Cytomegalovirus Mismatch as Major Risk Factor for Delayed Graft Function After Pancreas Transplantation

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Background. Risk factors for delayed graft function (DGF) in pancreas transplantation (PTx) and its implications on graft survival are poorly defined.

Methods. Eighty-seven consecutive first-time PTx for type I diabetes performed between January 2003 and December 2007 were retrospectively reviewed. DGF was defined as a reversible need for exogenous insulin beyond postoperative day 10 (DGF group [DGFG]). For statistical analysis, DGFG patients were compared with patients with immediate graft function (control group [CG]).

Results. DGF occurred in 16 patients (18.6%). C-peptide levels and DGF were inversely correlated ($r=0.24$, $P=0.03$). In univariate analysis, donor cytomegalovirus (CMV)+ antibody status, and D+/R− CMV mismatch were significantly associated with DGF (81.3% vs. CG 52.1%, $P=0.029$; and 62.5% vs. CG 21.1%, $P=0.002$, respectively). Compared with University of Wisconsin solution, histidine tryptophan ketoglutarate-preserved grafts displayed higher DGF rates (37.5% vs. CG 12.7%, $P=0.030$), similar to female recipients (DGFG 68.8% vs. CG 35.2%, $P=0.015$). On multivariate analysis, a significantly higher DGF incidence was noted in female recipients (DGFG 68.8% vs. CG 35.2%; $P=0.03$) and in recipients with D+/R− CMV mismatch (DGFG 62.5% vs. CG 21.1%; $P=0.03$). With a median follow-up of 40.4 months (range 0.7–74.2), graft survival at 5 years did not differ between both groups (94.4% CG vs. 93.8% DGFG; $P=0.791$).

Conclusion. This is the first study that identifies CMV mismatch (D+/R−) as an additional risk factor for DGF occurrence in PTx. In this particular cohort, DGF does not seem to affect graft survival.

Keywords: Pancreas transplantation, Delayed graft function, Cytomegalovirus.

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Recent refinements in immunosuppression, antimicrobial prophylaxis, and therapy and surgical technique have improved outcome and broadened indications for transplantation, thus widening the gap between demand for and supply of solid organ grafts. To counteract this development, it became evident that the donor pool needed to be expanded by extending donor criteria. Extended criteria donors have been defined for kidney transplantation. Similar criteria have also been proposed for liver transplantation (*1*, *2*), including advanced age, morbid obesity, extended intensive care unit stay, and use of high-dose catecholamines. Furthermore, manifest infection and non-heart beating donation may qualify donors for extended criteria donors. In pancreas transplantation (PTx), such criteria are not well established. This is partially because of the fact that pancreatic transplantation is not a life saving procedure, and there is genuine reluctance to use organs that may not function well or even develop graft pancreatitis. However, in some regions, there is a high demand for pancreatic allografts, and specialized centers have started to use grafts, which traditionally would have been discarded because of inadequate quality.

Between 1994 and 2007, the proportion of cadaveric donors aged more than 55 years increased from 20% to 38.5% in the Eurotransplant region (*3*). Advanced donor age is one of the most important factors for susceptibility to ischemic injury of grafts. In addition, natural aging of the parenchyma with degeneration of vascularity in conjunction with in-

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M.M. and M.B. conceived and designed the study, did the statistical analysis, and wrote the manuscript; H.B., T.R., C.M., and N.B. contributed to acquisition and analysis of data; G.G. contributed substantially to statistical analysis; S.S., G.B., and P.H. helped in collecting the data; W.M. did the majority of transplants; and R.M. and J.P. critically revised and finally approved the article.
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creased fragility of the tissue, all pose a significant risk factor for dysfunction or in severe cases nonfunction of the graft (*4*, *5*). Finally, age is associated with an increase in infectious prevalence comprising latent viruses that are commonly transmitted with allografts, in particular, cytomegalovirus (CMV) and Epstein Barr virus. Although in solid organ transplantation, CMV represents the most important pathogen that has been associated with patient survival and long-term graft function (*6*), there are no data for importance of CMV in early graft function.

Clinically, ischemia-reperfusion injury of allografts may be read out by delayed graft function (DGF) as suggested earlier (*7*). This has been defined as the need for temporary medical support for insufficient graft function early after transplantation. In kidney transplantation, DGF affects patient morbidity, incidence of acute rejection episodes and early development of chronic allograft nephropathy, and reduces short- and long-term graft survival (*8*). Moreover, cardiac, lung, and liver transplant recipients experiencing DGF are at excessive risk of developing severe infections and subsequent life-threatening (multi-) organ failure.

