



# Circulating cytokines are associated with human islet graft function in type 1 diabetes

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## KEYWORDS

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**Abstract** Islet cell transplantation has considerable potential as a cure for type 1 diabetes, but recurrent autoimmunity and allograft rejection in which both cytokines play an important role are major obstacles. Using a new approach considering confounders by regression analysis, we investigated circulating cytokines and their association with graft function in type 1 diabetes patients who underwent either simultaneous islet kidney (SIK) or islet after kidney (IAK) transplantation.

After transplantation, interleukin (IL)-10 was lower in SIK recipients with subsequent loss of graft function in comparison to recipients maintaining graft function.

Before transplantation, high IL-13 and IL-18 concentrations were prospectively associated for subsequent loss of graft function in IAK recipients, whereas in SIK recipients, high macrophage migration inhibitory factor (MIF) concentrations were associated with subsequent loss of graft function.

Circulating cytokines are associated with islet graft function in patients with long-standing type 1 diabetes when considering confounders.

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## Introduction

Type 1 diabetes is an immune-mediated disease characterized by selective destruction of insulin producing  $\beta$ -cells in the pancreas leading to lifelong administration of exogenous insulin for their survival [1]. Islet cell transplantation has considerable potential as a cure for type 1 diabetes, but multiple factors including quality, preparation and amount of islets, donor status, engraftment, instant blood-mediated

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inflammatory reaction, recipient pharmacological treatment, and metabolic status have shown to contribute to limited success of this promising approach. Besides these non-immunological factors, allograft rejection and recurrent autoimmunity in which cellular auto-, alloreactivity and cytokines play an important role are likely to modulate long-term islet function [2–6].

Autoreactive effector T cells have been found in the pancreas allograft of a type 1 diabetic recipient and were shown to be associated with islet transplantation outcome [7,8]. Another study reported expansion of autoreactive T cells after islet transplantation in patients with type 1 diabetes [9]. Cytokines play an important role in the selective and direct destruction of  $\beta$ -cells [10], whereas chemokines play a critical role in the recruitment, activation, and migration of immune cells during inflammation. Several immunological parameters including cellular islet-specific autoimmunity [11], lower incidence of islet donor-specific human leukocyte antigen class I antibodies [12], lower incidence of cytotoxic T lymphocyte alloreactivity towards donor human leucocytes antigen [13], allograft-specific cytokine profiles [14], and higher total and B cell counts and presence of T cell autoreactivity at baseline [8] have been shown to associate with islet graft function and clinical status in type 1 diabetes patients treated with human islet grafts. In addition, optimal primary graft function estimated by  $\beta$ -score and also fructosamine as a metabolic measure has been shown to associate with prolonged graft survival and better metabolic control after islet transplantation [15] and [22].

Recently, we were able to demonstrate that circulating cytokines and chemokines in humans are associated with  $\beta$ -cell function and  $\beta$ -cell stress in newly diagnosed type 1 diabetes patients [16,17].

In animal studies, Solomon et al. showed that xenograft rejection was associated with recruitment of inflammatory cells to pig islet tissue (proislet) xenografts in CBA/H mice after transplantation by early intra-graft transcript expression for chemokine (C–C motif) ligand 2 (CCL2), formerly known as monocyte chemoattractant protein-1 (MCP-1), chemokine (C–X–C motif) ligand 10 (CXCL10), formerly known as interferon-inducible protein-10 (IP-10) and chemokine (C–C motif) ligand 3 (CCL3), formerly known as macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) [18]. In contrast, revealing also the protective effect of cytokines, rat islets transfected with an adenoviral vector containing the viral IL-10 gene that has been associated with suppression of immune response have prolonged islet allograft survival in rats, which was reflected by high circulating concentrations of IL-10 [19]. Furthermore, a study investigating local inflammatory activation during allograft rejection in rats reported increased circulating concentrations of cytokines while tissue inflammatory activation was dependent on the transplanted organ [20].

A recent study in humans reported that high circulating concentrations of CCL2 in donors caused by brain death predicted graft-related complications and poor graft survival after kidney–pancreas transplantation [21]. These studies reflect the important role of cytokines in graft rejection and the relation of circulating cytokine concentrations to these processes.

Aim of this study was to investigate in patients with long-standing type 1 diabetes receiving islet transplantation

whether circulating concentrations of cytokines before and after transplantation were associated with subsequent graft function.

## Materials and methods

### Subjects

Patients with long-standing type 1 diabetes (>20 years) underwent either simultaneous islet kidney (SIK) transplantation or islet after kidney (IAK) transplantation according to the Giessen protocol [22–24]. In brief, intraportal islet transplantation was performed in pretransplant C-peptide negative patients with type 1 diabetes. Patients receiving IAK had a successful kidney transplant at least for 6 months and were under immunosuppressant therapy before islet transplantation. No immunosuppressant therapy was applied to patients receiving SIK before islet transplantation. From the time point of islet transplantation immunosuppression included triple therapy (steroids, cyclosporine, azathioprine/mykophenolatmofetil) in combination with an induction immunosuppressant Anti-T-Lymphocyte–Globulin Therapy (ATG, Fresenius, Bad Homburg, Germany) or Anti-Lymphocytic Purified Globulins Therapy (ALG). Treatment strategy: 1000 mg of steroids at day 0, 100 mg at day 1 with reduction of dosage until 10 mg after 3 months and 5 mg after 12 months; cyclosporine blood concentration 350 ng/ml for the first 3 months then 250 ng/ml; azathioprine or mykophenolatmofetil dosages were 100–150 mg/day or 1500–2000 mg/day, respectively. 4 mg/kg body weight ATG was applied for 10 days. For the purpose of this analysis, complete islet graft failure was defined as permanent C-peptide negativity (<0.2 ng/ml) on regular follow-up.

Clinical and biochemical data were available from 1 week before transplantation until subsequent lost or maintained graft function determined for 52 patients (29/23, m/w; median age 38.0 years, range 29–58 years) who were followed over a median observation time of 20 months; range 1–59 months. Serum samples were available 1 week before transplantation, and the time transplant was rejected or patients were released with a stable transplant to primary care.

In the morning, fasting venous blood was drawn. Serum samples were labeled and frozen at –20 °C until shipment on dry ice to the German Diabetes Center for determination of cytokines.

All patients gave informed consent according to the criteria of the Helsinki II Declaration.

### Systemic cytokines and chemokines

Circulating concentrations of cytokines were determined by ELISA. Matched antibody pairs were used for IL-10 and CXCL10 (Pharmingen, San Diego, USA), MIF, CCL2, and CCL3 (R&D Systems, Wiesbaden, Germany) and IFN- $\gamma$  (Endogen, Woburn, USA) as described [25,26]. IL-13, IL-6, and IL-8 (Endogen/PeliKine Compact, CLB, Amsterdam, The Netherlands) and IL-18 (Bender Med Systems, ORT, Germany) were determined by commercially available kits following the manufacturer's instructions. All cytokines were measured in a blinded fashion, e.g., clinical data were not known

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