Risk factors and outcome in clinical pancreas transplantation

Kopp, W.H.

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General discussion

GENERAL DISCUSSION

Pancreas transplantation is to date the only definitive treatment for patients with type 1 diabetes mellitus. Other types of diabetes, such as type 2 diabetes mellitus or mature-onset-diabetes of the young (MODY) in different forms may also be treated with transplantation. The former being an accepted treatment, the latter is not being performed as often and was not studied in this thesis. For patients with concomitant end stage renal disease, pancreas transplantation combined with kidney transplantation (either in a simultaneous or by consecutive procedures) does not only improve quality of life by rendering the patient off exogenous insulin and dialysis, but also by reversing secondary diabetic complications and protecting the kidney graft.[15-17] With this in mind, a successful procedure may be considered life-saving, even though the absence of endogenous insulin may not be life-threatening per se.[18,19] In the case of absence of endogenous insulin and when life-threatening hypoglycemic unawareness occurs, solitary or pancreas transplant alone (PTA) may be a feasible and life-saving option.[20,21]

This thesis focusses on a variety of risk factors that may play an important role in the outcome following pancreas transplantation. As was stated in the introduction, the equation predicting outcome contains the following factors: donor risk factors, recipient risk factors, center related factors and procurement related factors. Some of those factors were studied in this thesis, others were also studied, but are not a part of this thesis and will only be mentioned briefly in this discussion.

Prior to discussing outcome related data that was studied in this thesis, one important remark has to be made: pancreas transplantation research is lacking one uniform definition of pancreas graft failure. This makes comparison of outcome in different studies and centers difficult. Also, organ transplant registries, such as the Eurotransplant registry, encounter problems with the lack of adequate definitions. Sub-analyses on the definition of graft survival were performed using the data described in the first chapter.[22] This was the first study to evaluate the difference. It showed that the difference especially becomes relevant at a longer time after transplant, up to 28% after ten years, when exogenous insulin therapy use was used as definition (76% graft survival) compared to when the definition of DM, as defined by the American Diabetes Association (ADA) was used (48% graft survival).[23] The need for a uniform definition of graft failure does not necessarily apply to early graft failure. Graft failure early after transplantation is generally caused by surgical complications (such as thrombosis, bleeding or pancreatitis) which usually warrants direct organ removal and subsequent return to exogenous insulin therapy.[24] The definition of early graft failure (EGF) is clear and insulin has to be administered to keep the patient alive and euglycemic. In such cases, measuring HbA1c values, which may be of interest for long-term graft failure, will partly represent pre-transplantation values and would thus be futile. On the mid- and longer term, the difference in reported graft survival increases with the duration of follow up.[22]

Although one perfect definition of pancreas graft failure does not exist, there are definitions that have advantages over others. A definition that is based on regularly available data, should form the basis of a uniform definition. This allows for easy implementation in databases and registries. During the development of this thesis, it became clear that definitions that are constructed of multiple endpoints, such as the OPTN definition in chapter 1, are difficult to use for research purposes, since many clinical parameters (HbA1c, C- peptide, exogenous insulin use) would have to be entered in the database. Also, using a definition that is based on lab values only, is a snapshot analysis and does not allow individual assessment of the patient, which can only be done by a physician. For example: a definition states that a graft had failed in case of HbA1c > 48 mmol/mol and low c-peptide.

Given patient A, who has low c-peptide, has low bodyweight and is not-dependent on exogenous insulin, but suffers from in infection or rejection and has high HbA1c at time of measurement. This graft should be considered a failed graft based on the definition, even though, when evaluated by both physician and patient, the transplant might still be functioning. Furthermore, not every clinic does routine c-peptide measurements on their patients. Despite the limitations that are mentioned above, a workgroup consisting of members of both European Pancreas and Islet Transplantation Association (EPITA) and International Pancreas and Islet Transplantation Association (IPITA) elaborately evaluated all pros and cons and reached consensus on the definition of B-cell replacement therapy success and failure; the Igls definition of functional and clinical outcomes for ß-cell replacement therapy or 'Igls criteria' on pancreas graft failure (Table 1).[25] In this definition, which is based on lab values (HbA1c, C-peptide) and medical records (hypoglycemia due to exogenous insulin overdose, exogenous insulin requirement), ß -cell replacement is considered successful with good to optimal ß -cell graft function and considered failed with marginal or failed ß -cell graft function. This is the definition that is recommended when reporting pancreas transplantation results.

