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The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant Recipients with Type 2 Diabetes: A Systematic Review Protocol

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Title: The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant Recipients with Type 2 Diabetes: A Systematic Review Protocol

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Abstract

Introduction:

Metformin is a first line anti-hyperglycemic agent for Type 2 Diabetes (T2DM). In addition to glycemic control, it offers benefits related to cardiovascular health, weight neutrality, and metabolic syndrome. However, its benefits in kidney transplant recipients remain unclear. Hence, we seek to describe a protocol for a systematic review, which will assess the impact of metformin use on graft survival and mortality benefits in kidney transplant recipients.

Methods:

This protocol was guided by standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015). We will search empirical databases such as MEDLINE, Embase, Cochrane Library, CINAHL, and Web of Science Core Collection for relevant studies conducted in kidney transplant recipients using metformin, which report outcomes related to graft and patient survival. All studies meeting these criteria in adults - and published in English – from inception to 2023 will be included in our review.

Ethics and Dissemination:

Ethical approval will not be required for this review as the data used will be extracted from already published studies with publicly accessible data. As this study will assess the impact of metformin use on graft and patient survival in kidney transplant recipients, evidence gathered through it will be disseminated using traditional approaches that includes open-access peer-reviewed publication, scientific presentations, and a report. We will also disseminate our findings to appropriate academic bodies in charge of publishing guidelines related to T2DM and transplantation.

Article Summary:

Strengths and Limitations:

- The focus on metformin as an exposure allows us to capture a wide range of patients with diabetes, given its place in therapy.
- Utilizing multiple reviewers when screening abstracts and full texts will allow us to capture the most relevant studies.
- We will assess the quality of studies using a tool that incorporates assessments of risk of bias across core study domains: sampling, sampling technique and size, outcome measurement, response rate, and statistical reporting.
- The search strategy will include all relevant databases for peer-reviewed literature, hence ensuring a comprehensive analysis.
- A potential limitation of this study could be heterogeneity and number of studies of low quality which could affect pooled estimates and our ability to conduct a meta-analysis.

Introduction:

Metformin remains the first-line anti-hyperglycemic agent indicated for type 2 diabetes mellitus (T2DM) in the general population, as the UKPDS (United Kingdom Prospective Diabetes Study) Group demonstrated that metformin may decrease the risk of diabetes-related endpoints, especially in obese patients (1). In addition to glucose-lowering effects, metformin has also been touted to enhance insulin sensitivity, thereby conferring cardiovascular benefits by improving tissue plasminogen activator (tPA) activity, along with reduction in the activation of the endothelium (a necessary step for atherogenesis) (2). As such, the UKPDS study also demonstrated a reduction in myocardial infarctions in patients treated with metformin (2). Moreover, metformin also leads to a reduction in food intake, related to changes in leptin levels and insulin sensitivity (3). Hence, metformin is thought to have benefits related to metabolic syndrome, cardiovascular protection, while remaining largely weight neutral (2). As such, there is guideline-based consensus amongst experts to use metformin as a first line agent for T2DM, barring any contraindications. In kidney transplant recipients in whom cardiovascular mortality

is the leading cause of death (4), metformin appears to present itself as a reasonable cardioprotective option.

Nevertheless, there is some uncertainty surrounding the use of metformin – for new or pre-existing diabetes in kidney transplant recipients – given the lack of evidence regarding optimal regimens of anti-hyperglycemic agents in this population (5, 6). Diabetes Canada states that "there is not enough evidence to support specific recommendations regarding choice of antihyperglycemic therapy" for post-transplant diabetes mellitus. Manufacturers and guidelines also list poor kidney function (e.g., eGFR<30mls/min) as a barrier for its use (7). Furthermore, no controlled studies have been undertaken to elucidate optimal management for transplant recipients with pre-existing diabetes (8). Early after kidney transplantation, patients with pre-existing T2DM may often experience difficult to manage hyperglycemia, and those without pre-existing diabetes may develop New Onset Diabetes After Transplantation (NODAT), also called Post Transplant Diabetes Mellitus (PTDM). Peri-operative stress and diabetogenic effects of immunosuppressive medications (i.e., prednisone, calcineurin inhibitors and mTOR inhibitors), among other risk factors - such as coronary artery disease or smoking - can exacerbate the problem. Nevertheless, given the anti-hyperglycemic and cardioprotective effects of metformin,

it is important to ascertain the best management principles for the treatment of T2DM in this population.

Management of T2DM or hyperglycemia in the kidney transplant population may include insulin. Yet, there have not been any controlled head-to-head studies that have examined such treatment strategies for glycemic management after transplantation. Researchers have evaluated the use of dipeptidyl peptidase (DPP)-4 inhibitors in NODAT, and they have found them to be safe and beneficial with respect to lowering blood glucose levels in the short term, as well as mitigating weight gain (9, 10). Nevertheless, these studies included a very small number of participants, and did not study clinically relevant outcomes of graft survival or patient mortality.

Ideally, antihyperglycemic agents used to treat T2DM in a transplant population should preferably not promote weight gain, since steroid use and weight gain are important risk factors for post-transplant diabetes. Therefore, metformin appears to be a reasonable first-line agent, assuming well reserved kidney and liver function. GLP-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT2) are limited by high cost, and frequently require special authorization for coverage in Canada. In contrast, metformin presents itself as an economical option, covered through nearly all public and private plans. Furthermore, in immunosuppressed patients, the risks

of mycotic genitourinary infection with SGLT2 inhibitors may be increased, especially in kidney transplant recipients on immunosuppressive medications (11). Lastly, guidelines recommend that patients at increased risk for hypoglycemia (e.g., transplant recipients with impaired hepatic or kidney function) or pancreas transplant recipients with graft dysfunction avoid using insulin secretagogues agents. 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. In this context, the addition of metformin could serve to limit incremental insulin dosing and limit its adverse effects of hypoglycemia and weight gain.

Despite the noted advantages, the hesitation to use metformin for the kidney transplant population may stem from the tolerability or safety of metformin when used in conjunction with multiple medications indicated for post-transplant care (12). Furthermore, concerns regarding lactic acidosis with metformin when used in patients with impaired renal function (reflecting decreased ability to renally excrete drugs) have also been reported (13). As such, other classes of antihyperglycemics such as meglitinides can be preferred due to the perceived relative safety (12). Nevertheless, it is important to consider the role of metformin in type 2 diabetic kidney

transplant recipients. Metformin can provide cardiovascular benefits through mechanisms detailed earlier, which may help decrease death with graft function (DWGF) (14) - a significant cause of mortality in kidney transplant recipients (15).

Given the paucity of knowledge regarding metformin use in kidney transplant recipients, as well as the safety concerns with polypharmacy, we aim to conduct a systematic review of the literature on the use of metformin and its potential effect on graft and patient survival in kidney transplant recipients with T2DM.