However, in PTx, DGF has been poorly validated thus far. Although several groups have addressed this issue, a unique and reliable definition of DGF after PTx is still lacking. Furthermore, neither incidence of and risk factors for DGF, nor its impact on patient morbidity and long-term outcome has been explored so far (*9*, *10*).

The aim of this study was to retrospectively analyze our recent series of 119 consecutive pancreas transplants with respect to risk factors and the effect of DGF on patient and graft survival.

MATERIALS AND METHODS

Patients and Transplants

We retrospectively evaluated 119 consecutive PTx performed at our institution between January 2003 and December 2007. Potential confounders on initial graft function, such as type II diabetes mellitus (n=11), and retransplantation (n=12 including 10 pancreas after kidney transplants and two pancreas retransplants) were excluded from the analysis. Another nine patients were excluded for graft loss within 2 weeks with primary nonfunction (n=1), early venous thrombosis (n=7), or necrotizing pancreatitis requiring graft pancreatectomy (n=1). The final study group consisted of 87 patients suffering from insulin-dependent diabetes mellitus including 83 simultaneous pancreas kidney (SPK) transplants and four pancreas transplants alone. Our local institutional review board issued a waiver under a minimal risk protocol.

Definition of DGF

We defined endocrine DGF after PTx as need for scheduled exogenous insulin to keep blood glucose levels less than 150 mg/dL after postoperative day 10, as beyond this day, patients have been expected to be on regular care status and diet. Occasional need for exogenous insulin later than postoperative day 10 for instance on steroid-treated acute rejection episodes was not classified as DGF. On discharge, all patients with DGF were off exogenous insulin.

Surgical Procedure

Donor and recipient surgical procedures were performed as described previously (*11*). On retrieval, abdominal organs were perfused through the aorta with HTK (5–8 L) or University of Wisconsin (UW; 2–5 L) solution. Superior mesenteric and splenic arteries were reconstructed using a donor arterial Y-graft consisting of external and internal iliac arteries. The common iliac artery segment was anastomosed to the recipient's common iliac artery. The graft portal vein was anastomosed end-to-side to the recipient's inferior vena cava (n=70) or to the superior mesenteric vein (n=17). All grafts were enterically drained by anastomosing the graft duodenal segment to the second jejunal loop approximately 30 to 40 cm distal to the flexure of Treitz using a stapler device (*12–14*).

Immunosuppression and Postoperative Care

Standard immunosuppression included induction therapy with a single dose of 8 mg/kg antithymocyte globulin (*14*), tacrolimus with trough levels between 12 and 15 ng/mL for the first 3 months and 4 to 8 ng/mL thereafter, mycophenolate mofetil at a dose of 1 g twice daily or enteric-coated mycophenolic acid at a dose of 720 mg twice daily and a steroid taper (maintenance dose after 4 weeks of 5 mg/day) with an attempt to wean steroids at 1 year (*15*).

Antimicrobial prophylaxis consisted of tazobactam/piperacillin (4.5 g three times daily) and ciprofloxacin (200 mg twice daily) for 3 days. Fluconazole (400 mg/d) was given for 7 days. After CMV-mismatched (D+/R−) PTx, in all cases antiviral prophylaxis with valganciclovir 450 mg once daily was administered. CMV monitoring was performed on a weekly basis using CMV-polymerase chain reaction (Amplicor, Roche, Switzerland).

All patients received somatostatin for 10 days posttransplantation. On the intensive care unit, blood glucose levels were kept less than 120 mg/dL by continuous intravenous insulin infusion as indicated. Subsequently, blood glucose levels exceeding 150 mg/dL were treated with subcutaneous exogenous insulin.

Assessment and Treatment of Acute Rejection

An increase in serum amylase exceeding 160 U/L or a sudden increase in serum glucose levels together with a significant drop in serum C-peptide, and concomitant abdominal pain and sonographic swelling of the graft were considered signs of acute rejection. Diagnosis was confirmed by enteroscopy and histologic assessment of a biopsy taken from the duodenal segment of the graft (*16*). In the case of SPK transplant, a renal biopsy was performed to assess kidney rejection. Treatment of cellular rejection consisted of pulsed steroids (500 mg methylprednisolone on 3 consecutive days) and an increase in baseline immunosuppression.

