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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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Manuscripts

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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27 Transplantation
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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.

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5 **Article Summary:**
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8 ***Strengths and Limitations:***
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- 10
- 11 • The focus on metformin as an exposure allows us to capture a wide range of patients with
12 diabetes, given its place in therapy.
13
 - 14 • Utilizing multiple reviewers when screening abstracts and full texts will allow us to
15 capture the most relevant studies.
16
 - 17 • We will assess the quality of studies using a tool that incorporates assessments of risk of
18 bias across core study domains: sampling, sampling technique and size, outcome
19 measurement, response rate, and statistical reporting.
20
 - 21 • The search strategy will include all relevant databases for peer-reviewed literature, hence
22 ensuring a comprehensive analysis.
23
 - 24 • A potential limitation of this study could be heterogeneity and number of studies of low
25 quality which could affect pooled estimates and our ability to conduct a meta-analysis.
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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

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3
4 is the leading cause of death (4), metformin appears to present itself as a reasonable
5
6
7 cardioprotective option.
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10 Nevertheless, there is some uncertainty surrounding the use of metformin – for new or
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12
13 pre-existing diabetes in kidney transplant recipients – given the lack of evidence regarding
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16
17 optimal regimens of anti-hyperglycemic agents in this population (5, 6). Diabetes Canada states
18
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20 that “there is not enough evidence to support specific recommendations regarding choice of
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23
24 antihyperglycemic therapy” for post-transplant diabetes mellitus. Manufacturers and guidelines
25
26
27 also list poor kidney function (e.g., eGFR<30mls/min) as a barrier for its use (7). Furthermore,
28
29
30 no controlled studies have been undertaken to elucidate optimal management for transplant
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33
34 recipients with pre-existing diabetes (8). Early after kidney transplantation, patients with pre-
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37 existing T2DM may often experience difficult to manage hyperglycemia, and those without pre-
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39
40 existing diabetes may develop New Onset Diabetes After Transplantation (NODAT), also called
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44 Post Transplant Diabetes Mellitus (PTDM). Peri-operative stress and diabetogenic effects of
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47 immunosuppressive medications (i.e., prednisone, calcineurin inhibitors and mTOR inhibitors),
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50 among other risk factors - such as coronary artery disease or smoking - can exacerbate the
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54 problem. Nevertheless, given the anti-hyperglycemic and cardioprotective effects of metformin,
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4 it is important to ascertain the best management principles for the treatment of T2DM in this
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7 population.
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10 Management of T2DM or hyperglycemia in the kidney transplant population may include
11
12
13 insulin. Yet, there have not been any controlled head-to-head studies that have examined such
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17 treatment strategies for glycaemic management after transplantation. Researchers have evaluated
18
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20 the use of dipeptidyl peptidase (DPP)-4 inhibitors in NODAT, and they have found them to be
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24 safe and beneficial with respect to lowering blood glucose levels in the short term, as well as
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27 mitigating weight gain (9, 10). Nevertheless, these studies included a very small number of
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30 participants, and did not study clinically relevant outcomes of graft survival or patient mortality.
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34 Ideally, antihyperglycaemic agents used to treat T2DM in a transplant population should
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37 preferably not promote weight gain, since steroid use and weight gain are important risk factors
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40 for post-transplant diabetes. Therefore, metformin appears to be a reasonable first-line agent,
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43 assuming well reserved kidney and liver function. GLP-1 receptor agonist or sodium-glucose
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46 cotransporter-2 (SGLT2) are limited by high cost, and frequently require special authorization
47
48
49 for coverage in Canada. In contrast, metformin presents itself as an economical option, covered
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52 through nearly all public and private plans. Furthermore, in immunosuppressed patients, the risks
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3 of mycotic genitourinary infection with SGLT2 inhibitors may be increased, especially in kidney
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7 transplant recipients on immunosuppressive medications (11). Lastly, guidelines recommend that
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9
10 patients at increased risk for hypoglycemia (e.g., transplant recipients with impaired hepatic or
11
12
13 kidney function) or pancreas transplant recipients with graft dysfunction avoid using insulin
14
15
16 secretagogues agents. It is also worth considering that patients with NODAT or those that had
17
18
19 pre-existing diabetes prior to transplant will likely require insulin for diabetes control, given that
20
21
22 their poor diabetic control necessitated a transplant. In this context, the addition of metformin
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26
27 could serve to limit incremental insulin dosing and limit its adverse effects of hypoglycemia and
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29
30 weight gain.
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35 Despite the noted advantages, the hesitation to use metformin for the kidney transplant
36
37
38 population may stem from the tolerability or safety of metformin when used in conjunction with
39
40
41 multiple medications indicated for post-transplant care (12). Furthermore, concerns regarding
42
43
44 lactic acidosis with metformin when used in patients with impaired renal function (reflecting
45
46
47 decreased ability to renally excrete drugs) have also been reported (13). As such, other classes of
48
49
50 antihyperglycemics such as meglitinides can be preferred due to the perceived relative safety
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55 (12). Nevertheless, it is important to consider the role of metformin in type 2 diabetic kidney
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3 transplant recipients. Metformin can provide cardiovascular benefits through mechanisms
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7 detailed earlier, which may help decrease death with graft function (DWGF) (14) - a significant
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10 cause of mortality in kidney transplant recipients (15).
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14 Given the paucity of knowledge regarding metformin use in kidney transplant recipients,
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17 as well as the safety concerns with polypharmacy, we aim to conduct a systematic review of the
18
19
20 literature on the use of metformin and its potential effect on graft and patient survival in kidney
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23 transplant recipients with T2DM.
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30 **Objective:**