Objective:

Given that multiple observational studies (8, 16) have shown promise with metformin use in kidney transplant recipients with T2DM, we aim to assess the effect of metformin on graft and patient survival in kidney transplant recipients with T2DM.

Methods and Analysis:

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) to develop this protocol (17). As recommended by the PRISMA-P guidelines, this review protocol is registered with PROSPERO International

Prospective Register of Systematic Reviews on June 28, 2023: registration number CRD42023421799. For protocol amendments, we will report the date, description of the change, and rationale in a tabular format. These changes will not be incorporated into the protocol.

Criteria for Considering Studies for Review

Types of Studies

We aim to include observational studies and randomized control trials (RCTs) that evaluated graft survival and mortality in kidney transplant recipients using metformin. We restricted the study to articles published in the English language only.

Study Population

We will include studies that have kidney transplant only recipients over the age of 18, regardless of sex and ethnicity. These transplants can be of any type (living donor, deceased donor) and of any duration. The participants in these studies must also have a diagnosis of type 2 diabetes (as defined in the published studies to be reviewed) either before or after the receipt of kidney transplantation.

Types of Intervention

The intervention of interest will be metformin – at any dose – for the treatment of pre-existing T2DM or new-onset T2DM in kidney transplant recipients. To be eligible, patients must be receiving treatment with metformin – at any defined daily dose – for any length of time. Metformin usage may be demonstrated by (but not limited to) a history of metformin fills, prescriptions rendered, pharmacy claims data, and hospital records. Studies must have also reported on at least one outcome measure to be included. Comparators may include no medication, lifestyle interventions, insulin, GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas, meglitinides, and thiazolidinediones. Where comparators are not included, we will report the outcomes of studies based on metformin alone.

Types of Outcome Measures

The primary outcomes will include graft survival (defined as survival time from the onset of kidney transplantation) and all-cause patient mortality. Secondary outcomes may include effects of metformin toxicity (e.g., abdominal pain, time to metformin discontinuation) that patients may experience while on metformin therapy, as defined by study authors. We aim to utilize the definitions for these parameters as they are defined in the selected published studies for review.

Methods

The medical librarian (JYK) will develop and execute comprehensive searches in Ovid MEDLINE, Ovid Embase, CINAHL, Cochrane Library (via Wiley), and Web of Science Core Collection, from inception to present. Both qualitative and quantitative studies will be sought, with no limitations on study types. Searches will be limited to English language. To capture all relevant literature pertaining to metformin use and associations with adverse health outcomes in patients after undergoing kidney transplantation, relevant keywords and controlled vocabulary will be carefully selected (Supplementary Table S1). Literature search results will be uploaded to Covidence (www.covidence.org), a web-based tool, which will be used for abstract and full text screening. The reporting of this systematic review will be guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.

Data Collection and Analysis

Study selection

We intend to use a two-stage collaborative process for screening and study selection. Firstly, two reviewers (FS & ST) will independently assess and evaluate the titles and abstracts of the retrieved studies to ensure that the population studied was kidney transplant recipients with pre-

existing or new onset T2DM. The selected articles will then be included for full-text review. In the second stage, reviewers will assess the full-text articles to ensure that metformin was used as an intervention, and that one of the primary outcomes of graft survival or patient mortality was reported. An independent third reviewer will be utilized as an arbitrator to evaluate studies in the event of a disagreement of the two reviewers. In such cases, the final decision to select a study will then lie with the independent reviewer. We will also include reasons for exclusion of studies, and will exclude any studies that do not utilize metformin as an intervention. Figure 1 outlines the criteria of study selection (see Appendix).

Inclusion Criteria

- Studies conducted in kidney transplant recipients (deceased or living donor) with pre-existing or new-onset T2DM (NODAT)
- Studies using any metformin use as the intervention
- Studies reporting any primary outcome of graft survival or patient mortality
- Any study design (except exclusions listed below)
- From inception through to 2023 when the search will be conducted
- Languages limited to English
- Patients ≥ 18 years old

Exclusion Criteria

- Studies in which specific outcome of interest cannot be identified or extrapolated
- Age <18 years old
- Dual organ transplants (example, pancreas and kidney transplant, liver and kidney transplant, etc.)
- Patients with a clear diagnosis of type 1 diabetes (T1DM)
- Re-transplants of the kidney (receipt of transplant on more than one occasion)
- Case reports, case series, reviews, letters to the editor, editorials
- Articles with multiple publications (those with the largest samples will be included)
- No metformin as an intervention

Data Items, Data Extraction and Management

The two reviewers (FS and ST) will be responsible for independent extraction of data, using a standard data extraction sheet on Microsoft Excel. This sheet will include the details of the selected studies. The data collected will include study type (e.g., cohort, case-control, RCTs), study characteristics (e.g., country of publication, publication year), trial size, patient characteristics (age, gender) transplant types (e.g., living donor, deceased donor), onset of diabetes (e.g., new-onset post transplantation or pre-existing T2DM), types of interventions

utilized (e.g., metformin, insulin, other oral antihyperglycemics, lifestyle interventions), relevant parameters for subgroup analysis as outlined in this protocol (e.g., blood pressure readings, statin use) adverse effects experienced, duration of interventions, duration of follow-up, outcomes (graft survival, patient mortality) and conclusions. When multiple outcome times are reported, the longer outcome time will be extracted. Reviewers will resolve any conflicts in data extraction by discussion. The independent reviewer will be responsible for the adjudication of any unresolved conflicts. The quality of the evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation working group methodology.

Assessment of Risk of Bias in Included Studies

For the assessment of the risk of bias, we will employ the Cochrane Risk of Bias Tool 2 (ROB-2) (18) for RCTs and the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) for non-randomized studies (19). The ROB-2 uses signalling questions to assess 5 domains, which include risk of bias arising from randomization, risk of bias arising from deviations from intended interventions, missing outcome data, risk of bias in measurement of outcomes, and risk of bias in selection of the reported results. This helps elicit an overall risk of bias judgment for an RCT-type study.

The ROBINS-I preliminarily urges to consider confounding domains and co-interventions that could be within a study, and then proceeds to evaluate the study across 7 domains: bias due to confounding, bias due to participant selection, bias in classification of interventions, bias due to deviations from intended interventions, bias from missing data, bias in measurement outcomes, and bias in selection of the reported result.

We will also present the overall risk of bias per study in a summary table. If there is insufficient information to assess bias, we will assign it as 'unclear'. Finally, we will assess the possibility of any publication bias using a regression-based test and by visually inspecting funnel plots.

Measures of Treatment Effect

We will present dichotomous outcomes as risk ratios, and continuous outcomes as mean differences (MD) between the intervention and control groups. If any continuous outcomes have been measured in different ways across studies, we will utilize standardized MD between the intervention and controlled groups. Finally, we will present the intervention effect of any time-

to-event outcomes as hazard ratios. The 95% confidence intervals for all outcomes will be reported.

