## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant Recipients with Type 2 Diabetes: A Systematic Review Protocol |
| **AUTHORS** | Shamshad, Farooq; Tungsanga, Somkanya; Senior, Peter; shojai, soroush; Ghimire, Anukul; Ye, Feng; Kung, Janice; Hariramani, Vinash K.; Abdulrahman, Abdullah; Penney, Matthew; Sultana, Naima; Muneer, Shezel; Okpechi, Ikechi; Bello, A K |

## VERSION 1 – REVIEW

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| **REVIEWER** | Cheungpasitporn, Wisit<br>Mayo Clinic College of Medicine, Nephrology and Hypertension |
| **REVIEW RETURNED** | 19-Aug-2023 |

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| **GENERAL COMMENTS** | This article outlines a protocol for a systematic review that will evaluate the effect of metformin use on graft and patient survival in kidney transplant recipients with type 2 diabetes (T2DM).<br>Metformin is commonly used as a first-line treatment for T2DM, but its benefits in kidney transplant patients are unclear. The rationale for this review is that metformin may provide cardiovascular benefits and aid in glycemic control in these patients, but there are concerns about safety with metformin use in the setting of impaired kidney function.<br>The methods follow the PRISMA-P guidelines. The review will search major databases for observational studies and randomized trials involving adult kidney transplant recipients with T2DM that report on graft or patient survival outcomes with metformin use. Study selection and data extraction will be done in duplicate. Risk of bias will be assessed using standard tools. If studies are sufficiently homogeneous, meta-analysis will be done to pool results across studies. Otherwise, a narrative synthesis will summarize the evidence. Subgroup and sensitivity analyses are also planned. Limitations include the exclusion of non-English studies and potential issues with heterogeneity and study quality.<br>This review aims to clarify the impact of metformin use on clinically important outcomes in kidney transplant patients with diabetes.<br>Limitations:<br>• The restriction to English language studies only can introduce language bias and lead to the omission of potentially relevant studies published in other languages.<br>• The inclusion of observational studies, which are more prone to confounding and bias compared to randomized trials, may impact the strength of evidence generated from this review.<br>• There appears to be no assessment planned for evaluating the quality of included studies. A quality assessment using a standardized tool would be important to interpret study findings appropriately. |

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| | • If the included studies are heterogeneous in terms of study design, patient populations, interventions, comparators, and reported outcomes, this can limit the ability to quantitatively synthesize the data and perform meta-analysis.<br>• Publication bias is a possibility if studies with significant or positive results are more likely to be published than those with non-significant or negative findings.<br>Areas for improvement:<br>• Include non-English language studies during the searches to reduce language bias.<br>• Consider doing a 'Risk of bias' assessment for individual studies using a standard tool like Cochrane RoB or ROBINS-I.<br>• Use the GRADE approach to assess the overall quality and strength of evidence across studies for each outcome.<br>• Have a detailed plan for investigating, quantifying, and dealing with heterogeneity if present prior to data analysis.<br>• Include a funnel plot and statistical tests to assess potential publication bias and small-study effects.<br>• Plan for appropriate subgroup and sensitivity analyses to assess the robustness of review findings and explore heterogeneity.<br>• Incorporate patient and public involvement during the conduct and dissemination of the review.<br>• Register the final systematic review manuscript with PROSPERO once completed<br>Suggestions on how the authors could improve the clarity and readability of this article:<br>Abstract:<br>• Include more specific details in the methods section of the abstract, such as the databases that will be searched, risk of bias assessment tools, and quantitative synthesis methods.<br>• Provide more context in the rationale section about the uncertainty surrounding metformin use and the knowledge gap this review aims to address.<br>Introduction:<br>• Expand on the current clinical equipoise and uncertainty about using metformin in kidney transplant recipients to highlight the need for this review.<br>• Provide more background details about the mechanisms of metformin and its purported benefits relevant to this population.<br>• Elaborate on the safety concerns with metformin in kidney impairment and how this has impacted its use and dosing recommendations post-transplant.<br>Methods:<br>• Explain the rationale for excluding non-English studies, children, dual organ transplants etc.<br>• Provide the full search strategies in supplementary files rather than just for one database.<br>• Give more details about the data extraction process - specific variables, tools used, handling discrepancies.<br>• Describe the planned presentation of results - tables, forest plots, figures etc.<br>Discussion:<br>• Highlight strengths of this review compared to previous studies or reviews on the topic.<br>• Discuss implications of expected findings on clinical practice and future research.<br>• Provide details about dissemination plans beyond just publications - conferences, guideline bodies, patient groups etc.<br>Overall:<br>• Define all abbreviations when first used. |