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

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46
47 We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses for
48
49
50 Protocols 2015 (PRISMA-P 2015) to develop this protocol (17). As recommended by the
51
52
53 PRISMA-P guidelines, this review protocol is registered with PROSPERO International
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4 Prospective Register of Systematic Reviews on June 28, 2023: registration number

5
6
7 CRD42023421799. For protocol amendments, we will report the date, description of the change,

8
9
10 and rationale in a tabular format. These changes will not be incorporated into the protocol.

11 12 13 **Criteria for Considering Studies for Review**

14 15 16 ***Types of Studies***

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18
19
20 We aim to include observational studies and randomized control trials (RCTs) that
21
22
23 evaluated graft survival and mortality in kidney transplant recipients using metformin. We
24
25
26 restricted the study to articles published in the English language only.
27
28
29

30 31 ***Study Population***

32
33
34 We will include studies that have kidney transplant only recipients over the age of 18,
35
36
37 regardless of sex and ethnicity. These transplants can be of any type (living donor, deceased
38
39
40 donor) and of any duration. The participants in these studies must also have a diagnosis of type 2
41
42
43 diabetes (as defined in the published studies to be reviewed) either before or after the receipt of
44
45
46 kidney transplantation.
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54 55 ***Types of Intervention***

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4 The intervention of interest will be metformin – at any dose – for the treatment of pre-
5
6
7 existing T2DM or new-onset T2DM in kidney transplant recipients. To be eligible, patients must
8
9
10 be receiving treatment with metformin – at any defined daily dose – for any length of time.
11
12
13 Metformin usage may be demonstrated by (but not limited to) a history of metformin fills,
14
15
16 prescriptions rendered, pharmacy claims data, and hospital records. Studies must have also
17
18
19 reported on at least one outcome measure to be included. Comparators may include no
20
21
22 medication, lifestyle interventions, insulin, GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors,
23
24
25 sulfonylureas, meglitinides, and thiazolidinediones. Where comparators are not included, we will
26
27
28 report the outcomes of studies based on metformin alone.
29
30
31

32 33 *Types of Outcome Measures*

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35
36
37 The primary outcomes will include graft survival (defined as survival time from the onset
38
39
40 of kidney transplantation) and all-cause patient mortality. Secondary outcomes may include
41
42
43 effects of metformin toxicity (e.g., abdominal pain, time to metformin discontinuation) that
44
45
46 patients may experience while on metformin therapy, as defined by study authors. We aim to
47
48
49 utilize the definitions for these parameters as they are defined in the selected published studies
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52
53
54 for review.
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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-

1
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3 existing or new onset T2DM. The selected articles will then be included for full-text review. In
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7 the second stage, reviewers will assess the full-text articles to ensure that metformin was used as
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9
10 an intervention, and that one of the primary outcomes of graft survival or patient mortality was
11
12
13 reported. An independent third reviewer will be utilized as an arbitrator to evaluate studies in the
14
15
16 event of a disagreement of the two reviewers. In such cases, the final decision to select a study
17
18
19 will then lie with the independent reviewer. We will also include reasons for exclusion of
20
21
22 studies, and will exclude any studies that do not utilize metformin as an intervention. Figure 1
23
24
25
26
27 outlines the criteria of study selection (see Appendix).
28
29

