



September 26, 2018

Professor Maurizio Salvadori, MD

Editor-in-Chief, *World Journal of Transplantation*

Dear Professor Salvadori:

Re: Manuscript No: 40236

On behalf of my co-authors, I am pleased to submit revisions to the *World Journal of Transplantation* of the manuscript, titled "Solid Pancreas Transplantation: Pushing Forward". We believe the suggested changes in our revision have enhanced the quality of our submission.

We look forward to the remainder of the peer review process, and hope to see our work published in a future issue of the *World Journal of Transplantation*.

Sincerely,

A handwritten signature in black ink, appearing to read "E. Giorgakis", with a stylized flourish at the end.

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Comments from the Review:

All manuscript corrections have been highlighted in yellow within the main text.

1st reviewer

First of all, I would like to congratulate the authors for the initiative of putting together such a comprehensive review about pancreas transplantation. The paper is really well written. The currently shortage of donor organs leads to the need of acceptance of donor with extended criteria e.g. DCD and fatty organs. The authors have explored into this manuscript the hurdles with pancreas transplantation causing the need of increasing utilisation of these donors. The current limitations and potential benefits of their transplantation are deeply discussed. Thereafter, the authors detailed how other alternatives, such as centralization of retrieval teams, enhanced procurement surgical training and appropriate recipient selection could also contribute to the field impacting positively on patients' outcomes. I truly believe that it is a current relevant topic and the manuscript is going to add into the literature.

The authors appreciate the reviewer's comments and sincerely hope the quality of the paper has significantly improved after this revision.

However, I have some comments that I believe once addressed are going to improve the quality of the manuscript. Please find them below:

First section: Authors name should be revised to comply with the guidelines for manuscript preparation available on the publisher website (No period at the end of the middle name). Additionally, a core tip (no more than 100 words) should be included after the key words. For the correspondent author the complete name of the institution should be mentioned.

Authors' names have now been revised. A core tip has been added. Correspondent author institution has been included.

Abstract: The abstract would benefit from rewording. Abbreviations as DCD and UK are included without being previously explained. I would recommend just write it down without abbreviate it into the abstract. The phrase "pancreas procurements should be extended to DCDs and moderately obese donors" is a strong

statement for an abstract and should be softened. Also, a definition of what is a moderately obese donor is not provided or broadly understood, so better remove it (moderately term).

We appreciate the reviewer's comments. The abstract has now been modified accordingly.

Main text Background: According to the manuscript preparation publisher guideline no comma should be included on Arabic numerals (48000 and not 48,000).

Arabic numerals have now been corrected.

From the third paragraph it is not clear why we need to expand the donor acceptance. The authors describe a fall in the number of pancreas transplants in the US and then report recent improvements on outcomes. However, it lacks a clear sentence justifying why expand the pool of donor or why optimisation of pancreas allograft utilisation is needed. Better contextualisation of the necessity for those changes would make the point clearer for the readership.

We thank the reviewer for pointing this out. A paragraph justifying the need for expansion of donor pool has now been included.

On the first time an abbreviation is used its definition should come immediately before; and then authors should stick with the abbreviation (type 1 diabetes mellitus – T1DM) is repeated on the first paragraph of the “scope and types...” and on type 1 of pancreas transplantation. The abbreviation T2DM should be separated somehow from its meaning, e.g (as a surrogate marker of type 2 diabetes [T2DM]). On the first use BMI should be defined, also in definition 1 of type of pancreas transplantation.

Necessary changes have now been made in the use of abbreviations.

Definition 3 of pancreas transplantation says that PAK has “better survival rates compared with SPK recipients”, on the section outcomes the survival is lower (83% vs. 87%). These two sentences are contradictory and they need to be revised and corrected.

Necessary corrections have been made.

On the second paragraph of the outcomes section the abbreviation DDKT is used, however I could not find what it stands for.

The DDKT abbreviation has now been explained.

Donor pancreata section, on the current status paragraph, a reference from where all the data was extracted is missing and also it could be presented in a more direct way to make clearer to the reader the message that the authors want to transmit.

A reference has now been included.

Also, DCD would be better described as “donation after circulatory death”.

The abbreviation has been explained.

“Between 2003 to 2014” should be corrected to “Between 2003 and 2014”.

This has now been corrected.

On “Expanding the pancreatic donor pool” I missed a short paragraph justifying why we need to expand the donor pool.

We appreciate the reviewer’s comment. A paragraph justifying why we need to expand the donor pool has now been incorporated.

On the section “obese donors” a reference should be included in the first phrase.

A reference has now been included.

“Steatosis may result in microvesicular occlusion” is potentially “microvascular occlusion”, this should be corrected.

