Risk factors and outcome in clinical pancreas transplantation

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1 General introduction

GENERAL INTRODUCTION

Pancreas transplantation is to date the only definitive treatment option for patients with type 1 diabetes mellitus (T1DM). For patients with metabolic dysregulation-induced end stage renal disease (ESRD) a simultaneous kidney and pancreas transplantation is an option, whereas for non-uremic patients suffering from hypoglycemic unawareness solitary pancreas transplantation is a feasible option.

In December 1966, at the University of Minnesota Hospital, Kelly and Lillehei, performed the first pancreas transplantation, combined with a kidney transplantation, to treat a uremic, type I diabetic patient. The results of their series were published by another pancreas transplantation pioneer, David Sutherland, in a hallmark paper on pancreas transplantation in 2001.[1] More recently, other larger single center studies that were published came from Wisconsin, USA[2] and the first large European series was from Innsbruck.[3] Multiple other large pancreas transplantation centers and (inter)national registries have published results as well and all show excellent outcomes in terms of survival.[4-8] Table 1 represents an overview of their results.

Since the first transplantation, over 50.000 pancreas transplantations have been performed worldwide.[9] Most of these transplantations were performed as a simultaneous pancreas kidney (SPK) transplantation, which is still the most commonly performed type of pancreas transplantation. The first pancreas transplantation in the Netherlands was performed at the Academic Hospital Leiden (currently Leiden University Medical Center) in 1984.[10]

Both the increased experience in dedicated pancreas transplantation centers and ongoing success have paved the way and pancreas transplantation became an accepted treatment for a broader range of suitable recipients. This phenomenon has frequently been described as 'the transplant paradox'[11]: that by increasing the numbers of transplantation and thus increasing experience and awareness, the indications and recipient selection become increasingly more liberal. This leads to waiting lists increasing even more, and without a similar increase in organs leads to organ shortage and increased waiting time. On the other hand, it appears that for many healthcare professionals pancreas transplantation is still a black box and many still think of it as an experimental procedure. Through increasing awareness, the number of suitable candidates and transplantations may increase. This may have partially been the aim of Smets *et al.* in a study in which all Dutch type 1 diabetic patients that started renal replacement therapy (RRT) in The Netherlands were included.[12] Furthermore, this study was the first randomized trials that showed that, for patients suffering from (imminent) renal failure secondary to type 1 diabetes, a 50% reduction in long term mortality may be achieved by simultaneous pancreas kidney transplantation, as compared to kidney transplantation alone. This was a vital addition to previous reports that predominantly focused on prolonged kidney graft survival and increased quality of life after simultaneous pancreas

kidney transplantation and even contradicted each other on the benefit of addition pancreas transplantation.[13,14]

A large part of this thesis was made possible by Eurotransplant. Eurotransplant manages the above mentioned waiting list; acts as a mediator between the donor and the recipient and plays a key role in the distribution of organs in 8 European countries (The Netherlands, Belgium, Luxembourg, Germany, Austria, Slovenia, Croatia, Hungary).[15] In order to be able to perform this key task of allocation, Eurotransplant collects data on donors and recipients. In addition to allocation, Eurotransplant is continuously trying to improve allocation algorithms based on the latest medical, ethical and legal principles. In order to do so, Eurotransplant also collects data on outcome following transplantation. In this thesis, these Eurotransplant data, along with data derived from Leiden University Medical Center, will be analyzed.