30 *Inclusion Criteria*

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32
33 - Studies conducted in kidney transplant recipients (deceased or living donor) with pre-
34
35 existing or new-onset T2DM (NODAT)
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37
- 38
39 - Studies using any metformin use as the intervention
40
41
- 42
43 - Studies reporting any primary outcome of graft survival or patient mortality
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45
- 46
47 - Any study design (except exclusions listed below)
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- 50
51 - From inception through to 2023 when the search will be conducted
52
53
- 54
55 - Languages limited to English
56
57
- 58
59 - Patients \geq 18 years old
60

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

1
2
3 utilized (e.g., metformin, insulin, other oral antihyperglycemics, lifestyle interventions), relevant
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7 parameters for subgroup analysis as outlined in this protocol (e.g., blood pressure readings, statin
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9
10 use) adverse effects experienced, duration of interventions, duration of follow-up, outcomes
11
12
13 (graft survival, patient mortality) and conclusions. When multiple outcome times are reported,
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15
16
17 the longer outcome time will be extracted. Reviewers will resolve any conflicts in data extraction
18
19
20 by discussion. The independent reviewer will be responsible for the adjudication of any
21
22
23 unresolved conflicts. The quality of the evidence will be assessed by the Grading of
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25
26
27 Recommendations Assessment, Development and Evaluation working group methodology.
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29

30 *Assessment of Risk of Bias in Included Studies*

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34 For the assessment of the risk of bias, we will employ the Cochrane Risk of Bias Tool 2
35
36
37 (ROB-2) (18) for RCTs and the Risk of Bias in Non-randomized Studies of Intervention
38
39
40 (ROBINS-I) for non-randomized studies (19). The ROB-2 uses signalling questions to assess 5
41
42
43 domains, which include risk of bias arising from randomization, risk of bias arising from
44
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47 deviations from intended interventions, missing outcome data, risk of bias in measurement of
48
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50 outcomes, and risk of bias in selection of the reported results. This helps elicit an overall risk of
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52
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54 bias judgment for an RCT-type study.
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3 The ROBINS-I preliminarily urges to consider confounding domains and co-
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5
6 interventions that could be within a study, and then proceeds to evaluate the study across 7
8
9
10 domains: bias due to confounding, bias due to participant selection, bias in classification of
11
12
13 interventions, bias due to deviations from intended interventions, bias from missing data, bias in
14
15
16 measurement outcomes, and bias in selection of the reported result.
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20 We will also present the overall risk of bias per study in a summary table. If there is
21
22
23 insufficient information to assess bias, we will assign it as 'unclear'. Finally, we will assess the
24
25
26 possibility of any publication bias using a regression-based test and by visually inspecting funnel
27
28
29
30 plots.
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37 *Measures of Treatment Effect*

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40 We will present dichotomous outcomes as risk ratios, and continuous outcomes as mean
41
42
43 differences (MD) between the intervention and control groups. If any continuous outcomes have
44
45
46 been measured in different ways across studies, we will utilize standardized MD between the
47
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49
50 intervention and controlled groups. Finally, we will present the intervention effect of any time-
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4 to-event outcomes as hazard ratios. The 95% confidence intervals for all outcomes will be
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7 reported.

8 9 10 *Dealing with Missing Data*

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14 When we encounter missing or unclear data, we will attempt to contact the authors of the
15
16
17 relevant study to seek data or clarify information. Further, attempts will be made to calculate any
18
19
20 required parameters from the given data, as necessary and appropriate. All missing data will be
21
22
23 reported in our data extraction sheet and the risk of bias assessments.

24 25 26 27 *Assessment of Heterogeneity*

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29
30 We will assess heterogeneity between studies with respect to participant characteristics,
31
32
33 intervention types, duration of intervention, donor types, and outcomes. We will test statistical
34
35
36 heterogeneity using the χ^2 test and estimate the amount of heterogeneity using the I^2 value.

37 38 39 40 *Data Synthesis*

41
42
43
44 The data and study characteristics will be summarized in a table, and we will determine if
45
46
47 a meta-analysis can be performed by clinical and methodological heterogeneity. Statistical
48
49
50 heterogeneity will be quantified using I^2 statistics in each analysis (20). If the amount of
51
52
53 heterogeneity is deemed acceptable ($I^2 < 50\%$), we will perform a meta-analysis to summarize
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3 pooled results using a random effects model (21). If the study characteristics display excessive
4
5
6 heterogeneity ($I^2 > 50\%$), then we will report the data descriptively, and we will provide a
7
8
9 narrative synthesis of included studies using the Synthesis Without Meta-Analysis Reporting
10
11
12 Guideline as a framework (22). If quantitative synthesis of data is not possible, we will present a
13
14
15 narrative synthesis in a table format to summarize the findings of the appropriate studies.
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18

