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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 69200

Title: Impact of Immunosuppression on Incidence of Post-Transplant Diabetes Mellitus in Solid Organ Transplant Recipients: Systematic Review & Meta-analysis

Reviewer's code: 02726701
Position: Editorial Board
Academic degree: MD
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Reviewer's Country/Territory: Chile
Author's Country/Territory: Canada

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Comments on Relative Impact of Different Immunosuppressants on the Incidence of Post-Transplant Diabetes Mellitus across Solid Organ Transplant Recipients: Systematic Review and Meta-Analysis Introduction section The sentence "However, it is still associated with several complications including Post-Transplant Diabetes Mellitus (PTDM) in the post-transplant period" is confused, but understandable. Authors state that "PTDM is associated with increased cardiovascular risk, infection and graft failure". Please, add proper references. Not all PTDM cases can be explained by the immunosuppressive regimen. Maybe the main risk factor is steroid dose or the number of high steroid pulses and not the baseline immunossuppresive regimen itself. Please, add an explanatory comment. Is it important that the name NODAT was replaced by PTDM? Why? Both terms could describe the new appearance of diabetes after a solid organ implantation. Do authors recommend per protocol oral glucose tolerance tests to early diagnose PTDM? ADA 2021 criteria for diabetes states "A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assa (https://care.diabetesjournals.org/content/44/Supplement_1/S15). So, it could be that some of the PTDM diagnoses are misleading. Authors state "The pathophysiology is incompletely understood, both impaired insulin resistance and insulin secretion (destruction of pancreatic B-cells) have been implicated". The sentence is confused. If PTDM is associated to traditional risk factors, why is it necessary to search for more risk factors like the immunosuppressive treatment? Otherwise, do immunosuppressive add real risk over the traditional risk factors? The authors state: "PTDM has a significant impact on post-transplant outcomes. Various studies have reported decreased graft survival and an increase in cardiovascular, renal and infection complications". Please

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add proper references. Objective paragraph: Please replace cyclophosphamide by cyclosporine. A secondary objective could be to study the incremental risk of diabetes due to the immunosuppressive drugs over the classical baseline risk factors. Methods section Why the difference between the systematic literature review in February 2017 and he actual manuscript in June 2021? Is there new and significant new data in the meantime? For example, Lawendy et al found more relevant articles in a recent review in liver transplant recipients (https://doi.org/10.1111/ctr.14340). Sttistical analysis: Why the third time period is 5 or more years and not more than 3 years of follow-up? Why to exclude the 3-5 period after the transplantation? The following sentence is confused: "In this analysis, we only pooled data from cohort and randomized studies where pre-existing DM was known or studies where patients with pre-existing DM were excluded". Results section Population characteristics: Please add mean follow-up time of the solid organ recipients. Table 1: OK Figure 1: What is intending to represent with the red and black lines? It is not evident neither in the legend nor in the figure. The sentence: "Meta-analysis using the random-effects model was used to calculate the incidence of PTDM" this sentence belongs to Methods instead of the Results section. Please explain or clarify what is intending to compare with the red and black lines in the three graphs and between them as well. PTDM incidence numbers: Please, put the main result outside the 95% CI parenthesis. So, replace "(12.3%, 95% CI 10.6% - 14.3%, I2 = 95.4 %)" by "12.3% (95%...)" and the same in all analogous figures. Maybe, it would be easier to read if all these numbers could be contained in a single Table. NMA paragraph: Please, replace "oddz" by "odds". Subgroup analysis by organ transplanted. Please, replace "PTDM was 18.9" by "PTDM was 18.9%" Discussion section The variability in PTDM diagnosis also could be explained by different approaches to look for this complication. In authors' opinion and based in their own results. Which immunosuppressive drug choose for a patient waitlisted to receive a second solid organ

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transplantation that is older than 50 years, has high BMI and a family history of diabetes mellitus? Please, comment if some of the observed results could be related to different steroid tapering between all the articles reviewed in the meta- analysis and not to the main immunosuppressant drug used. Or if sirolimus receiving patients could have suffered more acute rejection episodes requiring high dose steroids in pulses as it was observed in the Elite-Symphony trial (DOI: 10.1056/NEJMoa067411). .