Dealing with Missing Data

When we encounter missing or unclear data, we will attempt to contact the authors of the relevant study to seek data or clarify information. Further, attempts will be made to calculate any required parameters from the given data, as necessary and appropriate. All missing data will be reported in our data extraction sheet and the risk of bias assessments.

Assessment of Heterogeneity

We will assess heterogeneity between studies with respect to participant characteristics, intervention types, duration of intervention, donor types, and outcomes. We will test statistical heterogeneity using the χ^2 test and estimate the amount of heterogeneity using the I^2 value.

Data Synthesis

The data and study characteristics will be summarized in a table, and we will determine if a meta-analysis can be performed by clinical and methodological heterogeneity. Statistical heterogeneity will be quantified using I^2 statistics in each analysis (20). If the amount of heterogeneity is deemed acceptable (I^2<50%), we will perform a meta-analysis to summarize

pooled results using a random effects model (21). If the study characteristics display excessive heterogeneity (I^2>50%), then we will report the data descriptively, and we will provide a narrative synthesis of included studies using the Synthesis Without Meta-Analysis Reporting Guideline as a framework (22). If quantitative synthesis of data is not possible, we will present a narrative synthesis in a table format to summarize the findings of the appropriate studies.

Subgroup Analysis

Subgroup analysis will be performed for the following parameters: study duration, donor type (living vs. deceased), NODAT, pre-existing T2DM, blood pressure, blood glucose, statin use, steroid use, metformin alone, metformin with other oral antihyperglycemics, and metformin with insulin.

Patient and Public Involvement

As this is a retrospective study of existing data, there is no public or patient involvement in this study.

Ethics and Dissemination

Ethics approval will not be required for this study, as it is entirely based on pre-existing data from published studies. Our dissemination strategy will consist of peer reviewed publications, presentations, and a report.

Discussion

Currently, there are no clinical care recommendations based upon controlled studies on the approach anti-hyperglycemic medication management in kidney transplant recipients with T2DM (8). As mentioned, patients who have pre-existing T2DM prior to their transplant, or those who develop it after their transplant face numerous challenges. Transplant recipients are predisposed to developing diabetes due to various risk factors such as post-operative stress, use of corticosteroids, and use of calcineurin inhibitors (23). Presently, the guidelines do not favour one pharmacological therapy over another in the setting of T2DM following kidney transplantation (24). Although some studies have shown promise regarding a glucose lowering effect, they have been limited by sample size, and did not study clinically relevant outcomes such as graft rejection or mortality (9, 10).

Ideally, the choice of therapy in T2DM affecting kidney transplant recipients should focus on: (1) minimizing adverse effects of medications related to graft function, (2) maintaining

adequate glycemic control, and (3) demonstrating a cardiovascular or overall mortality benefit. DPP-4 inhibitors and GLP-1 agonists show promise with a glucose lowering effect in this population (9, 10, 25), but they have not been studied for a mortality benefit. In addition, their costs also remain prohibitive in the context of the Canadian drug landscape (26). Furthermore, other option such as sulfonylureas may not be appropriate due to the risks of hypoglycemia and weight gain. Insulin therapies also induce hypoglycemia and weight gain, as well as requiring subcutaneous injections that may be inconvenient for patients. As such, metformin may be a favourable option in this setting. Metformin has been used for treatment of patients with T2DM patients in various settings, owing to its effectiveness and other metabolic and cardiovascular benefits. However, due to purported concerns about lactic acidosis, especially in patients with reduced kidney function, there is apprehension surrounding its use in kidney transplant recipients. We aim to evaluate the effects of metformin in kidney transplant recipients with T2DM – who are likely to be on advanced antihyperglycemic regiments - by conducting thorough subgroup analyses, which includes appraising the effects of metformin alone, metformin with other oral antihyperglycemics and metformin with insulin. In addition, parameters that are relevant to consider accounting for graft failure from cardiovascular causes

(e.g., blood pressure, steroid use, blood glucose), which may be responsible for the majority of kidney transplant failures, will also be considered in our subgroup analysis in order to separate the effects of metformin use.

Overall, this work will aim to provide much needed information on the effects of metformin use in kidney transplants recipients and determine its place in the pharmacologic management of kidney transplant recipients with T2DM. This would be invaluable for such patients and clinicians, no matter the outcome. If metformin is beneficial, it will serve as an inexpensive option for clinicians to consider for their patients. In addition, its other benefits – such as weight loss, minimal hypoglycemia – could also be leveraged in its favour. On the other hand, if we find it to be detrimental in kidney transplant recipients, clinicians may need to pursue other treatment options, as it is currently often prescribed for patients with T2DM.

Author contributions: FS and AKB conceived the idea of the study. FS drafted the protocol manuscript. AKB serves as the guarantor and supervisor of the research. All authors contributed to the development of the protocol. FY, ST, IGK, AKB advised on the risk of bias assessment strategy and data extraction criteria. JYK developed the search strategy. FY provided statistical expertise. PS and SS provided expertise on metformin pharmacology, study design, and transplant medicine. All authors read, provided feedback, and approved the final manuscript. AKB is the guarantor of the study and quality assurance for the data and its analysis.

Guarantor of Review:

Aminu K. Bello

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None

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Not required

Data sharing statement:

We will make data available on request.

