic hypotension postoperatively. The patient demographics are listed in Table 1, the perioperative data are shown in Table 2, and the preexisting neuropathy status data are shown in Table 3. The onset of orthostatic hypotension was 8 to 20 days after the transplant. All 7 patients had to discontinue their antihypertensive medications; 6 of these (83%) also required midodrine for symptomatic relief (Table 3). Orthostatic hypotension resolved spontaneously within 3 weeks to 9 months in all but 1 patient. On reviewing the perioperative events, patient No. 2 had posttransplant polyuria that was likely responsible for his orthostatic hypotension. Patient No. 6 had postoperative blood loss anemia that required transfusion. However, even after correction of the acute postoperative bleeding, this patient has

Table 1. Demographic data of patients with orthostatic hypotension

Patients	7
Male/female	4/3
Race	5 white/2 Hispanic
Age (mean ± SD)	36 ± 7.1 years
Duration of diabetes (mean ± SD)	23 ± 8.3 years
Surgical procedure	pancreas-enteric

Table 2. Perioperative data*

Patient No.	Admission BP (mm Hg)	Discharge BP (mm Hg)	Clinic visit follow-up BP (mm Hg)	Fluid intake/ output at discharge (mL)
1	190/90	164/84	85/60	2160/4150
2	212/117	110/60	98/58	1700/2050
3	155/60	125/85	100/56	1475/2100
4	174/76	110/60	110/65	1080/400
5	126/88	120/80	95/39	1700/1050
6	138/84	123/66	78/48	1510/1525

Abbrreviations: BP, blood pressure
*Complete patient 7 data are not available because surgery was performed elsewhere.

Table 3. Results of the study

Patient No.	Duration of orthostasis (days)	Use of midodrine	Past history of orthostasis	Past history of neuropathy	Past history of gastroparesis
1	124	Yes	No	Yes	No
2	262	Yes	No	No	Yes
3	179	Yes	No	Yes	No
4	20	No	No	Yes	Yes
5	37	Yes	No	Yes	No
6	346	Yes	No	Yes	Yes
7	200 *	Yes	No	Yes	Yes

*Surgery performed elsewhere, exact date of onset of orthostasis not known.

continued to have orthostatic hypotension until the present date. Patient No. 7 developed orthostatic hypotension 2 weeks after her transplant. She lost her pancreatic allograft because of a thrombosis 255 days after the transplant. The timing of the allograft loss also coincided with the resolution of her orthostasis.

As a group, only 1 kidney-pancreas patient had pretransplant orthostasis, 10 patients had gastroparesis, and 19 patients had evidence of peripheral neuropathy. The 7 orthostatic kidney-pancreas patients were no different from the other 18 kidney-pancreas patients in terms of preexisting neuropathy. No patient of these 7 had preexisting orthostasis compared with 1 of 18 patients in the group without orthostasis (P = 1.00). Four of 7 patients in the orthostatic group had a history of gastroparesis preoperatively compared with 6 of 18 patients in the nonorthostatic group who had a history of gastroparesis (P = .37). Six of 7 patients in the orthostatic group had history of peripheral neuropathy compared with 13 out of 18 patients in the nonorthostatic group who had history of peripheral neuropathy (P = .63).

Despite similar durations of diabetes in both groups, when we compared patients in the kidney-pancreas group with patients in the kidney-only group, 7 of 25 kidney-pancreas patients had postoperative orthostasis compared with only 1 of 43 kidney-only patients who had postoperative orthostasis (P = .002).

Discussion

Orthostatic hypotension is a known complication of pancreas transplant. Because these patients have long-standing diabetes, it is often thought to be a manifestation of preexisting autonomic neuropathy.

In our study, orthostatic hypotension was seen 28% of the patients. None of these 7 patients had a preexisting history of orthostasis. There was a lag period of 8 to 20 days after transplant before orthostasis was noted, and it resolved spontaneously and completely in all but 1 patient, sometimes as early as 3 weeks.

Diabetic sensorimotor polyneuropathy, essentially a large myelinated fiber neuropathy, improves after pancreas transplant with the restoration of euglycemia (1-3). Although patients report subjective improvement, data on objective improvement in autonomic function parameters has ranged from slow and incomplete to complete normalization (1, 4-9). However, this improvement, even if complete, takes several months to years before it is complete. The time course and complete reversibility of orthostasis in most of our patients (6 of 7 in this study) mean that the cause of this orthostasis is different from any preexisting neuropathy.