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| | • Use consistent terminology throughout for interventions, outcomes, transplant types.<br>• Use tables, figures and appendices to supplement clarity where helpful.<br>• Ensure correct reference formatting and in text-citations. |

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| **REVIEWER** | Raven, Lisa<br>St Vincent's Hospital Sydney, Department of Diabetes and Endocrinology |
| **REVIEW RETURNED** | 23-Dec-2023 |

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| **GENERAL COMMENTS** | Thank you for your work on this important issue. There is a lack of quality research on the management of diabetes after transplantation.<br>This will be a challenging systematic review as there are not a large number of studies; however, this should not stop the pursuit of research.<br>I raise a few issues below:<br>1. The preferred terminology is Post-transplant Diabetes Mellitus (PTDM) as per the 'Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions' which you reference in your manuscript (reference 8). Hence, NODAT should be replaced throughout.<br>2. It is confusing throughout the methods using the terminology "new-onset T2DM" after transplant, I suggest either using the terminology PTDM or categorising as the presence of diabetes in transplant recipients.<br>3. There are multiple references to 'no controlled studies' of diabetes treatments after transplant. I disagree with this statement. You have referenced some of the studies with DPP4 inhibitors, and there are studies with insulin (Hecking 2012, Schwaiger 2021), repaglinide (Turk 2006), SGLT2 inhibitors (Halden 2019, Hisadome 2021, Schwaiger 2018). It may be better to say that there are limited studies rather than no studies.<br>4. I would suggest including some review articles that are more recent than 2016 (e.g. reference 12) as the options of treatments available for diabetes have changed significantly with SGLT2 inhibitors and GLP-1 receptor agonists. At the very least the authors should read "Association of British Clinical Diabetologists and Renal Association guidelines on the detection and management of diabetes post solid organ transplantation" by Chowdhury et al, 2020.<br>5. The following sentence may benefit from change in tone regarding 'diabetic control': "It is also worth considering that patients with NODAT or those that had pre-existing diabetes prior to transplant will likely require insulin for diabetes control, given that their poor diabetic control necessitated a transplant." I would suggest reframing the point and highlighting that diabetes control may have contributed to diabetic nephropathy which may be an indication for transplantation.<br>6. The use of dashes throughout the manuscript is excessive and I suggest changing at least some to commas or not evening needing the pause in some cases.<br>7. In strengths and limitations, the first point needs to be elaborated "given its place in therapy" needs to be refined.<br>8. As this is an international journal it may be worth editing some of the comments about Canada specific factors (funding), they can still be included but could make a point that you are using Canada as an example and certainly newer agents are more expensive in |

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| | general. Meglitinides aren't necessarily available everywhere, and I am not sure that they are preferred due to their safety as mentioned in the text.<br>9. The first sentence in the discussion section does not make sense currently, I think it is missing a linking word.<br>10. It might be worth defining if there are any plans of other sources for the 'Additional records identified by other sources", such as through references of other texts, if this is planned. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Dr. Wisit Cheungpasitporn, Mayo Clinic College of Medicine

Comments to the Author:

This article outlines a protocol for a systematic review that will evaluate the effect of metformin use on graft and patient survival in kidney transplant recipients with type 2 diabetes (T2DM). Metformin is commonly used as a first-line treatment for T2DM, but its benefits in kidney transplant patients are unclear. The rationale for this review is that metformin may provide cardiovascular benefits and aid in glycemic control in these patients, but there are concerns about safety with metformin use in the setting of impaired kidney function.

The methods follow the PRISMA-P guidelines. The review will search major databases for observational studies and randomized trials involving adult kidney transplant recipients with T2DM that report on graft or patient survival outcomes with metformin use. Study selection and data extraction will be done in duplicate. Risk of bias will be assessed using standard tools. If studies are sufficiently homogeneous, meta-analysis will be done to pool results across studies. Otherwise, a narrative synthesis will summarize the evidence. Subgroup and sensitivity analyses are also planned. Limitations include the exclusion of non-English studies and potential issues with heterogeneity and study quality. This review aims to clarify the impact of metformin use on clinically important outcomes in kidney transplant patients with diabetes.

