Changes in inflammatory cytokine levels in the acute and subacute phases of islet engraftment after total pancreatectomy and islet autotransplantation (TPIAT).
KR McEachron, GJ Beilman, S Chinnakotla, TL Pruett, TB Dunn, V Kirchner, MD Bellin
University of Minnesota Medical School, Department of Surgery

Background:
Total pancreatectomy with islet autotransplantation (TPIAT) offers the potential for improved quality of life and reduced opioid dependence for patients with painful chronic pancreatitis. However, only 30-40% eventually wean completely off insulin (1, 2), with the islet mass transplanted (IEQ) as the strongest predictor of insulin independence (2-4). The islet infusion procedure is complicated by inflammatory insults which limit islet survival and future function (5-8); the inflammatory cytokines TNFα and Interferon-γ-induced protein 10 (IP-10/CXCL10) are proposed to be directly damaging to islets (9-11) and have negative effects on transplant outcomes (12). Inflammatory cytokines in this setting represent a potential target for clinical intervention. We sought to characterize the cytokine response profiles of TPIAT patients during the acute transplantation and engraftment phases.

Methods:
Plasma levels of six known inflammatory cytokines (IL-6, IL-8, IP-10, MCP-1, TNFα, and IL-1β) were collected in a pilot cohort of 25 patients undergoing TPIAT at these timepoints: prior to surgery, after pancreatectomy but before islet infusion, then 15 min, 30 min, 60 min, 3 hours, 6 hours, 12 hours, 24 hours, 3 days, 5 days, 7 days, 14 days, 21 days, 30 days, and 90 days post-infusion of islets. Area under the curve (AUC) for cytokine exposure was calculated using the trapezoidal method including the baseline pre-islet infusion level. Cytokine status at 90 days was classified as returned to baseline or elevated. Diabetes outcomes and islet graft function were assessed at day 90 by: insulin dose, mixed-meal tolerance testing (MMTT), intravenous glucose tolerance testing (IVGTT), and glucose-potentiated arginine stimulating testing (AST). Multiple linear regression was used to measure and test associations between predictors and the potentiated acute insulin response to glucose (AIRpot). Total IEQ transplanted was also converted into a categorical variable (<299,999 IEQ = low (n=9), 300,000-399,999 = medium (n=8), >400,000 = high (n=8)) and ANOVA was used to compare the cytokine trends between these categorical groups.

Results:
After infusion of islets during TPIAT, mean IP-10 levels increased to greater than twice-baseline immediately following islet infusion (15- and 30-minute timepoints), then returned to baseline by 3 hours post-infusion, followed by a slow but lesser trend upward through 90 days post-transplant (Figure 1a). On average, elevations in TNFα levels were seen later, not exceeding baseline levels until 5-7 days post-transplant, and only exceeding baseline levels by 1.3 times (Figure 1b). Notably, most patients had elevations also observed in MCP-1, IL-8, and IL-6. When adjusted for transplanted IEQ, neither the AUC IP-10 nor AUC TNFα were associated with the acute insulin response to glucose potentiation (AIRpot) at 90 days post-transplant, or the insulin dose at 90 days (p>0.1 for all models). Those with persistently elevated cytokine levels at day 90 did not show differences in metabolic outcomes (p>0.05). There was no significant
difference in the total AUC of either cytokine between the categorical groups of IEQ transplanted (low, medium, or high; all p>0.5).

Conclusions:
There is a general increase in inflammatory cytokine levels following islet autotransplant, with some patients having persistently high inflammatory markers, as long as 90 days post-transplant. The latter is unlikely a consequence of the infusion, but rather may represent a pro-inflammatory milieu maintained by ongoing illness, infection, or other stressors in this population. IP-10 rose more quickly and to a greater magnitude than TNFα following islet infusion, suggesting IP-10 might be considered as a potential therapeutic target. However, in this small cohort, we did not observe any association of cytokine levels with islet mass infused or the diabetes outcomes at 3 months. Given the multiple patient and islet graft variables that can impact diabetes outcomes, our cohort may have been too small to detect these associations.

![Graphs](image-url)