Graft Monitoring

Posttransplant, C-peptide serum levels were routinely assessed on postoperative day 2 and twice a week thereafter. Factors with potential effect on carbohydrate metabolism such as inflammation, graft pancreatitis, and immunosuppression were assessed daily during the entire postoperative period. In addition, body temperature, blood pressure and heart rate, urine output, serum creatinine and BUN, complete blood count, dose and trough levels of immunosuppressants and C-reactive protein (CRP), and serum amylase and lipase levels were continuously monitored and recorded. Data were collected from the patients' charts.

Statistical Analysis

Data are reported as mean±SD or total numbers (%) and were analyzed as case-control study stratified by occurrence of DGF. In addition, graft survival was prospectively followed in all patients. Univariate analysis of risk factors for DGF was performed using Fischer's exact test for dichotomous variables and Mann-Whitney *U* test and Student's *t* test for continuous variables as indicated. After univariate analysis, factors significantly associated with DGF, and several donor and recipient factors discussed in the literature as potential risk factors for diminished graft function were entered in a stepwise Cox regression model for multivariate analysis of DGF risk factors. For validation of the predefined factors (all of which did not show statistical significance in the univariate analysis of this patient cohort), we used a hierarchical cluster analysis model to test for association between the factors and the occurrence of DGF. Posttransplant patient and graft survival was analyzed using the Kaplan-Meier estimator and log-rank tests. Patient death was also counted as graft loss.

For statistical analysis, SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL) and GraphPad Prism software (GraphPad Software, La Jolla,

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CA) were used. Statistical significance was assumed if the value of *P* was less than 0.05.

RESULTS

Mean age of the 87 study patients was 42.9±8.7 years with a female:male ratio of 1:1.4. DGF was observed in 16 patients (18.6%, DGF group [DGFG]), whereas 71 patients (81.4%, control group [CG]) did not require exogenous insulin after day 10. C-peptide levels showed a significant inverse correlation with occurrence of DGF ($r=0.24$, $P=0.03$) and were within normal range after a mean of 5.2±4.2 days in CG patients compared with 8.4±6.2 days in DGFG patients ($P=0.037$). Neither the type of transplantation (SPK versus pancreas transplants alone; $P=0.366$) nor the route of venous drainage (portal [19.5%] vs. systemic drainage [80.5%]; $P=0.619$) had significant effect on the occurrence of DGF. Mean postoperative follow-up was 41.2±21.5 months.

Donor- and Graft-Related Factors

Donor age (DGFG 34.1±2.7 vs. CG 29.5±10.8 years, $P=0.128$), donor BMI (DGFG 24.0±0.5 vs. CG 23.3±2.1, $P=0.261$), and female donor sex (DGFG 31.3% vs. CG 32.4%; $P=0.590$) did not correlate with DGF. Mean panel reactive antibody levels were low in both groups (DGFG 4.4%±4.3% vs. CG 2.2%±8.2%; $P=0.724$). Cold and warm ischemia times were 770±38.8 vs. 837±197.0 min (DGDF vs. CG, $P=0.211$), and 35.4±1.9 vs. 32.27±8.1 min (DGFG vs. CG, $P=0.164$), respectively. DGF was more often observed in HTK perfused grafts compared with UW perfusion (DGFG 37.5% vs. CG 12.7%, $P=0.030$). Positive CMV antibody status of the donor was significantly associated with postoperative DGF (DGFG 81.3% vs. CG 52.1%, $P=0.029$), as was CMV (D+/R−) mismatch (DGFG 62.5% vs. CG 21.1%, $P=0.002$).

Recipient-Related Factors

Mean recipient age and BMI at the time of transplantation were 41.7±1.9 vs. 43.2±9.0 years and 22.9±0.5 vs. 23.1±3.1 (DGFG vs. CG, $P=0.529$ and $P=0.668$), respectively. Recipient female gender was associated with DGF (DGFG 68.8% vs. CG 35.2% female patients, $P=0.015$). Donor/recipient sex mismatch did not influence occurrence of DGF ($P=0.410$).