ß-cell graft functional status	HbA1c, % (mmol/mol)	Severe hypoglycemia, events per yr	Insulin requirements, U/kg/day	C-peptide	Treatment success
Optimal	≤ 6.5(48)	None	None	>Baseline	Yes
Good	< 7.0 (53)	None	<50% baseline	>Baseline	Yes
Marginal	Baseline	< Baseline	≥50% baseline	>Baseline	No
Failure	Baseline	Baseline	Baseline	Baseline	No

Table 1. Igls definition of functional and clinical outcomes for ß-cell replacement therapy (25)

Prediction models have become increasingly more important in transplantation. Such models, and in particular donor risk indices (DRI), were initially developed to predict outcome following transplantation.[1-4] This was thought to be helpful in clinical decision making, as well as physician-to-patient communication. In pancreas transplantation, the

first prediction model was described by Vinkers *et al*.[5] Using routine data on organ acceptance, the preprocurement pancreas allocation suitability score (P-PASS) was developed. This score was implemented in Eurotransplant in 2010, assisting transplant coordinators and other professionals to estimate whether it would be suitable to report the pancreas for transplantation. Also, it has been validated to predict survival.[26] It has been widely used since then and is still being used in some countries. Data in this thesis, amongst other reports, have repeatedly shown the limited value of P-PASS.[27,28] One recent study from Poland reported that PDRI was not related to outcome, however even with low risk donors (PDRI < 1.0), 1 year death-uncensored graft survival was only 66% and therefore their results seem incomparable to other reports.[29] Even more, 8 years after its introduction, the PDRI is considered superior, as is shown in this thesis.[30,31] More recently, another study from Germany also reported that PDRI but not P-PASS is associated with pancreas graft survival.[32]

The first step was to validate the newly constructed PDRI by Axelrod in the contemporary database that was described in chapter 2[33] Also, the P-PASS was evaluated in this cohort to predict graft survival. This was the first time that the PDRI would be validated in another cohort. The results are described in chapter 3. Following the first study on DRI, our aim was to re-evaluate and basically re- do the study that was performed by Vinkers.[5] In close collaboration with Eurotransplant a similar, but larger database was constructed to repeat the experiment Vinkers carried out. This database contained 10 444 pancreas donors. The P-PASS that was constructed by Vinkers was compared to the PDRI constructed by Axelrod, but modified to contain only donor factors.

The modified PDRI, contained only donor factors and was, in that regard, in line with the concept of Vinkers' P-PASS. This study clearly revealed the limitations of the P-PASS. The P-PASS does not include all factors that are believed relevant in pancreas transplantation, because it was designed based on a historic database with strict age and BMI limits. Another important factor here is DCD, which nowadays contributes to a large proportion of all donors in the Netherlands. Only donors below 50 years old were included, with a mean of 35 years old. This study shows, that this in no way represents the current donor population and recently the German EXPAND trial advocated that older and higher BMI donors should be used for pancreas transplantation.[34] When comparing both models side by side in their ability to predict allocation outcome (that is, the organ being accepted), it appeared that the PDRI was superior over the P-PASS. Unfortunately, this database did not include the most clinically relevant endpoint, namely pancreas graft survival, since outcome after transplantation is not routinely recorded in the Eurotransplant database. Nevertheless, since the PDRI had been validated to graft survival in the above mentioned study by Axelrod[4], the study advised to use PDRI for donor selection instead of P-PASS. Unfortunately, the P-PASS is still a tool that is used in the Eurotransplant community, despite its limitations.

In general, there is a lot of discussion about the clinical usefulness of prediction models, such as the PDRI. Advocates of these models claim that they might be used in clinical deci-

sion making, for example to accept or decline a graft that is offered for transplantation. It is stated that, by using the PDRI, a structured and evidence based decision can be achieved. Opponents on the other hand, claim that the data included in a model is too scarce to draw any solid conclusions and that there are many more factors that need to be taken into account when making this decision. Based on the data in this thesis, especially in chapter 3 and 4, arguments for both statements can be found. Clearly, the PDRI performs better than the P-PASS in predicting outcome. The poor performers should not be used in a clinical setting.