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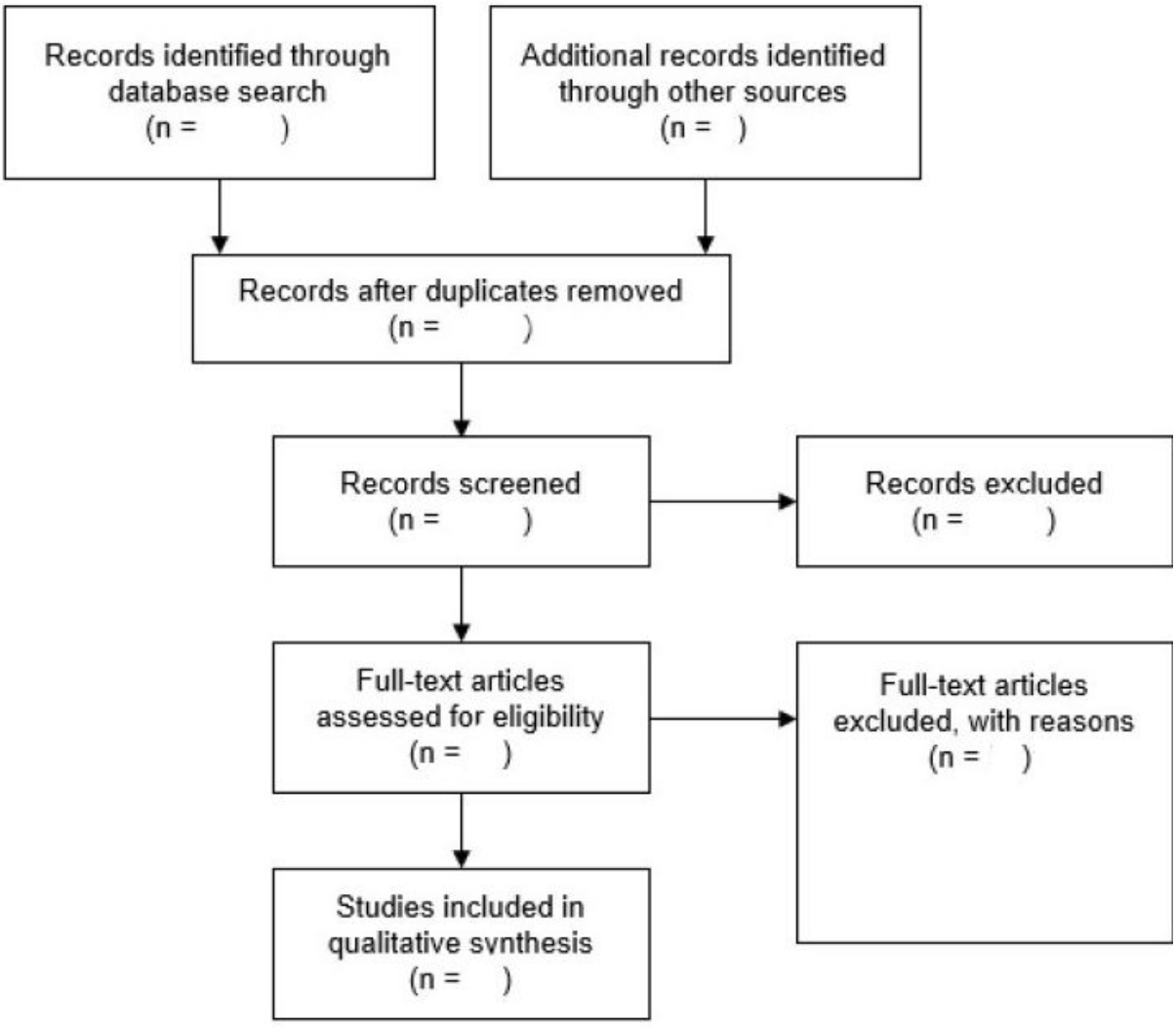
Supplementary Table S1: Search Strategies to be used for study identification and selection

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to April 14, 2023	1. (kidney adj3 transplant*).mp. 2. (renal adj3 transplant*).mp. 3. exp Kidney Transplantation/ 4. ((kidney or renal) and (graft* or allograft*)).mp. 5. exp Organ Transplantation/ and exp Diabetes Mellitus, Type 2/ 6. (diabetes and (post-transplant* or posttransplant* or (after adj2 transplant*))).mp. 7. or/1-6 8. metformin.mp. 9. (dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance).mp. 10. 8 or 9 11. 7 and 10 12. limit 11 to english language
Embase **Ovid Embase** 1974 to 2023 April 14	1. (kidney adj3 transplant*).mp. 2. (renal adj3 transplant*).mp. 3. exp kidney transplantation/ 4. ((kidney or renal) and (graft* or allograft*)).mp. 5. exp organ transplantation/ and exp non insulin dependent diabetes mellitus/ 6. (diabetes and (post-transplant* or posttransplant* or (after adj2 transplant*))).mp. 7. or/1-6 8. metformin.mp. 9. (dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance).mp. 10. 8 or 9

	11. 7 and 10 12. limit 11 to english language
CINAHL	S1 kidney N3 transplant* S2 renal N3 transplant* S3 (MH "Kidney Transplantation+") S4 (kidney or renal) and (graft* or allograft*) S5 (MH "Organ Transplantation+") S6 (MH "Diabetes Mellitus, Type 2") S7 S5 AND S6 S8 diabetes and (post-transplant* or posttransplant* or (after N2 transplant*)) S9 S1 OR S2 OR S3 OR S4 OR S7 OR S8 S10 metformin S11 dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance S12 S10 OR S11 S13 S9 AND S12 Limiter: English language
Cochrane Library via Wiley	#1 kidney NEAR/3 transplant* #2 renal NEAR/3 transplant* #3 [mh "Kidney Transplantation"] #4 ((kidney or renal) and (graft* or allograft*)) #5 [mh "Organ Transplantation"] and [mh "Diabetes Mellitus, Type 2"] #6 diabetes and (post-transplant* or posttransplant* or (after NEAR/2 transplant*)) #7 {OR #1-#6} #8 metformin #9 dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance #10 #8 AND #9

	#11 #7 AND #10
Web of Science Core Collection	TS=((kidney NEAR/3 transplant*) or (renal NEAR/3 transplant*) or ((kidney or renal) and (graft* or allograft*)) or (diabetes and (post-transplant* or posttransplant* or (after NEAR/2 transplant*)))) AND TS=(metformin or dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance) Languages: English
Google Scholar	(kidney transplant OR renal transplant OR kidney graft OR renal allograft) AND (metformin OR dimethylbiguanidine OR dimethylbiguanidium OR dimethylguanylguanidine OR glucophage OR glucovance)

Figure 1: PRISMA Flowchart



Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1, 2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	7
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	7
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	20-21
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant Recipients with Type 2 Diabetes: A Systematic Review Protocol

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Title: The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant Recipients with Type 2 Diabetes: A Systematic Review Protocol

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Keywords: Metformin; Kidney Transplantation; Diabetes Mellitus, Type 2; Organ Transplantation

Abstract

Introduction:

Metformin is a first line anti-hyperglycemic- agent for Type 2 Diabetes (T2DM). In addition to glycemic control, it offers benefits related to cardiovascular health, weight neutrality, and metabolic syndrome. However, its benefits in kidney transplant recipients remain unclear as metformin use is controversial in this population due to a lack of evidence and there are recommendations against its use in patients with poor kidney function. Hence, we seek to describe a protocol for a systematic review, which will assess the impact of metformin use on graft survival and mortality in kidney transplant recipients.

Methods:

This protocol was guided by standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015). We will search empirical databases such as MEDLINE, Embase, Cochrane Library, CINAHL, and Web of Science Core Collection for relevant studies conducted in kidney transplant recipients using metformin, which report outcomes related to graft and patient survival. All studies meeting these criteria in adults and published in English from inception to 2023 will be included in our review. We will employ the Cochrane Risk of Bias Tool 2 (ROB-2) for randomized-controlled trials (RCTs) and the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) for non-randomized studies. We will present our data and study characteristics in a table format and determine if a meta-analysis can be performed by clinical and methodological heterogeneity, using the I^2 statistics. If a meta-

analysis cannot be performed, we will provide a narrative synthesis of included studies using the Synthesis Without Meta-Analysis Reporting Guideline.