This has now been corrected.

At the phrase “Donor obesity is a surrogate indicator”, the definition of obesity should be included and therefore removed from the following phrase.

The respective adjustment has been made.

Some words as “Class I” and “mildly” obese are questionable and can be removed without affecting the content.

These words have now been erased.

Most importantly, authors discuss about donor obesity throughout the paragraph and at the end say, “appearances satisfy the accepting transplant surgeon”. I was wondering if you could explain further what those characteristics of the appearance of a steatotic pancreas are and how it correlates with a histological assessment.

This phrase has now been deleted.

What are the results of transplantation of a steatotic pancreas? Primary non-function? What are the risk to the recipient?

Interacinar pancreatic steatosis increases the risk of pancreatic allograft thrombosis i.e. primary non-function, and graft pancreatitis.

“DCD pancreatic donors” section, first phrase needs a reference.

A reference has now been included.

The discussion about injuries can be kept into the “organ damage” section.

We appreciate the reviewer’s comment. These comments have now been moved.

The phrase “Even though the use of DCD pancreatic allografts in the US is very low...” is repeating information already presented in the first paragraph of the section.

The phrase has now been deleted.

The phrase “DCD is associated with ischemia-reperfusion injury” should be reworded. Those organs are more vulnerable to ischemia-reperfusion injury or have an ischemic insult during organ procurement.

The phrase has now been reworded.

Moreover, only one study is described for DCD pancreas transplantation. Are there more studies to justify why the authors are advocating to expand the use of these donors? I truly believe that the inclusion of a table summarising clinical series of DCD and steatotic pancreas transplanted would be beneficial for the review. In this table limitations and differences between studies should be clear for the reader to understand differences in results.

More studies have been described for DCD pancreas transplantation. A table summarizing these series has now been included.

“discards due to organ damage” section, the phrase “There was no difference in overall graft survival between damaged and undamaged...” as arterial and parenchymal damage were associated. A direct order in the sentence would make the message easily understandable.

The phrase has now been revised.

“Organ recovery for islet transplantation” the abbreviation HbA1c should be followed by the definition on the first use.

Islet transplantation has now been excluded from this review.

Second paragraph, “steatotic pancreata are not suitable for whole organ transplantation”, to justify this sentence the section about obese donor should have explained what the problems with steatotic pancreas

transplantation are. Following this phrase, the authors advocate the use of fatty pancreata for islet transplantation. However, there is no reference from where this information came from. I was wondering if the authors are only speculating or if there is concrete evidence for that. This should be clarified.

Discussion over islet transplantation has now been eliminated from the manuscript. The risks associated with steatotic pancreata have been described earlier.

“Living donor segmental pancreas” section, final phrase of the first paragraph goes again against the statement on the definition of types of transplantation “PAK allograft survival is inferior to the SPKs”.

This has now been corrected.

Second paragraph definition of LDSPTs is missing. “Pancreas transplantation candidates” the first phrase of the first paragraph is too long. Could it be split? Also, please add reference to it.

This has now been revised.

Second paragraph, “Recent reports indicate that pancreas transplantation is safe and beneficial if performed on diabetics beyond the established pancreas transplant criteria” needs reference and if possible briefly summarises the criteria.

Necessary adjustments have been made.

“The T2DM phenotype” section, “Type I diabetic” and “hemoglobin A1c” should have already an abbreviation.

Abbreviations have been added.

Last paragraph it is not clear with each group the C-peptide negative and C-peptide positive are compared, this should be better described.

Paragraph has been revised to make the message clear.

The subheading “The overweight (BMI 25-30 kg/m2)...” the definitions of overweight and obese should be removed from here and added into the first citation into the text.

Necessary changes have been made.

“bariatric surgery” section, references should be added into the first paragraph, mainly first phrase.

References have now been included in the first paragraph.

Second paragraph, the phrase “Moreover, on a large scale SRTR analysis, Bedat et al. demonstrated...” is repeated and can be deleted.

The phrase has now been deleted.

The heading “The chronic pancreatitic” should be pancreatitis I believe, please change it.

This has now been corrected.

“Islet allotransplantation” section, the first phrase does not fully agree with the following of the paragraph. It could be better explained. Third paragraph the statement “those derived from obese donors, consist perfect substrate for islet isolation” is really strong, are the authors speculating? Suggesting it? Or is there literature to support it? If the former so please add a reference in here. “Encapsulation technologies” section, TheraCyte is produced by a company? So please mention company name, city, country. “Personalised medicine and stem cells” section, references should be included for the first and last phrase of the paragraph. At the second paragraph, how likely it is that encapsulation technologies are to advance? This should be clarified otherwise all the strategies that were advocated can be considered irrelevant.