Furthermore, only a small percentage of the variation in graft survival is explained by DRIs, even when correcting for other factors that may play a role (recipient factors, center factors). In conclusion, using DRIs for clinical decision making has to be done with great caution. The greatest advantage of the PDRI, or any validated risk index for that matter, is that it allows comparison of large groups of donors in a standardized way. Chapter 3 and 4 of this thesis provide such examples. By providing these insights, we may be able to better communicate with each other about how to improve the transplantation community and thereby improving transplantation numbers and outcome.

Chapter 5 shows that there is a clear relationship with the annual number of transplantations performed in a center and outcome. Striking is the fact that not only is the procedure more successful in higher volume centers, but also that patients survive longer after transplantation when they are transplanted in a high volume center. This study shows that higher volume centers are more willing to accept higher risk organs for transplantation and still have better results as compared to low volume centers. This is a vicious circle that will be even more pronounced in the future since centers will be forced to accept higher risk donors due to organ shortage. Therefore smaller centers are less likely to accept organs for transplantation and subsequently will become smaller and smaller. This will lead to a loss of expertise and even more reluctance to accept higher risk organs. This is the first study to actually show such a relationship, one which obviously was thought to exist by many professionals, because such relationships had been published for other fields of organ transplantation.[35,36] Similar studies on both pancreas, but also liver transplantation have been published afterwards and have shown similar results.[37,38] Because of the perceived relationship with volume and outcome, collecting data for such a study is problematic, because lower volume centers may feel reluctant to provide data. Unfortunately, in Europe, or in the Eurotransplant area, there are no mandatory registries.

Another problem in transplantation and especially in pancreas transplantation is procurement related injury. A study has shown that procurement related pancreas injury may occur in up to 50% of the cases, and this is often the most important reason of the organ being declined for transplantation.[39] At Leiden University, in close collaboration with the 'Nederlandse Transplantatie Stichting' (Dutch Transplantation Foundation, NTS), a novel method was developed to assess procurement related injury and it was used to analyze

procurement quality in a prospective nationwide study.[40] Quality forms had to be completed by both the procurement and the accepting surgeon (which is usually not the same surgeon because in The Netherlands separate teams perform the donor procedure). In this study, a new method to describe similarities and discrepancies between both forms was introduced. It appeared that in 23% of the cases there was a discrepancy between both surgeons. It could be that accepting surgeons are either more critical in their appraisal of an organ, that they are more experienced in evaluating this particular organ or that circumstances to evaluate are simply more optimal (better lighting, back table procedure). Regardless, this system allows evaluation of the procurement quality in The Netherlands in a prospective study. Especially in pancreas procurement, there was an association between procurement related injury and the number of organs procured, where lower procurement volume was a risk factor for injury.

These data are in line with the data that was used in chapter 5, which show a similar relationship in outcome after pancreas transplantation and clearly both studies provide arguments for (further) centralization of pancreas transplantation and procurement.

Whether centralization will lead to higher outcome remains to be seen, however high volume centers might be more willing to accept donors with certain risk factors. Risk factors that are related to poor outcome, are usually attributed to the donor. Factors such as donor age, BMI, cause of death and impaired kidney function are related to early graft failure due to technical failure, caused by graft thrombosis, bleeding or pancreatitis.[24] It is acknowledged that still, after many years of pancreas transplantation, graft thrombosis remains the Achilles' Heel of pancreas transplantation. Usually, complete graft thrombosis occurs within the first 2 weeks after transplantation and may be secondary to rejection or surgical complications. The Virchow triad of endothelial injury, venous stasis and hypercoagulability is believed to also play a role in the development of thrombosis.[10,41] Venous stasis is caused by changes in splanchnic blood flow (from high flow in de the donor to low flow in the recipient due to exclusion of splenic and intestinal blood flow). Hemodynamic instability in the peri-operative period, sudden changes in extent of uremia following kidney transplantation or calcineurin inhibitor use may also be associated with thrombosis. Complete thrombosis is extensively studied and multiple strategies have been proposed to prevent and treat this complication. For example, the positioning of the graft and type of enteric drainage of the pancreas graft, may be associated with graft thrombosis.[42,43] Currently, in most centers, the pancreas is anastomosed 'head up' to either part of the small intestine from duodenum to terminal ileum, to prevent the graft from kinking due to gravitational forces or to allow duodeno-duodenal anastomosis *(expert opinion)*. Complete thrombosis usually leads to immediate graft failure, although endovascular or surgical salvage procedures and even conservative treatment have been reported with varying rates of success.[44-46] These studies state that salvage procedures in case of complete thrombosis should be considered. Partial graft thrombosis remains a far less studied entity. Questions still remain whether