Ethics and Dissemination:

Ethical approval will not be required for this review as the data used will be extracted from already published studies with publicly accessible data. As this study will assess the impact of metformin use on graft and patient survival in kidney transplant recipients, evidence gathered through it will be disseminated using traditional approaches that includes open-access peer-reviewed publication, scientific presentations, and a report. We will also disseminate our findings to appropriate academic bodies in charge of publishing guidelines related to T2DM and transplantation, as well as patient and research centered groups.

Article Summary:

Strengths and Limitations:

- The focus on metformin as an exposure allows us to capture a wide range of patients with diabetes, as it is commonly prescribed as a 1st-line agent or as an adjunct with other therapy.
- Utilizing multiple reviewers when screening abstracts and full texts will allow us to capture the most relevant studies.
- We will assess the quality of studies using a tool that incorporates assessments of risk of bias across core study domains: sampling, sampling technique and size, outcome measurement, response rate, and statistical reporting.

- This study could potentially be subject to language bias, as we excluded any non-English studies.
- The inclusion of observational studies may impact the strength of evidence generated from this review.

Introduction:

Metformin remains the first-line anti-hyperglycemic agent indicated for type 2 diabetes mellitus (T2DM) in the general population, as the UKPDS (United Kingdom Prospective Diabetes Study) Group demonstrated that metformin may decrease the risk of diabetes-related endpoints, especially in obese patients (1). The primary action of metformin appears to involve the inhibition of the mitochondrial respiratory chain necessary to generate ATP for gluconeogenesis (2). In the gut, metformin is purported to increase anaerobic glucose metabolism in enterocytes, resulting in reduced glucose uptake (2). Further, it also causes glucagon-like peptide 1 (GLP-1) release, an incretin that enhances the release of endogenous insulin in a glucose-dependent manner, leading to a reduction in plasma glucose levels (2). In addition to glucose-lowering effects, metformin has also been touted to enhance insulin sensitivity, thereby conferring cardiovascular benefits by improving tissue plasminogen activator (tPA) activity, along with reduction in the activation of the endothelium (a necessary step for

atherogenesis) (3). The UKPDS study also demonstrated a reduction in myocardial infarctions in patients treated with metformin (3). Moreover, metformin also leads to a reduction in food intake, related to changes in leptin levels and insulin sensitivity (4). Hence, metformin is thought to have benefits related to metabolic syndrome, cardiovascular protection, while remaining largely weight neutral (3). As such, there is guideline-based consensus amongst experts to use metformin as a first line agent for T2DM, barring any contraindications. In kidney transplant recipients in whom cardiovascular mortality is the leading cause of death (5), metformin appears to present itself as a reasonable cardioprotective option.

Nevertheless, there is some uncertainty surrounding the use of metformin – for new or pre-existing diabetes in kidney transplant recipients – given the lack of evidence regarding optimal regimens of anti-hyperglycemic agents in this population (6, 7). Diabetes Canada states that "there is not enough evidence to support specific recommendations regarding choice of antihyperglycemic therapy" for post-transplant diabetes mellitus. Manufacturers and guidelines also list poor kidney function (e.g., eGFR<30mls/min) as a barrier for its use (8). This stems from the concern of lactic acidosis, which arose partly due to case reports of metformin-associated lactic acidosis in patients with CKD (8). Furthermore, there are limited controlled

studies have been undertaken to elucidate optimal management for transplant recipients with pre-existing diabetes (9). Early after kidney transplantation, patients with pre-existing T2DM may often experience difficult to manage hyperglycemia, and those without pre-existing diabetes may develop New Onset Diabetes After Transplantation (NODAT), also called Post Transplant Diabetes Mellitus (PTDM). Peri-operative stress and diabetogenic effects of immunosuppressive medications (i.e., prednisone, calcineurin inhibitors and mTOR inhibitors), among other risk factors, such as coronary artery disease or smoking, can exacerbate the problem. Nevertheless, given the anti-hyperglycemic and cardioprotective effects of metformin, it is important to ascertain its place in therapy for the treatment of T2DM in this population.

Management of T2DM or hyperglycemia in the kidney transplant population may include insulin. Yet, there have been limited head-to-head studies that have examined such treatment strategies for glycemic management after transplantation. Researchers have evaluated the use of dipeptidyl peptidase (DPP)-4 inhibitors in PTDM, and they have found them to be safe and beneficial with respect to lowering blood glucose levels in the short term, as well as mitigating weight gain (10, 11). Nevertheless, these studies included a very small number of participants, and did not study clinically relevant outcomes of graft survival or patient mortality. Furthermore,

newer agents such as GLP-1 agonists and SGLT-2 inhibitors also have limited evidence in PTDM. For instance, a small placebo-controlled study showed a small reduction of 0.2% in HbA1C with no difference in adverse events (12). Another study involving dulaglutide showed no improvement in glycemic control (12).

Ideally, antihyperglycemic agents used to treat T2DM in a transplant population should preferably not promote weight gain, nor increase the risk of metabolic syndrome and cardiovascular disease. In addition to this, corticosteroid use as part of post-transplant management is an important risk factor to consider, as it can lead to hyperglycemia and worsen or cause PTDM. Therefore, metformin, which appears protective against the aforementioned risk factors, appears to be a reasonable first-line agent assuming well reserved kidney and liver function. GLP-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT2) are limited by high cost, and may require special authorization for coverage, as is the case in Canada. In contrast, metformin presents itself as an economical option, covered through nearly all public and private plans. Furthermore, in immunosuppressed patients, the risks of mycotic genitourinary infection with SGLT2 inhibitors may be increased, especially in kidney transplant recipients on immunosuppressive medications (13). Lastly, guidelines recommend that patients at increased

risk for hypoglycemia (e.g., transplant recipients with impaired hepatic or kidney function) or pancreas transplant recipients with graft dysfunction avoid using insulin secretagogues agents. It is also worth considering that patients with PTDM or those that had pre-existing diabetes prior to transplant will likely require insulin for diabetes control, given that their diabetic control eventually led to diabetic nephropathy, which necessitated a transplant. In this context, the addition of metformin could serve to limit incremental insulin dosing and limit its adverse effects of hypoglycemia and weight gain.

Despite the noted advantages, the hesitation to use metformin for the kidney transplant population may stem from the tolerability or safety of metformin when used in conjunction with multiple medications indicated for post-transplant care (14). Furthermore, concerns regarding lactic acidosis with metformin when used in patients with impaired renal function (reflecting decreased ability to renally excrete drugs have also been reported (15). As such, other classes of antihyperglycemics such as meglitinides can be used due to the perceived relative safety (14). Nevertheless, it is important to consider the role of metformin in type 2 diabetic kidney transplant recipients. Metformin can provide cardiovascular benefits through mechanisms

detailed earlier, which may help decrease death with graft function (DWGF) (16) - a significant cause of mortality in kidney transplant recipients (17).

Given the paucity of knowledge regarding metformin use in kidney transplant recipients, as well as the safety concerns with polypharmacy, we aim to conduct a systematic review of the literature on the use of metformin and its potential effect on graft and patient survival in kidney transplant recipients with T2DM.