Immunological Factors and Immunosuppression

Donor/recipient human leukocyte antigen (HLA) matching did not influence early postoperative function (HLA-A mismatch $P=0.961$, HLA-B mismatch $P=0.814$, HLA-DR mismatch $P=0.930$). Postoperative tacrolimus trough levels were maintained at 10 to 15 ng/mL and did not correlate with occurrence of DGF as measured on postoperative days 2 ($P=0.181$), 5 ($P=0.788$), and 10 ($P=0.862$; DGFG 14.7±1.7, 12.2±0.9, 13.3±1.0 vs. CG 11.8±6.7, 13.5±4.3, 13.5±5.1, respectively). Acute rejection episodes occurred in 16.1% of patients, which was not associated with DGF (DGFD 18.8% vs. CG 15.5%, $P=0.500$).

Postoperative Course and Infections

Postoperative CRP and serum amylase and lipase levels were not associated with DGF (Table 1). Perioperative infections developed in 55.2% of patients and were not correlated with early endocrine dysfunction (DGFG 62.5% vs. CG 53.5%, $P=0.357$).

TABLE 1. Postoperative results of serum amylase, serum lipase, and C-reactive protein

	DGFG	CG	*P*
Serum amylase (U/L)			
Day 1	312.3±102.1	189.6±122.0	0.290
Day 5	90.0±18.3	73.0±60.0	0.272
Day 10	100.1±23.2	83.1±73.0	0.487
Serum lipase (U/L)			
Day 1	462.8±217.5	215.5±123.0	0.701
Day 5	61.3±8.5	49.5±45.0	0.165
Day 10	87.1±24.4	67.8±59.0	0.722
C-reactive protein (mg/dL)			
Day 1	6.4±1.0	5.9±4.4	0.712
Day 5	1.8±0.3	2.4±2.8	0.956
Day 10	2.4±0.7	4.2±6.4	0.346

Values are represented as mean±SD.
DGFG, delayed graft function group (N=16); CG, control group (N=71).

TABLE 2. Multivariate logistic regression analysis of potential risk factors for delayed graft function after pancreas transplantation

	95% CI for Exp (B)	*P*
Donor BMI	0.95–2.34	0.08
Donor age	0.95–1.10	0.51
Recipient sex (F vs. M)[a]	0.03–0.81	0.03
Sex mismatch	0.89–2.24	0.33
CMV status donor[a]	0.19–8.61	0.80
CMV (D+/R−) mismatch[a]	1.23–45.70	0.03
Cold ischemia time	0.99–1.00	0.10
Perfusion solution (HTK vs. UW)[a]	0.05–1.24	0.09
HLA–DR mismatch	0.40–3.96	0.69

[a] Factors associated with DGF on univariate analysis.
CMV, cytomegalovirus; CI, confidence interval; HLA, human leukocyte antigen; UW, University of Wisconsin.

Multivariate Analysis

Data from multivariate logistic regression analysis are shown in Table 2. Female recipient gender and CMV (D+/R−) mismatch remained the only statistically significant risk factors for DGF ($P=0.03$ for both comparisons).

Patient and Graft Survival

Postoperative graft (not censored for death) and patient survival are shown in Figures 1 and 2, respectively. Graft survival at 1, 3, and 5 years was 98%, 94.4%, and 94.4% in the CG and 93.8%, 93.8%, and 93.8% in the DGF group ($P=0.791$), respectively. Patient survival was 100%, 100%, and 97.2% in the CG and 100%, 100%, and 81.3% in the DGF group ($P=0.004$), respectively.

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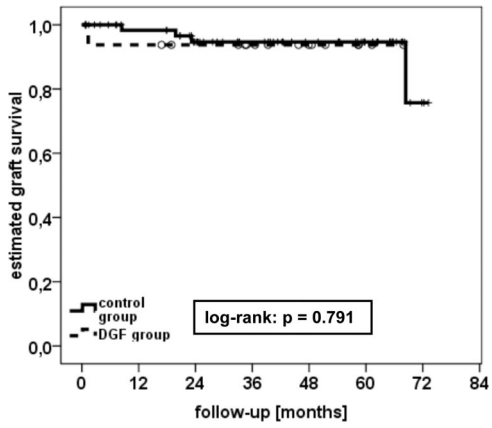

FIGURE 1. Estimated graft survival according to occurrence of delayed graft function (DGF).