Patients suffering from ESRD due to T1DM that are eligible for kidney transplantation are the prime candidates for SPK. In patients with ESRD, the benefits of a simultaneous pancreas kidney transplantation outweigh the burden of life-long immunosuppression and the surgical risks of the operation. The goal of pancreas transplantation, in the context of simultaneous pancreas transplantation is to achieve exogenous insulin independence. By achieving insulin independence, the benefits are rendering patients free from intensive blood glucose self-monitoring and insulin administration, protection of the kidney transplant, as well as counteracting, stabilizing, and perhaps even reversing, the progression of other secondary complications such retinopathy and neuropathy.[16,17] Patients with ESRD that already received a kidney transplant might be candidates for pancreas after kidney (PAK) transplantation, then also gaining the benefits SPK recipients have. In case of life-threatening hypoglycemic unawareness, patients not suffering from ESRD might still be considered as candidates for pancreas transplantation alone (PTA) in case of brittle diabetes or failure to achieve euglycemia on intensive exogenous therapy.[14,18] SPK may also be a suitable option for patients not yet suffering from ESRD, but who are expected to become RRT dependent in the nearby future: a so-called pre-emptive transplantation.[6] To date, the selection of patients with type 2 diabetes mellitus for pancreas transplantation is controversial and, although pancreas transplantation is performed for T2DM, this constitutes only a very small minority and is therefore, beyond the scope of this thesis.[19] Some patients with maturity onset diabetes of the young (MODY) may, on the other hand, be suitable candidates for transplantation.[20]

In selected cases, islet of Langerhans transplantation is a feasible option, which may be performed to render the recipient insulin independent.[21,22] However, in most cases, islet transplantation is performed to protect the recipient and the graft from the secondary complications of the underlying disease. Due to inferior graft survival rates (in terms of insulin independence) of islet transplantation, as compared to vascularized pancreas, vascularized transplantation is still the preferred first step in beta-cell replacement therapy in

our hospital. Furthermore, the islet yield from one single donor is frequently not enough to render the recipient off exogenous insulin and islets of two or more donors are combined to get an adequate islet yield for one recipient. Islet after kidney transplantation may be a less surgically invasive and thus suitable option for patients that may not be fit for surgery or following multiple previously failed vascularized pancreas transplants to protect the kidney graft against secondary complications associated with diabetes, without rendering the patient insulin independent.[23]

Outcome following pancreas transplantation is excellent, with death censored graft survival rates around 80% after 5 years and patient survival rates around 90% after 5 years (table 1). While improvements in immunosuppressive regimes have improved mid- to long term outcome by protecting the recipient and his/her graft from rejection, short term outcome is still limited by a high incidence of surgical complications. This early graft failure is usually well-defined, since most patients require immediate graft explantation and exogenous insulin therapy. Defining longer term graft failure on the other hand is more difficult. Different definitions are being used around the world.

Table 1. Overview of results of large single center or national registry studies

			Patient survival		Pancreas graft survival		Definition of pancreas graft failure
Authors	Center/Country	Year	1 year	5 years	1 year	5 years	
Sutherland et al.	Minneapolis, Minnesota, USA	2001	92%	88%	79%	73%	Non-death censored insulin independence
Thai et al.	Pittsburgh, USA	2004	100%		94%		Not-stated
Sollinger et al.	Madison, Wisconsin, USA	2009	97%	89%	88%	76%	Not-stated
Ollinger at al.	Innsbruck, Austria	2011	98%	94%	88%	82%	Insulin independence
Muthusamy et al	United Kingdom	2012	95-96%		87-88%		Death censored insulin independence
Walter et al.	Bochum, Germany	2014	96%	91%	80%	73%	Not-stated
Kopp et al.	Leiden, The Netherlands	2015	96%	87%	84%	76%	OPTN defined
Kopp et al.	Eurotransplant region	2016	94%	91%*	84%	79%*	Death censored, center reported

* 3-year survival

Failure may be defined as return to exogenous insulin therapy. Failure may also be defined as poor glycemic control (for example based on ADA definition of T1DM) or even absent c-peptide. Clearly, using one definition would be preferable, as different definitions yield different results and different different suggestions for the best definition have been proposed.[24,25]