Response: Thank you.

Limitations:

• The restriction to English language studies only can introduce language bias and lead to the omission of potentially relevant studies published in other languages.

Response: This is certainly a valid concern. A language restriction can potentially lead to unintended exclusion of useful data. However, in our case, we believe that the data on the subject matter for our systematic review is limited. This was confirmed by our preliminary searches at the inception of this systematic review. This can be for many reasons, not limited to the recommendation to avoid metformin use in poor kidney function, which can be common for kidney transplant populations. As such, we are unlikely to capture additional data by expanding our language limit. This is further substantiated by Morrison et al. (2012), who found “no evidence of a systematic bias from the use of language restrictions in systematic review-based meta-analyses in conventional medicine.”

Nevertheless, we noted this as an important point and added to the “Strengths and Limitations” section as part of our limitations. Please see page 5, lines 1-2 of the protocol.

Reference: Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-144

• The inclusion of observational studies, which are more prone to confounding and bias compared to randomized trials, may impact the strength of evidence generated from this review.

Response: We agree with this statement and have acknowledged this in the “Strengths and Limitations” section of our final report (page 5, lines 3-4). As there is not a lot of preliminary data on the subject, we opted to keep a broad criterion with respect to the types of studies in order to capture a wide range of data.

• There appears to be no assessment planned for evaluating the quality of included studies. A quality assessment using a standardized tool would be important to interpret study findings appropriately.

Response: We will evaluate the quality of included studies via the assessment of a risk of bias. We will use standard tools such as ROB-2 and ROBINS-I to achieve this. Please refer to page 14 of our protocol, lines 10-21.

• If the included studies are heterogeneous in terms of study design, patient populations, interventions, comparators, and reported outcomes, this can limit the ability to quantitatively synthesize the data and perform meta-analysis.

Response: Thank you for this feedback. We agree that there may be a possibility that heterogenous characteristics of included studies may limit our ability to synthesize the data and perform a meta-analysis. We have now provided more details to address this under the “Data Synthesis” heading. Please see page 15, lines 20-23 and page 16, lines 1-6 of the protocol.

• Publication bias is a possibility if studies with significant or positive results are more likely to be published than those with non-significant or negative findings.

Response: Thank you for this comment. We acknowledge the possibility of publication bias and planned to handle this in the analysis by using a regression-based test and by examination of the resultant funnel plots. This has now been added for clarity on page 15, lines 1-2 of the protocol.

Areas for improvement:

• Include non-English language studies during the searches to reduce language bias.

Response: We have commented on this in this document under the “Limitations” section. There is limited data on the subject of our systematic review based on our preliminary searches, and removing the language restriction is unlikely to provide more data, as shown by Morrison et. al (2012)

Reference: Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-144

• Consider doing a 'Risk of bias' assessment for individual studies using a standard tool like Cochrane RoB or ROBINS-I.

Response: Thank you for this suggestion. As previously pointed out in the above sections, we will leverage standard frameworks, ROB-2 and ROBINS-I tools in our risk of bias assessment, as mentioned on page 14, lines 10-21.

• Use the GRADE approach to assess the overall quality and strength of evidence across studies for each outcome.

Response: We really appreciate this insightful suggestion. As there is a lack of randomized controlled trials in the field of study, and the much of the data for our study will be coming from small observational studies, the outcomes that we would assess using the GRADE approach would likely not garner sufficient strength to inform clinical decisions.

• Have a detailed plan for investigating, quantifying, and dealing with heterogeneity if present prior to data analysis.

Response: We also hope to address heterogeneity between studies in the following way, as mentioned on page 15, lines 16-18 of our protocol.

• Include a funnel plot and statistical tests to assess potential publication bias and small-study effects.

Response: Thank you for this comment. We will assess the possibility of any publication bias using a regression-based test and by visually inspecting funnel plots as previously pointed out. Please see page 15, lines 1-2 of our protocol.

• Plan for appropriate subgroup and sensitivity analyses to assess the robustness of review findings and explore heterogeneity.