this entity requires treatment, for example whether patients with partial graft thrombosis require anticoagulation with heparin. LUMC results, as presented in chapter 6 clearly show that using heparin and vitamin K antagonists leads to excellent outcome, however, it is not known what the outcome would have been if patients would not have been treated. Perhaps, outcome would have been similar. Using, by some considered as controversial, CT imaging allows visualization of partial thrombosis that may be amenable to treatment. Using color enhanced doppler ultrasound may also be an option to investigate thrombosis, but can only be used in experienced hands.[47] This requires either training of transplant surgeons in the use of doppler or intensive collaboration with radiologists. The former may be preferable, because ultrasound analysis may then be done daily and/or instantly upon indication. Also, another advantage lies in the omission of intravenous contrast, which may damage the newly transplanted kidney. Evaluating recent data, contrast induced acute kidney injury (CI-AKI) due to iodine based contrast media occurs in about 2.5% of patients with chronic kidney disease undergoing contrast based CT, although kidney transplant recipients are excluded from those studies.[48]

Future studies should focus on identifying and investigating factors that may be associated with thrombosis. Also, intra-operative measurements may be investigated. For example, ROTEM or thromboelastrography[11,49] analysis during and after transplantation may provide more insight. Also maintaining hemodynamic stability throughout the transplantation may influence the risk of thrombosis. Whether this is achieved by transplanting the kidney first, as is done in our center, or whether the use of catecholamines should be limited or used liberally, remains unclear.

In the 7th chapter, another recent cohort of pancreas transplantations in our center was analyzed. The main goal of the study was to compare the results of DCD pancreas transplantation, which is generally considered to be a high risk pancreas transplantation, to standard DBD pancreas transplantation. By analyzing the specific outcome of DBD to DCD pancreas transplantation and showing good results for the DCD group, we aimed to increase the potential donor pool. It became clear from this study that results following DCD pancreas transplantation were at least equal to those of DBD pancreas transplantation. This however, has to be interpreted with caution due to multiple issues raised in the study. The first issue is donor selection: DCD donors were generally younger and had considerably fewer risk factors. This reflected in a relatively low PDRI in the DCD group and when DCD was not taken into account, these donors could otherwise be considered low risk. The relatively higher risk of graft loss could be largely attributed to the numbers of early graft loss in the DBD group, mainly due to thrombosis. Simultaneously, the risk of bleeding was lower in the DBD group. Obviously, this suggests some form of yin and yang analogy. The suggestion of factor Xa accumulation was raised in the study. This would be caused by impaired kidney function following DCD transplantation, due to the higher incidence of DGF. In this retrospective study, factor Xa was not measured, therefore the relationship could not

be proven. In any case, the study shows that simply declining DCD donors for vascularized pancreas transplantation seems unjustified and not based on data. Especially, with younger and donors with less other risk factors, excellent results can be achieved following DCD pancreas transplantation.

CONCLUSION

Beta-cell replacement therapy, and in particular pancreas transplantation is the only curative treatment for patients with complicated type 1 diabetes mellitus. Due to organ shortage, transplantation professionals are forced to accept higher risk organ donors to meet the increasing demand. This thesis investigates these risks and shows that it is justified to accept a certain risk, for example by transplanting grafts from DCD donors. Graft thrombosis is still the main cause of early graft failure, but in the light of long term outcome, the risk is acceptable and the majority can be treated with good outcome. Preferably performed in high volume centers with good outcomes, pancreas transplantation is life-saving for patients with type 1 diabetes mellitus, especially when combined with kidney transplantation in case of concomitant end stage renal disease.