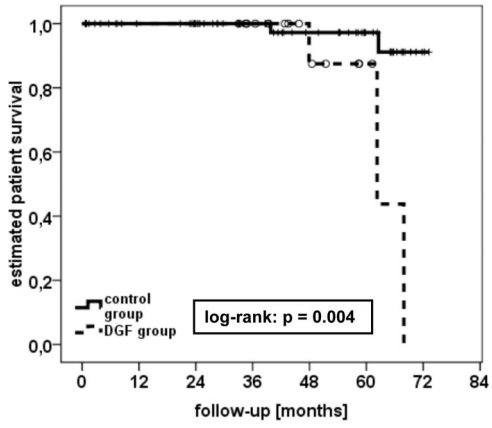

FIGURE 2. Estimated patient survival according to occurrence of delayed graft function (DGF).

DISCUSSION

DGF is well recognized as detrimental factor on the outcome of "immediately" life-saving heart or liver transplantation. The negative effect of DGF on graft survival has also been described for renal transplantation (*7*) In PTx, however, DGF has been poorly documented.

No validated definition of DGF in PTx has been established. Although Tan et al. (*9*) defined DGF as a need for scheduled exogenous insulin at the time of discharge, others calculated a maximum tolerable daily exogenous insulin dose during the early postoperative period and defined DGF as insulin need surpassing this threshold (*10*). Both definitions imply limitations in that the postoperative course may be complicated after PTx thereby causing variable length of hospitalization. Differences in diet, patient weight and composition, and level of applied immunosuppression need to be addressed in the definition of DGF.

In the early postoperative period, a variety of graft and recipient-related factors including uremia, postoperative distress, and high early cortisone dosage (*17*, *18*) affect early endocrine function. Further, calcineurin inhibitors are well known to be diabetogenic (*19*). In addition, many intensive care units, including our own, maintain tight blood glucose control with aimed glucose levels less than 120 mg/dL (*20*). To account for these early factors after PTx, we hypothesized that it would be more robust to define DGF as the need for any continuous exogenous insulin to keep blood glucose levels less than 150 mg/dL beyond postoperative day 10. Using this definition for DGF, we found a statistically significant inverse correlation with early posttransplant restoration of normal C-peptide levels in patients without DGF, corroborating this definition.

We have found DGF in 18.6% of cases (n=16). Because of the different definitions of DGF, rates vary in the literature between 33% (*9*) and 60% (*10*). However, other possible factors have to be taken into account. In view of our results regarding the significant association of CMV D+/R− mismatch with DGF, the different (*9*) or even absent CMV prophylaxis (*10*) may also be responsible for relatively lower DGF incidence found in this study as compared with others. Nevertheless, which antiviral prophylaxis is the most beneficial is still under debate. Although a recent meta-analysis does not support valganciclovir as first-line agent (*21*), a review of the Cochrane library suggests a better CMV prophylaxis with this agent (*22*) as compared with acyclovir. The addition of anti-CMV hyperimmunoglobulin has not been studied but may be a future option for high-risk patients. Finally, testing donors for CMV replication with polymerase chain reaction and potentially treating them may be another approach, and this may be subject of a prospective trial.

In kidney transplantation, it has been shown that different ATG regimens influence DGF occurrence rates. In contrast to divided-dose regimens, a single-dose rATG significantly improved early graft function after kidney transplantation (*23*). In contrast to our immunosuppressive regimen, Troppmann et al. (*10*) did not use induction therapy at all. In the more recent study of Tan et al. (*9*), the administered ATG dose was not mentioned. In addition, subsets of their patients were given IL-2R antagonist induction. However in renal transplantation, IL-2 antagonists have been found to be inferior to ATG with regard to DGF occurrence (*24*) and CMV disease posttransplantation (*25*).

Previously identified donor risk factors influencing early endocrine pancreas graft function such as age (*9*, *10*, *26*), donor BMI (*26*), and prolonged cold ischemia time (CIT) (*9*, *27*) did not reach statistical significance in our cohort. This is probably because of our stringent donor selection, with the donor BMI rarely exceeding 25 in our patient cohort and CIT exceeding 20 hr in only one patient.

The role of type and volume of perfusion solutions remain matters of debate. Although a recently published prospective trial reported comparable outcomes for both HTK and UW in patients with short CIT (*28*), several retrospective studies suggest a negative effect of HTK on PTx outcome (*29*). Stevens et al. (*30*) noted in HTK-perfused kidney and pancreatic allografts a significantly increased occurrence of early complications without influencing patient or graft mid-term survival. In renal allografts procured from extended criteria donors, a higher incidence of early graft loss after DGF may suggest caution in using HTK for these organs. For pancreatic grafts, an increased incidence of graft pancreatitis and venous graft thrombosis could be observed (*31*). In line with these observations, in two retrospective United Network for Organ Sharing database analyses, Stewart et al. (*32*) observed a

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higher susceptibility for complications in HTK-perfused kidney grafts and an increased risk of early pancreatic graft loss with prolonged CIT (*33*). In our study, we observed a higher rate of DGF in HTK-perfused grafts using univariate analysis, which however reached no statistical significance in the multivariate logistic regression analysis.

