Author’s response to reviews

Title: Short and Long-Term Metabolic Outcomes in Patients with Type 1 and Type 2 Diabetes receiving a Simultaneous Pancreas Kidney Allograft

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Author’s response to reviews:

Dear Editor in Chief,

With greatest enthusiasm and passion, we have revised our manuscript entitled “Short and Long-Term Metabolic Outcomes in Patients with Type 1 and Type 2 Diabetes receiving a Simultaneous Pancreas Kidney Allograft” (BEND-D-19-00102) according to the editors and referees’ comments.

We would like to express our appreciation and gratitude for reviewing our manuscript. To our understanding your remarks are clear. The editors’ comments on our manuscript have been addressed by us in detail and we believe the paper has hence improved significantly. Since editors´ comments at some points differ from the referees comment we had to decide either addressing the editors´ comments or the referees comments and we chose the first option.

All corrections were made in “Review Tracking mode” for your convenience.

Please find attached a point by point response for the referees. We hope that our revision is convenient and appreciated. We belief the manuscript has improved a lot and hope you may now consider it appropriate for publication in your prestigious journal.
Editor Comments:

I agree with reviewer #1 regarding the need of a major revision but not necessarily by including a new control group. My view is that the authors should not focus in comparing the groups in terms of a typical statistical analysis but rather presenting the results descriptively. It is clear that due to the different criteria applied for performing transplantation in various groups, the number of confounding factors is very large and it’s virtually impossible to account for them in a statistically proper way, since the groups are too small.

Hence I propose to eliminate all p-values, which are in this case of minor significance, and focus on the experience and results of an "unconventional" transplantation such as the SPK in type 2 diabetic patients.

Corrections on p-values have been made accordingly. We strongly agree on the editors strategy, and the manuscript has been revised in the way that we increasingly focused on experiences and results of SPK in IDDM II.

In addition, there is a number of issues that need to be clarified and further discussed:

- What is the rational behind offering the option of pancreas transplantation in patients who are C-peptide positive, ie the organ to be replaced is not (at least totally) deficient?

- The characteristics of T2D patients who underwent SPK transplantation are by no doubt quite different not only from those of the other groups but also from those of a “typical” T2D population. Most noticeably, looking at the mean age at onset (28 years) combined with the need for insulin therapy and the low (for T2D) BMI, one may hypothesize that these are not true T2D cases but actually type 1 cases lacking autoimmunity or converted to antibody negativity through time. Monogenic diabetes could also be the case. The authors should also discuss the possible confounding role of kidney disease in C-peptide levels.

This relevant topic was dressed by a short paragraph including reference.

End stage renal disease (ESRD) is a serious development in diabetes mellitus and represents a serious clinical problem which lacks effective therapy for the last 20 years. A great body of evidence supports the fact that C-peptide has a beneficial effect on disturbed physiologic pathways which lead to the development of diabetic nephropathy and short term studies of C-peptide therapy in patients with ESRD have indicated beneficial effects such as lowered hyperfiltration rate and reduced albuminuria (REF: Hills CE. et al Am J Nephrol. 2010;31(5):389-97.)

- The authors should clarify whether T2D cases were insulin-requiring or insulin-dependent. Were they all under basal-bolus therapy? Were some of them still receiving oral antidiabetic agents?

Clarification is now included into the text.

All of the T2DM recipients of SPK and 25 of 26 T2DM recipients with kidney alone transplantation were on exogenous insulin and had a history of oral antidiabetic medication for at least 6 months.
• Was diabetic kidney disease the cause of renal damage in all cases?

Yes

With regard to renal damage patients with multiple or other causes than diabetic kidney disease as the lead reason for renal damage were excluded from analysis.

• The authors should further discuss previous results on the topic

Previous results have been inserted into the discussion section including references.

Improved success rates, favorable risk-benefit ratios and novel immunosuppressive therapies developed over the last decades definitely made pancreas transplantation a story of success, not only for T1DM but also for T2DM patients, and those with brittle pancreaticogenic diabetes. Today the efficacy of SPK especially in T2DM, C peptide positive patients with end stage renal disease is well accepted. However, the current literature lacks prospective randomized trial on SPK for this set of patients and as a limitation our study also does not address this need.