Islet allotransplantation has now been omitted altogether from the study.

“Conclusions” sections is too long. Firstly I would suggest to change its title to discussion. Secondly there is not a single reference along the whole section, this needs to be addressed. Additionally, 3rd, 4th, 5th and 7th paragraphs repeat information that was previously described. They can be briefly summarised into few phrases to highlight the findings. A new paragraph should be included in here describing the limitations of the manuscript. First, it is a narrative review and not a systematic review. Therefore, it has a strong vulnerability to personal bias on selection of articles; and, databases are not searched in a pragmatic way. Second limitations of number of studies exploring the subject is likely to be a problem. The authors have not described many studies into each section (e.g. only one study exploring DCD pancreas transplantation). A table could summarise more articles without add more to the text. Furthermore, what are the barriers to implement all those suggestions? What could we do to overcome those hurdles? Finally, a brief real conclusion of one paragraph could be added to close the review.

We appreciate the reviewer’s comments on this section. The section’s title has now been revised and discussion has been shortened. A paragraph on the limitations of the study has been included. A total of three tables has now been incorporated.

Other comments: Acknowledgements sections should be provided after the abbreviations at the end of the manuscript or a statement made that there are no acknowledgements.

Acknowledgements have been included (none).

Overall, the use of headings and subheadings should be corrected. Some subheadings titles are not clear.

Headings and subheadings have been modified.

For all the references the citation within the text should be superscripted in squares brackets at the end of the sentence.

Reference citations have been reviewed and corrected.

The use of at al. within the text should be standardised, always include a period after al (et al.), citation at the end of the sentence.

The use of *et al.* has now been standardized.

Be careful with the use of abbreviations, as a general rule if it is used less than 3 times write it despite include a new abbreviation. Many abbreviations included were used few times (one or two). Please check it.

Abbreviations have been reviewed and corrected.

References should follow the format for reference guidelines. Now references are completely different between each other. The guideline provides guidance regarding the correct format for each reference. This should be changed.

Reference citations have been reviewed and corrected.

2nd reviewer

With great interest, I have read the manuscript entitled, “Pancreas transplant: Pushing forward”, by Giorgakis and colleagues. This is a review paper covering beta cell replacement therapy (both pancreas and islet transplants). As such, the title and the abstract should be modified.

We appreciate this reviewer’s comments. Beta cell replacement therapy with islet transplants has now been excluded from this study. The study has been modified to focus on solid pancreas transplantation only. The title has been adjusted accordingly.

There are several other issues that the authors should address in order to improve the manuscript. 1. For keywords, “islet pancreas transplantation” should be “islet transplantation”.

Islet transplantation has been excluded from the review.

2. On page 3, line 5 from bottom. “...from 2004 (to approximately 1,500) to 2014 (approximately 1,000) in 2014.” should be “...from 2004 (to approximately 1,500) to 2014 (approximately 1,000).”

This has now been changed.

3. “World Journal of Transplantation” is an international journal. When the authors describe something specific to the USA, they should indicate so. For example, on page 5, # 5 and #7, the authors are talking about current situation in the USA regarding islet autotransplant and islet allotransplant without specifically saying so.

Whenever there is a comment specifically related to the US territory, it is now specified into the text.

4. On page 7, section “Donor pancreata”, subsection “Current status”, there is disconnection between the first sentence (Presently ...) and the second sentence (As such, ...).

A connecting paragraph has now been incorporated.

5. There are numerous errors and inappropriateness in citation.

All citations have now been reviewed and corrected.

(1) Regarding DCD for pancreas transplant, the authors failed to cite the recent paper: “Outcomes From Pancreatic Transplantation in Donation After Cardiac Death: A Systematic Review and Meta-Analysis” Transplantation 2017;101:122-130.

We appreciate the reviewer for mentioning this interesting work which had not been published when the first draft of this manuscript was made. That systematic review has now been incorporated in the study.

(2) For type 2 DM patients, the study analyzed metabolic control after pancreas transplantation in type 1 versus type 2 diabetic patients over a 5-year time period is missing: “Long-term Metabolic Outcomes of Functioning Pancreas Transplants in Type 2 Diabetic Recipients” Transplantation 2017;101:1254-1260.

This study has now been included.

(3) On page 17, section “Islet allotransplantation”: the authors cite Ref#17 twice. Ref #17 is not relevant here. (4) On page 18, the authors state that DCD pancreatic islet donors have been used successfully in Netherlands (without citation) and the University of Pittsburgh (citing Ref # 66). Ref # 66 is describing only one case of islet transplantation using DCD. The authors should cite the following paper: “Clinical

islet isolation and transplantation outcomes with deceased cardiac death donors are similar to neurological determination of death donors” Transplant Int 2016; 29:34-40.