Interestingly, in this report, female recipient gender represents a significant risk factor for DGF occurrence. These gender-specific differences in DGF incidence may be related to immunological, hormonal, or even total body fat differences between genders in nonobese patients (because most of our graft recipients had a BMI less than 25). Although a female to male transplantation is a known risk factor for diminished graft outcome in heart and kidney transplantation (*34*, *35*), there are only few reports dealing with the influence of recipients' gender on graft outcome. One group has reported higher rates of early pancreatic graft loss in women after SPK (*36*). However, compared with male recipients long-term graft outcome did not differ significantly as did the rate of kidney graft failure in these individuals. Although this observation suggests that differences in immune response may be unlikely, others report a higher incidence of acute rejection episodes in female recipients after kidney transplantation (*37*). Also, different animal studies revealed the influence of endocrine factors on graft survival (*38*) (*39*).

Apart from the retrospective nature of our study hampered by all shortcomings inherent to this type of data analysis, we cannot rule out certain limitations because of the cohort size of the DGFG. Specifically, the cohort size may be accountable for the statistically significantly decreased patient survival curve in the DGFG ($P<0.004$). As a consequence—because of a lacking overt causal relationship (two patients of the DGFG died more than 5 years after transplantation because of myocardial infarction, one patient of the DGFG died almost 4 years after transplantation because of a severe gastrointestinal bleeding), and the low event numbers in both groups (two patients in the CG and three patients in the DGFG)—this statistical finding was considered as clinically not relevant.

However, the key finding of our study was a significantly higher incidence of DGF in CMV-negative recipients receiving a CMV-positive organ. Interestingly, this observation had no influence on graft survival during a mean follow-up of 40 months, which contrasts results of the CsA era in PTx (*10*). In addition, ganciclovir (GCV) prophylaxis, which was given to all our CMV-mismatched patients, was not available at that time. In our series, only three patients developed breakthrough CMV infection, this was successfully treated with an increase in the GCV dose.

CMV mismatch is recognized as a major risk factor affecting graft and recipient survival (*40*). Although universal prophylactic application of GCV in high-risk solid organ recipients lead to a decreased incidence and prevalence of CMV-associated complications, late-onset CMV infection and disease remain common events (*41*, *42*). Moreover, it is still unclear whether CMV prophylaxis may abrogate indirect effects caused by the virus. Transmission of CMV through the graft or endogenous reactivation promotes CMV infection, which may increase the rate of acute and chronic rejection of kidney grafts (*43*). The highest risk for CMV infection or disease results from CMV D+/R− mismatched transplantation of solid organs including PTx (*44*) and has also been correlated with increased risk of pancreatic graft loss (*45*). Low-level replication of CMV may already occur in the donor while being on intensive care unit, which has been shown recently for latent viruses (*46*). Brain death and perfusion/reperfusion injury further increase tumor necrosis factor-α secretion followed by increased activation of nuclear factor-κB, which in turn also promotes intragraft CMV replication (*47*). Therefore, in presence of immunosuppression after transplantation, CMV replication is even more difficult to control in the recipient. Of note, even though CMV represents the most important single pathogen in organ transplantation and CMV-related molecular phenomena are well documented, CMV has never been analyzed in the context of DGF after PTx. In addition to other infectious agents, CMV has been associated with the development of diabetes mellitus and new onset of diabetes after transplantation (*48*, *49*). Maria et al. (*50*) reported on CMV-triggered development of antibodies against GAD and IA2 in a recipient of a pancreas graft. In this context, one might speculate that insulinitis along with CMV infection may relate to DGF after PTx. This hypothesis is strongly supported by our findings that CMV is a major risk factor for DGF after PTx.

In conclusion, this is the first report on CMV-associated DGF in PTx. Our data further suggest that female recipients do have an increased risk for DGF occurrence and that higher donor BMI, prolonged CIT, and HTK perfusion solution may also affect DGF incidence. Of note, along with modern immunosuppression, antiviral prophylaxis, and intensified antiviral therapy, DGF has not been associated with decreased pancreatic graft survival in our series.

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