Response: Thank you. We will perform subgroup analyses to ensure robustness of our findings, and this has now been made clearer on page 16, lines 8-11.

• Incorporate patient and public involvement during the conduct and dissemination of the review.

Response: Thank you for this thoughtful comment. We have added this information on page 16, lines 13-18 of the protocol. Overall, we will involve critical stakeholders (patients, physicians and other allied health professionals, researchers) for input in the design, conduct and reporting of this work. The authors of the study include the Director and some members of the Canada's largest stand-alone research facility dedicated to translating discovery science into health solutions for the prevention, treatment, and cure of diabetes: The Alberta Diabetes Institute. This creates a huge opportunity to disseminate our findings into practice. Further, our team is comprised of people with leadership roles in advocacy for diabetes and kidney care and development of care guidelines, such as Diabetes Canada, Canadians Seeking Solutions for Kidney Disease (C`anSOLVE CKD), Diabetes Action Canada, and several other international organizations supporting diabetes, kidney and transplant medicine. We will involve patients playing roles in these critical initiatives and programs to ensure their voice is well-represented in this work.

• Register the final systematic review manuscript with PROSPERO once completed

Response: This has been done, and added to the relevant section, page 9, lines 21-23 of the protocol.

Suggestions on how the authors could improve the clarity and readability of this article:

Abstract:
• Include more specific details in the methods section of the abstract, such as the databases that will be searched, risk of bias assessment tools, and quantitative synthesis methods.

Response: This has been done. We have added the necessary details about risk of bias assessment tools and our data synthesis methods. The databases that are to be searched are currently listed in the abstract as “MEDLINE, Embase, Cochrane Library, CINAHL, and Web of Science Core Collection.” This information is found on page 3, lines 15-26 of the protocol, under the “Methods” heading.

• Provide more context in the rationale section about the uncertainty surrounding metformin use and the knowledge gap this review aims to address.

Response: We have added greater detail in the “Introduction” section of abstract to provide greater context to the knowledge gap our review aims to address. Please see page 3, lines 7-11 of the protocol.

Introduction:
• Expand on the current clinical equipoise and uncertainty about using metformin in kidney transplant recipients to highlight the need for this review.

Response: Thank you for this comment. This has been done, please see page 6, lines 1-23 and page 7, lines 1-15.

• Provide more background details about the mechanisms of metformin and its purported benefits relevant to this population.

Response: This has been done, please see page 6, lines 5-10.

• Elaborate on the safety concerns with metformin in kidney impairment and how this has impacted its use and dosing recommendations post-transplant.

Response: This has been done, please see page 6, lines 22-23, and page 7, lines 1-15.

Methods:
• Explain the rationale for excluding non-English studies, children, dual organ transplants etc.

Response: Thank you for this comment. We have added brief explanations for this in our “Types of Studies” and “Study Population” sections. Please see page 10, lines 6-8 and lines 10-21.

• Provide the full search strategies in supplementary files rather than just for one database.

Response: This has been done. Please see supplementary table 1 listing the specific database on the left column, and the search strategy on the right column. We did this for each database to be searched for the study.

• Give more details about the data extraction process - specific variables, tools used, handling discrepancies.

Response: This has been done. Please see section “Data Items, Data Extraction, and Management” on page 13, lines 32-37 and page 14, lines 1-8.

• Describe the planned presentation of results - tables, forest plots, figures etc.

Response: This has been done, please see page 14, line 22, page 15, lines 20-21, and page 16, lines 4-6.

Discussion:
• Highlight strengths of this review compared to previous studies or reviews on the topic.

Response: Thank you for this comment. We have added additional details as suggested by the reviewer. Please see page 18, lines 12-23.

• Discuss implications of expected findings on clinical practice and future research.

Response: This has now been made clearer, please see page 18, lines 16-23.

• Provide details about dissemination plans beyond just publications - conferences, guideline bodies, patient groups etc.

Response: Thank you for this excellent advice. Please see previous response on the same issue on page 5 of this document. We have also updated our Ethics and Dissemination section. Please see pages 16, lines 20-23, and page 17, lines 1-2.

Overall:

• Define all abbreviations when first used.

Response: Thank you. We have now defined all abbreviations.

• Use consistent terminology throughout for interventions, outcomes, transplant types.