19 20 *Subgroup Analysis*

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23 Subgroup analysis will be performed for the following parameters: study duration, donor
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25
26 type (living vs. deceased), NODAT, pre-existing T2DM, blood pressure, blood glucose, statin
27
28
29 use, steroid use, metformin alone, metformin with other oral antihyperglycemics, and metformin
30
31
32 with insulin.
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35

36 37 *Patient and Public Involvement*

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40 As this is a retrospective study of existing data, there is no public or patient involvement
41
42
43 in this study.
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46

47 48 *Ethics and Dissemination*

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4 Ethics approval will not be required for this study, as it is entirely based on pre-existing
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7 data from published studies. Our dissemination strategy will consist of peer reviewed
8
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10 publications, presentations, and a report.
11
12

13 Discussion

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15
16
17 Currently, there are no clinical care recommendations based upon controlled studies on
18
19
20 the approach anti-hyperglycemic medication management in kidney transplant recipients with
21
22
23 T2DM (8). As mentioned, patients who have pre-existing T2DM prior to their transplant, or
24
25
26 those who develop it after their transplant face numerous challenges. Transplant recipients are
27
28
29 predisposed to developing diabetes due to various risk factors such as post-operative stress, use
30
31
32 of corticosteroids, and use of calcineurin inhibitors (23). Presently, the guidelines do not favour
33
34
35 one pharmacological therapy over another in the setting of T2DM following kidney
36
37
38 transplantation (24). Although some studies have shown promise regarding a glucose lowering
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40
41 effect, they have been limited by sample size, and did not study clinically relevant outcomes
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43
44 such as graft rejection or mortality (9, 10).
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51 Ideally, the choice of therapy in T2DM affecting kidney transplant recipients should
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54 focus on: (1) minimizing adverse effects of medications related to graft function, (2) maintaining
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3 adequate glycemic control, and (3) demonstrating a cardiovascular or overall mortality benefit.
4
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6
7 DPP-4 inhibitors and GLP-1 agonists show promise with a glucose lowering effect in this
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9
10 population (9, 10, 25), but they have not been studied for a mortality benefit. In addition, their
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12
13 costs also remain prohibitive in the context of the Canadian drug landscape (26). Furthermore,
14
15
16 other option such as sulfonylureas may not be appropriate due to the risks of hypoglycemia and
17
18
19 weight gain. Insulin therapies also induce hypoglycemia and weight gain, as well as requiring
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21
22 subcutaneous injections that may be inconvenient for patients. As such, metformin may be a
23
24
25 favourable option in this setting. Metformin has been used for treatment of patients with T2DM
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27
28 patients in various settings, owing to its effectiveness and other metabolic and cardiovascular
29
30
31 benefits. However, due to purported concerns about lactic acidosis, especially in patients with
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34 reduced kidney function, there is apprehension surrounding its use in kidney transplant
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36
37 recipients. We aim to evaluate the effects of metformin in kidney transplant recipients with
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40 T2DM – who are likely to be on advanced antihyperglycemic regimens - by conducting
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43 thorough subgroup analyses, which includes appraising the effects of metformin alone,
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46 metformin with other oral antihyperglycemics and metformin with insulin. In addition,
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49 parameters that are relevant to consider accounting for graft failure from cardiovascular causes
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4 (e.g., blood pressure, steroid use, blood glucose), which may be responsible for the majority of
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7 kidney transplant failures, will also be considered in our subgroup analysis in order to separate
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10 the effects of metformin use.

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13 Overall, this work will aim to provide much needed information on the effects of
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16 metformin use in kidney transplants recipients and determine its place in the pharmacologic
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19 management of kidney transplant recipients with T2DM. This would be invaluable for such
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22 patients and clinicians, no matter the outcome. If metformin is beneficial, it will serve as an
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25 inexpensive option for clinicians to consider for their patients. In addition, its other benefits –
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28 such as weight loss, minimal hypoglycemia – could also be leveraged in its favour. On the other
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31 hand, if we find it to be detrimental in kidney transplant recipients, clinicians may need to pursue
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34 other treatment options, as it is currently often prescribed for patients with T2DM.
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17 **Author contributions:** FS and AKB conceived the idea of the study. FS drafted the protocol
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20 manuscript. AKB serves as the guarantor and supervisor of the research. All authors contributed
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23 to the development of the protocol. FY, ST, IGK, AKB advised on the risk of bias assessment
24
25
26 strategy and data extraction criteria. JYK developed the search strategy. FY provided statistical
27
28
29 expertise. PS and SS provided expertise on metformin pharmacology, study design, and
30
31
32 transplant medicine. All authors read, provided feedback, and approved the final manuscript.
33
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36
37 AKB is the guarantor of the study and quality assurance for the data and its analysis.
38
39