In the past, when a pancreas-to-bladder anastomosis was the surgical procedure of choice, there were significant losses of pancreatic secretions in the urine. However, the current pancreas-enteric anastomosis does not cause such fluid losses or volume depletion. Fluid losses and volume depletion can occur postoperatively, including volume depletion from proximal tubular dysfunction of the transplanted kidney (11). Postoperatively, polyuria was responsible for orthostatic hypotension in only 1 patient in our study.

The postoperative orthostasis in the other 6 patients seems to have a different pathogenesis. Because postoperative orthostasis was not seen at such an increased frequency in diabetic patients with a kidney-only transplant, our results suggest that it is related to the pancreas transplant. Hricik and colleagues have observed that blood pressures are lower in patients with kidney-pancreas transplant than they are in recipients of kidney-only transplants (12). When patients with bladder drainage were converted to enteric drainage, the beneficial effect on the blood pressure persisted, suggesting that it was not related with volume depletion issues but with the transplanted pancreas itself (12).

Our center performs only a systemic vascular anastomosis of the pancreas allograft. This procedure has a different anatomic arrangement to the native pancreas, in which it receives blood for the mesenteric vessels and drains into the portal vein. The question then arises whether orthostasis after transplant is related to vasoactive mediators from the pancreas, which are released into the systemic circulation without first being metabolized in the liver. Pancreas transplant patients with systemic anastomoses are known to have hyperinsulinemia as a result of this phenomenon, partly due to the loss of feedback inhibition of insulin release (13). The use of high-dose glucocorticoids in the initial post-transplant period also causes impaired tissue sensitivity and increased insulin resistance. Physiologic dosages of insulin have vasoconstrictive effects because of their effect on the sympathetic

system and angiotensin II. However, in supra-physiological concentrations, insulin has been known to decrease peripheral vascular resistance and cause vasodilatation (up to 113% as measured by venous occlusion plethysmography) (14, 15). This effect is thought to be mediated through nitric oxide (15).

It is possible that the initial hyperinsulinemia after transplant is responsible for this vasodilatation and orthostasis. A study of metabolic changes in 38 pancreas transplant patients failed to show any changes in insulin sensitivity in patients over a period of 10 years (16). However, there was an increase in glucagon secretion with time (16). Whether this rise in glucagon secretion has any role in counteracting the vasodilatation induced by hyperinsulinemia is not known, but it does offer an attractive explanation for the spontaneous resolution of this process with time.

The other possibility includes the role of neuropeptides. In a rat model of pancreatic transplant, reinnervation occurs through sensory neurons carrying mediators like calcitonin gene-related peptide and sympathetic nerve endings that carry neuropeptide Y (3, 17-19). This reinnervation occurs from the nerve fibers present around the blood vessels and the duodenal neuronal plexuses. Evidence of parasympathetic supply to the grafted pancreas in this model is generally lacking (13). Sympathetic innervation starts within a few weeks after the transplant but has been seen as early as 5 days after the transplant (13, 17, 18). These mediators have varying effects including vasodilatation (calcitonin gene-related peptide, substance P) and vasoconstriction (neuropeptide Y) (19-21). Calcitonin gene-related peptide expression has been noted to increase after pancreas transplant in studies by Adeghate, although similar results were not reproduced by Korsgren and associates (13, 18, 19). It is possible that vasodilator/ vasoconstrictor imbalances occur when the process of reinnervation of the pancreas allograft occurs. Vasodilator/ vasoconstrictor imbalances then tend to subside when the innervation is complete and other competing vasoconstrictors are synthesized. Because of the systemic venous drainage, the effects may be more prominent in patients in whom the pancreas has been anastomosed to the iliac veins. Reinnervation of the pancreas allograft has not been shown to occur in humans and thus, this hypothesis requires further studies for confirmation.

Orthostatic hypotension is a commonly seen phenomenon in systemically drained pancreas transplants. Whether it happens with similar frequency in portal anastomosed pancreas transplant patients is unknown. It occurs with a frequency higher than expected in patients with a previous history of autonomic dysfunction and does not seem to be related to the patient having a previous history of orthostasis, gastroparesis, or peripheral neuropathy. It responds well to the alpha adrenergic agonist drug, midodrine, which works by causing peripheral vasoconstriction (10). In some cases, it is related to posttransplant polyuria, but in most patients, its cause is unclear. Its spontaneous resolution with time signifies that it is a reversible process in most cases.

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