Response: Thank you, we have thoroughly proofread the protocol to ensure consistent terminology.

• Use tables, figures and appendices to supplement clarity where helpful.

Response: Thank you. We intend to add these as we develop our full report.

• Ensure correct reference formatting and in text-citations.

Response: Thank you. We have ensured consistent reference formatting and appropriate in text-citations.

Reviewer: 2
Dr. Lisa Raven, St Vincent's Hospital Sydney, Garvan Institute of Medical Research

Comments to the Author:
Thank you for your work on this important issue. There is a lack of quality research on the management of diabetes after transplantation.
This will be a challenging systematic review as there are not a large number of studies; however, this should not stop the pursuit of research.

Response: Thank you. We really appreciate the kind words and the wonderful feedback that you have provided to us.

I raise a few issues below:

1. The preferred terminology is Post-transplant Diabetes Mellitus (PTDM) as per the 'Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions' which you reference in your manuscript (reference 8). Hence, NODAT should be replaced throughout.

Response: Thank you. We have made amendments to the protocol to reflect this. We replaced NODAT with PTDM throughout the manuscript.

2. It is confusing throughout the methods using the terminology "new-onset T2DM" after transplant, I suggest either using the terminology PTDM or categorising as the presence of diabetes in transplant recipients.

Response: Thank you. We have made amendments to the protocol to reflect this. “New-onset T2DM” is now called PTDM throughout the manuscript.

3. There are multiple references to 'no controlled studies' of diabetes treatments after transplant. I disagree with this statement. You have referenced some of the studies with DPP4 inhibitors, and there are studies with insulin (Hecking 2012, Schwaiger 2021), repaglinide (Turk 2006), SGLT2 inhibitors (Halden 2019, Hisadome 2021, Schwaiger 2018). It may be better to say that there are limited studies rather than no studies.

Response: Thank you. We have edited our wording to state that there are a limited number of studies on the topic in our “Introduction” and “Discussion” sections. Please see page 7, line 6, 17; page 18, line 14.

4. I would suggest including some review articles that are more recent than 2016 (e.g. reference 12) as the options of treatments available for diabetes have changed significantly with SGLT2 inhibitors and GLP-1 receptor agonists. At the very least the authors should read "Association of British Clinical Diabetologists and Renal Association guidelines on the detection and management of diabetes post solid organ transplantation" by Chowdhury et al, 2020.

Response: Thank you. We found the article you suggested to be most helpful. We have added a brief discussion about new diabetic options (GLP1 agonists, SGLT-2 inhibitors) in the “Introduction” and referenced it appropriately. Please see page 7, lines 22-23 and page 8, lines 1-3.

5. The following sentence may benefit from change in tone regarding 'diabetic control': "It is also worth considering that patients with NODAT or those that had pre-existing diabetes prior to transplant will likely require insulin for diabetes control, given that their poor diabetic control necessitated a transplant." I would suggest reframing the point and highlighting that diabetes control may have contributed to diabetic nephropathy which may be an indication for transplantation.

Response: Thank you for this feedback. We acknowledge that the change in tone would be beneficial and have amended that sentence. Please see page 8, lines 17-20.

6. The use of dashes throughout the manuscript is excessive and I suggest changing at least some to commas or not evening needing the pause in some cases.

Response: Thank you. This has now been rectified as suggested.

7. In strengths and limitations, the first point needs to be elaborated "given its place in therapy" needs to be refined.

Response: Thank you. This has been done. Please see “Strengths and Limitations” section, page 4, lines 12-14.

8. As this is an international journal it may be worth editing some of the comments about Canada specific factors (funding), they can still be included but could make a point that you are using Canada as an example and certainly newer agents are more expensive in general. Meglitinides aren't necessarily available everywhere, and I am not sure that they are preferred due to their safety as mentioned in the text.

Response: Thank you. This has been rectified as suggested. Please see page 8, lines 10-11.

9. The first sentence in the discussion section does not make sense currently, I think it is missing a linking word.

Response: Thank you for this. This has been rectified, Please see page 17, line 5.

10. It might be worth defining if there are any plans of other sources for the 'Additional records identified by other sources'', such as through references of other texts, if this is planned.

Response: Thank you for this suggestion. We have defined this parameter under our “Methods” section. Please see page 12, lines 6-7.