The most feared complication is graft thrombosis. Because its etiology is still not fully understood, there is still no consensus on how to deal with this 'Achilles heel' of pancreas transplantation.[26] Not only the change from high blood flow in the donor to low blood flow in the recipient, ischemia reperfusion injury and procurement related tissue damage with subsequent leakage of lytic enzymes[27], but also the change from uremic to non-uremic recipients are thought to play a role. Center specific protocols concerning surgical technique, immunosuppression, inotropic support may also play a role. Several strategies have been undertaken to deal with this complication, including tailor made high dose anticoagulants using thromboelastography (TEG)[28], strict radiological follow up[29,30] and different operating techniques.[4,31] In case of complete thrombosis, donor pancreatectomy is usually required. Some studies report on graft salvage, either by endovascular or surgical interventions.[32,34] In case of partial thrombosis, which is considered to be 'normal' due to the changes in vascularization (especially by ligation of the splenic vein) by some physicians, grafts may be preserved by treating the patients with intravenous heparin and oral anticoagulants.[35]

In general, outcome following transplantation depends on several factors and might best be described as the following equation: donor + procurement + recipient + center and experience = outcome. Next to those 4 factors, yet unknown or unidentified factors, play a role. This thesis contains data that might further fill in the equation, by elaborating on most individual factors and measuring their association with outcome.

Outline of this thesis

Chapter 2 of this thesis provides an overview of 30 years of pancreas transplantation at the LUMC. Pancreas graft survival is defined by multiple factors in this chapter.

Currently, there is a worldwide debate on how pancreas graft failure should be defined. Whether death censored or uncensored and whether this should be reinstitution of exogenous insulin therapy, the use of oral anti hyperglycemic agents, absent c-peptide, return of diabetes mellitus, yet remains unclear and without consensus. In general, graft failure in this thesis was defined as death censored and return to exogenous insulin therapy, unless defined otherwise in specific chapters.

Next to valid definition of outcome, valid measures to evaluate which factors enter the equation are just as important. **Chapters 3 and 4** of this thesis elaborate on tools to measure pancreas donor quality, which are an important factor in the equation. In 2008, a Eurotransplant derived tool, called the Preprocurement Pancreas Allocation Suitability Score (P-PASS) was introduced.[36] This was the first tool to describe pancreas donor quality in an evidence-based model. In 2010, Axelrod introduced the Pancreas Donor Risk Index (PDRI).[37] In **chapter 3**, we aimed to validate the UNOS based PDRI in our center, since in liver transplantation had previously shown that differences in populations exist. This would be the first step in the possible implementation of the PDRI. **Chapter 4** elaborates on the use of different risk indices in organ allocation policies. After investigating risk indices in

our own center (chapter 3), we evaluated both existing risk indices (P-PASS and PDRI) in a large Eurotransplant donor database for their ability to predict allocation outcome. In this study, factors unknown at time of allocation, were set to reference.

In **chapter 5**, using a similar Eurotransplant database, supplemented with outcome data, the center effect is investigated as a part of the equation. Using a large Eurotransplant database, the relationship between center volume and outcome was demonstrated.

Chapter 6 elaborates on one of the major concerns following pancreas transplantation: pancreas graft thrombosis.[38] This feared complication has frequently been described as the 'Achilles heel' of pancreas transplantation. In this chapter, we aimed to investigate a less frequently reported problem: partial graft thrombosis and its clinical implications. In **chapter 7**, another risk factor is investigated. In order to keep up with organ shortage, transplant professionals are increasingly forced to accept grafts from extended criteria donors, such as grafts from donation after circulatory death (DCD) donors. In this chapter, the Leiden University Medical Center experience with DCD pancreas transplantation is described.

Chapter 8 summarizes and discusses all results and conclusions described in this thesis. **Chapter 9** is a general discussion and **chapter 10** contains future perspectives in the field of pancreas transplantation and in particular the clinical research field. **Chapter 11** is the Dutch summary of this thesis and contains explanations for people less experienced in the medical field.

Since the first pancreas transplantation in 1966, the procedure has gone from an experimental surgical treatment to the, to date, single definitive treatment for T1DM. Multiple factors have to be considered when determining and interpreting outcome following pancreas transplantation, amongst them the factors studied in this thesis. Even though the experience around the world is steadily increasing, the way to fully understand all physiological, pathophysiological and clinical aspects of this highly complex procedure is still long and the equation remains yet to be completed.

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