Objective:

Given that multiple observational studies (9, 18) have shown promise with metformin use in kidney transplant recipients with T2DM, we aim to assess the effect of metformin on graft and patient survival in kidney transplant recipients with T2DM.

Methods and Analysis:

This protocol was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) (19). As recommended by the PRISMA-P guidelines, this review protocol is registered with PROSPERO International Prospective Register of Systematic Reviews on June 28, 2023: registration number CRD42023421799. For protocol

amendments, we will report the date, description of the change, and rationale in a tabular format. These changes will not be incorporated into the protocol.

Criteria for Considering Studies for Review

Types of Studies

We aim to include observational studies and randomized control trials (RCTs) that evaluated graft survival and mortality in kidney transplant recipients using metformin. We restricted the study to articles published in the English language only, as our preliminary research on the topic revealed a paucity of studies regardless of the language.

Study Population

We will include studies that have kidney transplant only recipients over the age of 18, regardless of sex and ethnicity. We excluded children and adolescents from our study, as we intended to focus solely on the adult population. Pediatric patients may have distinct physiological and pharmacokinetic characteristics compared to adults. By focusing on adult populations, the review aims to provide more relevant and specific findings for the target population of adult kidney transplant recipients. The kidney transplants can be of any type (living donor, deceased donor) and of any duration. We excluded any dual organ transplants as

limiting the scope to kidney transplantation allows for a more focused and specific analysis of the effects of metformin in this context. Dual organ transplants involve additional complexities and variations in patient outcomes, which could introduce heterogeneity into the review. To maintain clarity and specificity, the decision was made to concentrate solely on kidney transplant recipients. Finally, the participants in these studies must also have a diagnosis of type 2 diabetes (as defined in the published studies to be reviewed) either before or after the receipt of kidney transplantation.

Types of Intervention

The intervention of interest will be metformin, at any dose, for the treatment of pre-existing T2DM or PTDM in kidney transplant recipients. To be eligible, patients must be receiving treatment with metformin at any defined daily dose for any length of time. Metformin usage may be demonstrated by (but not limited to) a history of metformin fills, prescriptions rendered, pharmacy claims data, and hospital records. Studies must have also reported on at least one outcome measure to be included. Comparators may include no medication, lifestyle interventions, insulin, GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas,

meglitinides, and thiazolidinediones. Where comparators are not included, we will report the outcomes of studies based on metformin alone.

Types of Outcome Measures

The primary outcomes will include graft survival (defined as survival time from the onset of kidney transplantation) and all-cause patient mortality. Secondary outcomes may include effects of metformin toxicity (e.g., abdominal pain, time to metformin discontinuation) that patients may experience while on metformin therapy, as defined by study authors. We aim to utilize the definitions for these parameters as they are defined in the selected published studies for review.

Methods

The medical librarian (JYK) will develop and execute comprehensive searches in Ovid MEDLINE, Ovid Embase, CINAHL, Cochrane Library (via Wiley), and Web of Science Core Collection, from inception to present. Both qualitative and quantitative studies will be sought, with no limitations on study types. Searches will be limited to English language. To capture all relevant literature pertaining to metformin use and associations with adverse health outcomes in patients after undergoing kidney transplantation, relevant keywords and controlled vocabulary

will be carefully selected (Supplementary Table S1). Literature search results will be uploaded to Covidence (www.covidence.org), a web-based tool, which will be used for abstract and full text screening. The reporting of this systematic review will be guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. Studies or records identified by other sources, such as through references of other texts, will not be under consideration for review. The planned start date for the study is April 1, 2023, and the planned end date is August 31, 2024.

Data Collection and Analysis

Study selection

We intend to use a two-stage collaborative process for screening and study selection. Firstly, two reviewers (FS & ST) will independently assess and evaluate the titles and abstracts of the retrieved studies to ensure that the population studied was kidney transplant recipients with pre-existing or PTDM. The selected articles will then be included for full-text review. In the second stage, reviewers will assess the full-text articles to ensure that metformin was used as an intervention, and that one of the primary outcomes of graft survival or patient mortality was reported. An independent third reviewer will be utilized as an arbitrator to evaluate studies in the

event of a disagreement of the two reviewers. In such cases, the final decision to select a study will then lie with the independent reviewer. We will also include reasons for exclusion of studies and will exclude any studies that do not utilize metformin as an intervention. Supplementary Figure 1 outlines the criteria of study selection (see Appendix).

Inclusion Criteria

- Studies conducted in kidney transplant recipients (deceased or living donor) with pre-existing diabetes or PTDM
- Studies using any metformin use as the intervention
- Studies reporting any primary outcome of graft survival or patient mortality
- Any study design (except exclusions listed below)
- From inception through to 2023 when the search will be conducted
- Languages limited to English
- Patients ≥ 18 years old

Exclusion Criteria

- Studies in which specific outcome of interest cannot be identified or extrapolated
- Age <18 years old

- Dual organ transplants (example, pancreas and kidney transplant, liver and kidney transplant, etc.)
- Patients with a clear diagnosis of type 1 diabetes (T1DM)
- Re-transplants of the kidney (receipt of transplant on more than one occasion)
- Case reports, case series, reviews, letters to the editor, editorials
- Articles with multiple publications (those with the largest samples will be included)
- No metformin as an intervention

Data Items, Data Extraction and Management

The two reviewers (FS and ST) will be responsible for independent extraction of data, using a standard data extraction sheet on Microsoft Excel. This sheet will include the details of the selected studies. The data collected will include study type (e.g., cohort, case-control, RCTs), study characteristics (e.g., country of publication, publication year), trial size, patient characteristics (age, gender) transplant types (e.g., living donor, deceased donor), onset of diabetes (e.g., PTDM or pre-existing T2DM), types of interventions utilized (e.g., metformin, insulin, other oral antihyperglycemics, lifestyle interventions), relevant parameters for subgroup analysis as outlined in this protocol (e.g., blood pressure readings, statin use) adverse effects experienced, duration of interventions, duration of follow-up, outcomes (graft survival, patient

mortality) and conclusions. When multiple outcome times are reported, the longer outcome time will be extracted. Reviewers will resolve any conflicts in data extraction by discussion. The independent reviewer will be responsible for the adjudication of any unresolved conflicts. The quality of the evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation working group methodology.

Assessment of Risk of Bias in Included Studies

For the assessment of the risk of bias, we will employ the Cochrane Risk of Bias Tool 2 (ROB-2) (20) for RCTs and the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) for non-randomized studies (21). The ROB-2 uses signalling questions to assess 5 domains, which include risk of bias arising from randomization, risk of bias arising from deviations from intended interventions, missing outcome data, risk of bias in measurement of outcomes, and risk of bias in selection of the reported results. This helps elicit an overall risk of bias judgment for an RCT-type study.