An initial report from Light et al in 2005 (Ref: Light JA, Barhyte DY. Simultaneous pancreas-kidney transplants in Type I and Type II diabetic patients with end-stage renal disease: similar 10-year outcomes. Transplant Proc 2008; 40:438–440.) investigated the outcomes of 135 insulin dependent patients undergoing SPK for either T1DM or T2DM. The groups were defined by the level of C Peptide with a cut-off point of 0.8ng/ml. In their 10-year follow up patient and graft survival were similar although groups differed significantly in terms of age, BMI and ethnicity.

A subsequent analysis by Singh et al. (Ref: Singh RP, Rogers J, Farney AC, et al. Do pretransplant C-peptide levels influence outcomes in simultaneous kidney–pancreas transplantation? Transplant Proc 2008; 40:510–512.) used higher C peptide cut of levels (2.0 ng/ml) for the better discrimination of T1DM and T2DM patients. Not surprisingly, patients with higher C peptide levels were older, had a higher BMI and a later onset and shorter duration of diabetes mellitus, as well as a longer duration of pre-transplant dialysis. And again, death censored kidney and pancreas graft survival rates were similar for both groups. These early studies demonstrate that comparable outcomes can be achieved for PTX in T1DM and T2DM patients.

• There is an important typo in page 11, line 311. Replace 371 by 37.1.

corrected

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Reviewer reports:
Anne Marie Weissenbacher (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.
Dear authors,

you have picked an often discussed topic. The date you presented in regards to your pancreas outcomes after T1DM and T2DM is interesting and illustrates that your institution is able to perform both. However, the kidney comparison group is not adequate as a control group; recipients and donors significantly older, dialysis time longer etc. - essentials to take into account. Please provide a matched control group before you draw any conclusions. According to the results you presented in the current manuscript, someone can conclude that your kidney cohort is doing significantly worse than anyone else in your paper.

We agree with the referee on this group dilemma, however decided to follow the editors` suggestion and hence increasingly focused on our experiences and results of SPK in IDDM II in a more descriptive and not comparative way. A matched comparison group (e.g. age. etc.) furthermore might be theoretically hard to find since from a patient demographic perspective, IDDM II falls into a totally different demographic segment and few e.g. young patients with IDDM II and end stage kidney disease already receiving a transplant might exist (at least in our database).

In addition: Delayed graft function (DGF) of the kidney was defined as the need for dialysis at hospital time but without further need after discharge - this is not a correct, internationally used, definition. Please provide a legitimate one.

The definition of delayed graft function (DGF) is based on range of clinical criteria and there are more than 10 definitions reported in the literature.


Despite shortfalls, in our study, DGF was defined as the need for dialysis at hospital time but without further need after discharge, since it still offers the most used standard, by which transplant centers pragmatically report outcomes and which furthermore makes a comparison of published studies especially on this topic possible.
Stefan Schneeberger (Reviewer 2): This is an interesting and well written report. The comparison between SPK in DMI and DMII and KTA in DMII is highly interesting and still debated controversially. Hence this report is a valuable contribution to the field. The content and data are well presented. The only shortcoming is the natural limitation resulting from a comparison between different patient groups with diverse demographics and different prioritization on the waiting list.

It is surprising to see the difference in the donor profile between SPK in DMI vs DMII. The authors could elaborate on the cause.

The comparison between the outcome of the KTx in SPK vs KTA alone is most likely impacted by the different organ quality. Further to this the time on the waiting list may impact on the results. This could be discussed in greater depth in the discussion. Also the limitation in the comparison between these groups should be emphasised in the discussion.

The assessment displayed the picture of the clinical reality. The one element most underrepresented in the discussion is the indirect effect of the longer waiting time and the inferior organ quality when listed for a KTx alone. The authors could focus their manuscript on this aspect. Ideally, an intention to treat analysis looking at the outcome starting on the initiation of dialysis could be added.

Well done!

Raised recommendations were incorporated into the manuscript respecting the editors concerns.