Islet allotransplantation section has been entirely deleted.

(5) Surprisingly, the authors cite 7 conference proceedings from Transplant Proc, which is not ideal as peer review process is questionable. There should be more appropriate full papers.

Transplantation Proceedings is an internationally recognized peer reviewed Journal representative of multiple affiliated transplant societies (specifically the American Society for Reconstructive Transplantation, Asian Transplantation Society, Andalusian Transplantation Society, Brazilian Transplantation Society, Belgian Transplantation Society, Catalan Transplantation Society, Chilean Transplantation Society, Hellenic Transplantation Society, Hungarian Transplantation Society, International Hand and Composite Tissue Allotransplantation Society, International Pancreas and Islet Transplant Association, International Society of Organ Donation and Procurement, International Society of Small Bowel Transplantation, Italian Transplantation Society, Japan/Korea Transplantation Society Forum, Latin America and the Caribbean Transplantation Society, Middle East Society for Organ Transplantation, Polish Transplantation Society, Portuguese Transplantation Society, Scandinavian Transplantation Society, Spanish Transplantation Society, Spanish Liver Transplantation Society, Turkish Transplantation Centers Coordination Association, Turkish Transplantation Society..). The cited papers have been written by established figures in the field (Sutherland *et. al*, Najarian *et. al*, Gruessner *et. al*, Chakkerla *et.al...*). The reviewer is kindly asked to elaborate on this comment.

(6) There are many other examples of error. The authors should thoroughly re-check all papers cited.

Thank you for pointing this out. All cited papers have been revised to ensure their accuracy and format.

6. On page 16, line 1 from top. “T1DM diabetics” should be “patients with T1DM”.

This has now been revised.

7. On page 16, line 3 from top. “type I” should be “type 1”.

This has now been revised.

Similarly, on page 13 type II should be type 2.

This has now been revised.

8. On page 16, section III. “The chronic pancreatitic” should be “The chronic pancreatitis”.

This has now been revised.

9. On page 19. “...islet transplantation is limited by the donor shortage...”. At least in North America, there are enough pancreas donors.

All discussion over islet transplantation has now been omitted, including this phrase. Even though the authors agree there are probably enough pancreas donors in the US territory, data indicate underutilization of all potentially transplantable pancreatic allografts, with resultant relative organ shortage.

10. Conclusions section is too long. One paragraph with several sentences would be appropriate.

Conclusions section has now been revised.

11. Entire section of “Encapsulation technologies can be deleted because information given is outdated.

This has now been deleted.

3rd reviewer

The authors have written a review article on pancreas transplantation. This reviewer has several comments: -In general there are many grammatical errors that should be fixed –

The text has now been reviewed by native American speakers to eliminate any grammatical errors.

It is unclear to this reviewer how the authors selected their references. For example, did the authors actually read the 1894 article from the British Medical Journal, or did they get this reference from a text book? Not many libraries keep journals dating back to 1894.

This is in reference to an interesting article by Williams PW, which the authors find of undoubted historical significance on diabetes and the first reported attempts of endocrine pancreas replacement. There is a multitude of monumental scientific manuscripts written at the beginning of the 19th or even by the end of the 18th century, which might be hard to track. The authors believe that this should not preclude the respective scientists from being honored with an appropriate reference on their pioneering work.

-There are many factual/reference errors. Here are some examples: 1. Page five, section 1: the BMI for type 2 DM is now 30, not 28.

We appreciate the comment. This has now been updated.

2. Page five, section 3: neither one of the two references states PAK survival being "better" than SPK. One reference state they have "similar" survival.

This has now been corrected.

3. Page eight: I believe the authors looked up the SRTR data from 2014, but there is no reference to that effect.

We appreciate the reviewer's comment. Appropriate citation has now been added.

4. Page nine: in the section regarding pancreatic discards, the authors reference SRTR data, but the reference inserted is a Dutch reference discussing the Netherlands experience.

This was actually a British paper commenting on pancreatic discards written by authors representing the UK (Guy's Hospital, London and Freeman Hospital, Newcastle) and Spain (Hospital Xeral, Vigo); not a Dutch paper ^[48]. The authors were commenting upon pancreatic discards based on the UK database and the 2014 SRTR data (Kandaswamy R *et. al*) ^[47]. Both author groups (Ausania *et. al* and Kandaswamy *et. al*) have been appropriately cited within the text.

There are many more examples. The authors should review their manuscript ensure accuracy.

The authors appreciate the reviewer's comments. The manuscript has now been reviewed and revised multiple times to ensure its accuracy.