The ROBINS-I preliminarily urges to consider confounding domains and co-interventions that could be within a study, and then proceeds to evaluate the study across 7 domains: bias due to confounding, bias due to participant selection, bias in classification of

interventions, bias due to deviations from intended interventions, bias from missing data, bias in measurement outcomes, and bias in selection of the reported result.

We will also present the overall risk of bias per study in a summary table. If there is insufficient information to assess bias, we will assign it as 'unclear'. Finally, we will assess the possibility of any publication bias using a regression-based test and by the examination of the resultant funnel plots.

Measures of Treatment Effect

We will present dichotomous outcomes as risk ratios, and continuous outcomes as mean differences (MD) between the intervention and control groups. If any continuous outcomes have been measured in different ways across studies, we will utilize standardized MD between the intervention and controlled groups. Finally, we will present the intervention effect of any time-to-event outcomes as hazard ratios. The 95% confidence intervals for all outcomes will be reported.

Dealing with Missing Data

When we encounter missing or unclear data, we will attempt to contact the authors of the relevant study to seek data or clarify information. Further, attempts will be made to calculate any

required parameters from the given data, as necessary and appropriate. All missing data will be reported in our data extraction sheet and the risk of bias assessments.

Assessment of Heterogeneity

We will assess heterogeneity between studies with respect to participant characteristics, intervention types, duration of intervention, donor types, and outcomes. We will test statistical heterogeneity using the χ^2 test and estimate the amount of heterogeneity using the I^2 value.

Data Synthesis

The data and study characteristics will be summarized in a table, and we will determine if a meta-analysis can be performed by clinical and methodological heterogeneity. Statistical heterogeneity will be quantified using I^2 statistics in each analysis (22). If the extent of heterogeneity is deemed acceptable ($I^2<50\%$) based on previous works, we will perform a meta-analysis to summarize pooled results using a random effects model (23). If the study characteristics display excessive heterogeneity ($I^2>50\%$), then we will report the data descriptively, and we will provide a narrative synthesis of included studies using the Synthesis Without Meta-Analysis Reporting Guideline as a framework (24). If quantitative synthesis of

data is not possible, we will present a narrative synthesis in a table format to summarize the findings of the appropriate studies.

Subgroup Analysis

Subgroup analysis will be performed for the following parameters: study duration, donor type (living vs. deceased), PTDM, pre-existing T2DM, blood pressure, blood glucose, statin use, steroid use, metformin alone, metformin with other oral antihyperglycemics, and metformin with insulin.

Patient and Public Involvement

We will be providing our findings to a Canadian research initiative known as CanSOLVE CKD, which comprises of patients, healthcare providers, and researchers collaborating to transform the care received by patients affected by chronic kidney disease. In addition, we will also share our results with Diabetes Action Canada, a non-profit organization made of patient-partners, researchers and healthcare providers that execute research projects benefiting patients living with diabetes.

Ethics and Dissemination

Ethics approval will not be required for this study, as it is entirely based on pre-existing data from published studies. Our dissemination strategy will consist of peer reviewed publications, presentations, and a report. We will disseminate our findings to major organizations, patients, and professional societies such as the International Diabetes Federation (IDF), International Society of Nephrology (ISN), Diabetes Canada, Kidney Foundation of Canada and related patient organizations and professional bodies.

Discussion

Currently, there are no clinical care recommendations based upon controlled studies on the approach to anti-hyperglycemic medication management in kidney transplant recipients with T2DM (9). As mentioned, patients who have pre-existing T2DM prior to their transplant, or those who develop it after their transplant face numerous challenges. Transplant recipients are predisposed to developing diabetes due to various risk factors such as post-operative stress, use of corticosteroids, and use of calcineurin inhibitors (25). Presently, the guidelines do not favour one pharmacological therapy over another in the setting of T2DM following kidney transplantation (26). Although some studies have shown promise regarding a glucose lowering

effect, they have been limited by sample size, and did not study clinically relevant outcomes such as graft rejection or mortality (10, 11).

Ideally, the choice of therapy in T2DM affecting kidney transplant recipients should focus on: (1) minimizing adverse effects of medications related to graft function, (2) maintaining adequate glycemic control, and (3) demonstrating a cardiovascular or overall mortality benefit. DPP-4 inhibitors and GLP-1 agonists show promise with a glucose lowering effect in this population (10, 11, 27), but they have not been studied for a mortality benefit. In addition, they are expensive agents and can be limited by cost (28). Furthermore, other options such as sulfonylureas may not be appropriate due to the risks of hypoglycemia and weight gain. Insulin therapies also induce hypoglycemia and weight gain, as well as requiring subcutaneous injections that may be inconvenient for patients. As such, metformin may be a favourable option in this setting. Metformin has been used for treatment of patients with T2DM patients in various settings, owing to its effectiveness and other metabolic and cardiovascular benefits. However, due to purported concerns about lactic acidosis, especially in patients with reduced kidney function, there is apprehension surrounding its use in kidney transplant recipients. We aim to evaluate the effects of metformin in kidney transplant recipients with T2DM, who are likely to

be on advanced antihyperglycemic regiments, by conducting thorough subgroup analyses, which includes appraising the effects of metformin alone, metformin with other oral antihyperglycemics and metformin with insulin. In addition, other parameters that are relevant to consider include accounting for graft failure from cardiovascular causes (e.g., blood pressure, steroid use, blood glucose), which may be responsible for the majority of kidney transplant failures. As such, this will also be included in our subgroup analysis in order to separate the effects of metformin use alone.

Overall, this work will aim to provide much needed information on the effects of metformin use in kidney transplants recipients and determine its place in the pharmacologic management of kidney transplant recipients with T2DM. Currently, there are limited studies on this topic in the literature. An evaluation of the literature via a systematic review will be helpful in assessing their overall conclusions. This would be invaluable for such patients and clinicians, no matter the outcome. If metformin is beneficial to positively impact patient-relevant outcomes in the study, the information may inform guideline recommendations for the use of this agent as an inexpensive option for clinicians to consider for their patients with diabetes and kidney transplant. In addition, its other benefits, such as weight loss or minimal hypoglycemia, could

also be leveraged in its favour. On the other hand, if we find metformin to be detrimental in kidney transplant recipients, clinicians may need to pursue other treatment options, as metformin is currently often prescribed for patients with T2DM.

Author contributions: FS and AKB conceived the idea of the study. FS drafted the protocol manuscript. AKB serves as the guarantor and supervisor of the research. All authors contributed to the development of the protocol. FY, ST, IGO, AKB advised on the risk of bias assessment strategy and data extraction criteria. JYK developed the search strategy. FY provided statistical expertise and data analysis. PS and SS provided expertise on metformin pharmacology, study design, and transplant medicine. AG, VKH, AA, MP, NS, and SM provided feedback on design, data extraction, and thoroughly proofread the study. All authors reviewed and approved the final manuscript. AKB is the guarantor of the study and quality assurance for the data and its analysis.

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We will make data available on request.

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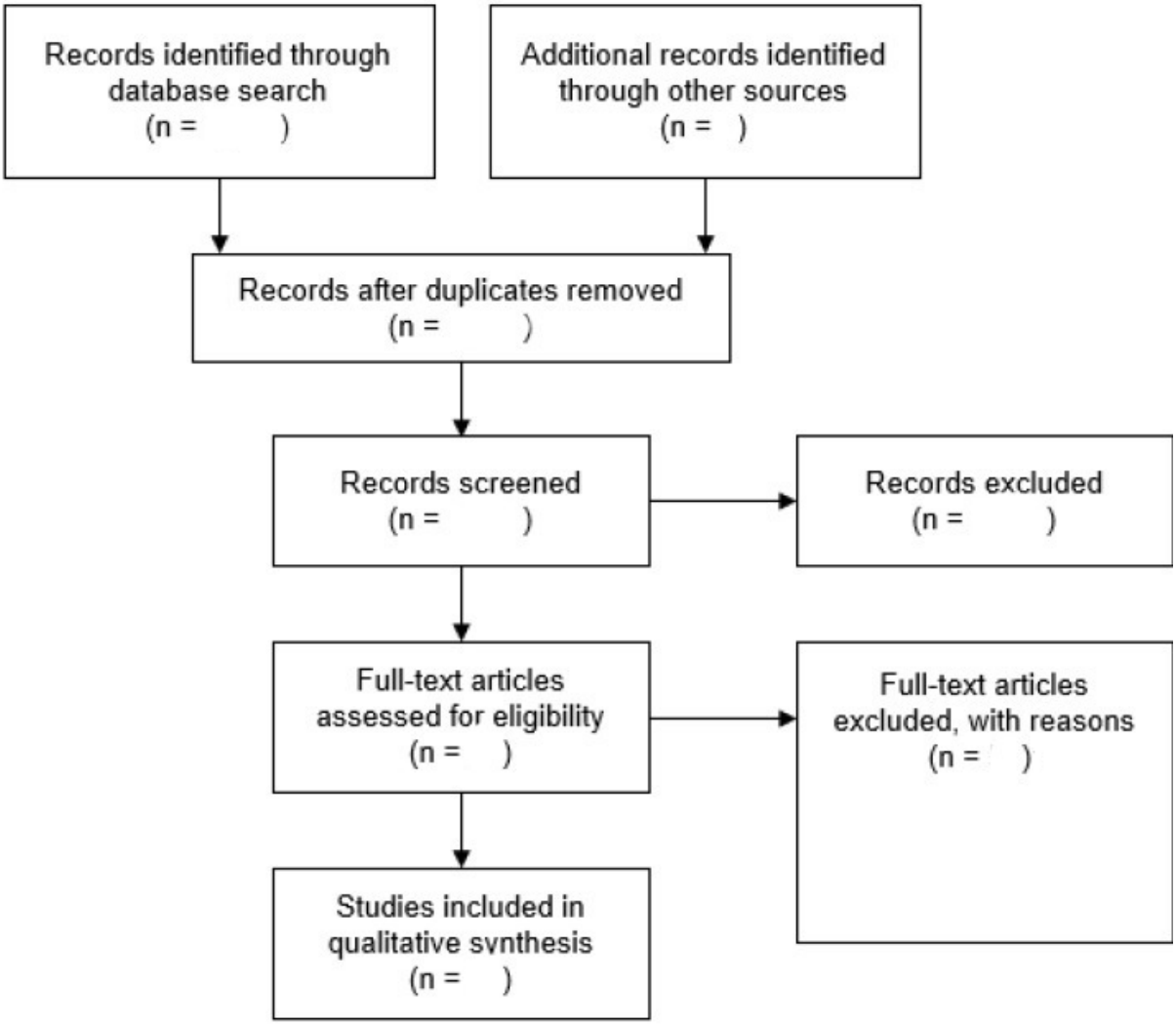
Supplementary Table S1: Search Strategies to be used for study identification and selection

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to April 14, 2023	1. (kidney adj3 transplant*).mp. 2. (renal adj3 transplant*).mp. 3. exp Kidney Transplantation/ 4. ((kidney or renal) and (graft* or allograft*)).mp. 5. exp Organ Transplantation/ and exp Diabetes Mellitus, Type 2/ 6. (diabetes and (post-transplant* or posttransplant* or (after adj2 transplant*))).mp. 7. or/1-6 8. metformin.mp. 9. (dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance).mp. 10. 8 or 9 11. 7 and 10 12. limit 11 to english language
Embase **Ovid Embase** 1974 to 2023 April 14	1. (kidney adj3 transplant*).mp. 2. (renal adj3 transplant*).mp. 3. exp kidney transplantation/ 4. ((kidney or renal) and (graft* or allograft*)).mp. 5. exp organ transplantation/ and exp non insulin dependent diabetes mellitus/ 6. (diabetes and (post-transplant* or posttransplant* or (after adj2 transplant*))).mp. 7. or/1-6 8. metformin.mp. 9. (dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance).mp. 10. 8 or 9 11. 7 and 10 12. limit 11 to english language
CINAHL	S1 kidney N3 transplant* S2 renal N3 transplant* S3 (MH "Kidney Transplantation+") S4 (kidney or renal) and (graft* or allograft*) S5 (MH "Organ Transplantation+") S6 (MH "Diabetes Mellitus, Type 2") S7 S5 AND S6 S8 diabetes and (post-transplant* or posttransplant* or (after N2 transplant*)) S9 S1 OR S2 OR S3 OR S4 OR S7 OR S8 S10 metformin

	S11 dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance S12 S10 OR S11 S13 S9 AND S12 Limiter: English language
Cochrane Library via Wiley	#1 kidney NEAR/3 transplant* #2 renal NEAR/3 transplant* #3 [mh "Kidney Transplantation"] #4 ((kidney or renal) and (graft* or allograft*)) #5 [mh "Organ Transplantation"] and [mh "Diabetes Mellitus, Type 2"] #6 diabetes and (post-transplant* or posttransplant* or (after NEAR/2 transplant*)) #7 {OR #1-#6} #8 metformin #9 dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance #10 #8 AND #9 #11 #7 AND #10
Web of Science Core Collection	TS=((kidney NEAR/3 transplant*) or (renal NEAR/3 transplant*) or ((kidney or renal) and (graft* or allograft*)) or (diabetes and (post-transplant* or posttransplant* or (after NEAR/2 transplant*)))) AND TS=(metformin or dimethylbiguanidine or dimethylbiguanidium or dimethylguanylguanidine or glucophage or glucovance) Languages: English
Google Scholar	(kidney transplant OR renal transplant OR kidney graft OR renal allograft) AND (metformin OR dimethylbiguanidine OR dimethylbiguanidium OR dimethylguanylguanidine OR glucophage OR glucovance)

Supplementary Figure 1: PRISMA Flowchart



Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1, 2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	7
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	7
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	20-21
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11