40 **Guarantor of Review:**

41
42 Aminu K. Bello
43
44

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49

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51
52 None
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3 None
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5 **Patient consent:**

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7 Not required
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10 **Data sharing statement:**

11 We will make data available on request.
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For peer review only

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

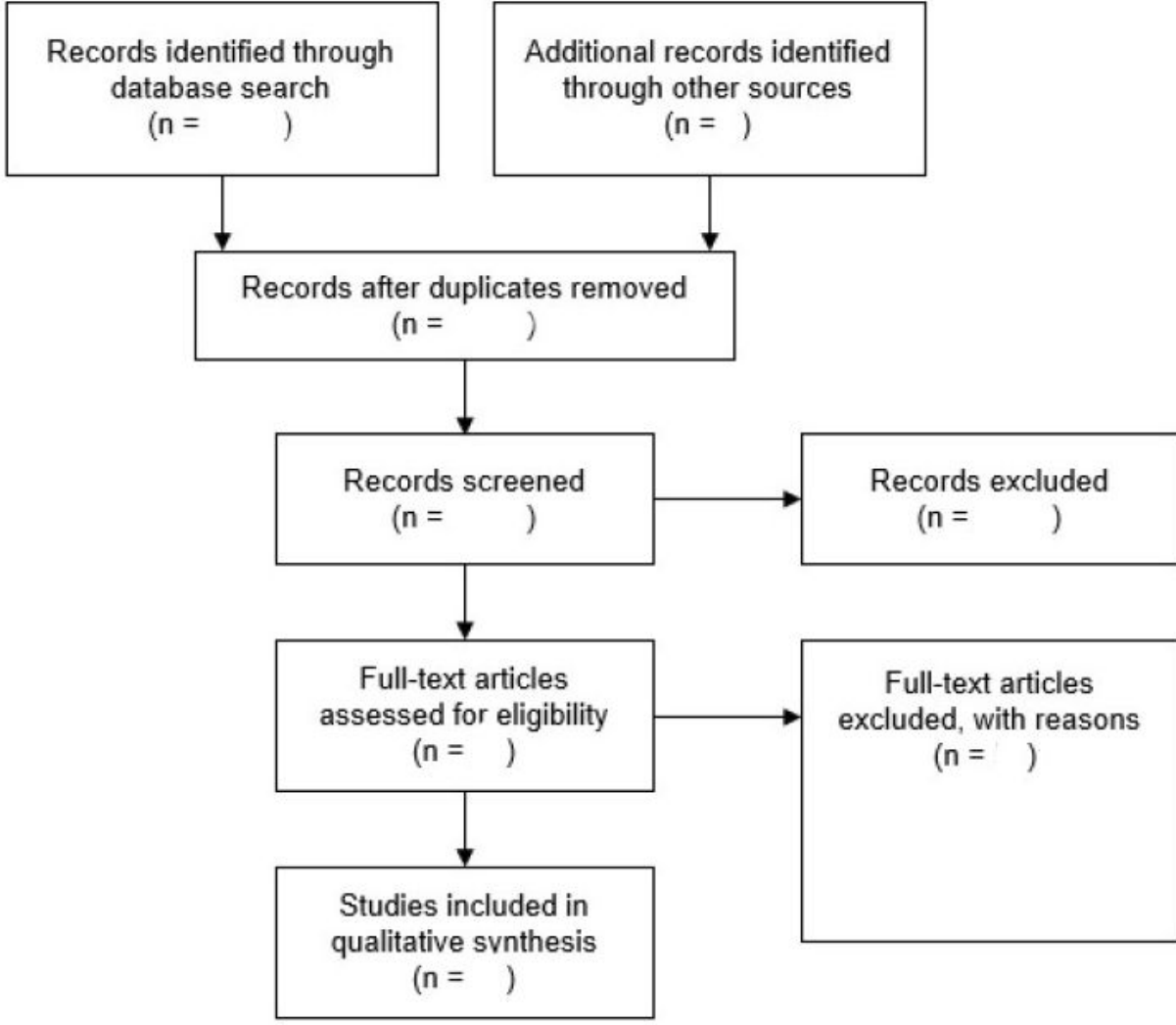
Database	Search Strategy
MEDLINE Ovid MEDLINE(R) ALL 1946 to April 14, 2023	<ol style="list-style-type: none"> 1. (kidney adj3 transplant*).mp. 2. (renal adj3 transplant*).mp. 3. exp Kidney Transplantation/ 4. ((kidney or renal) and (graft* or allograft*)).mp. 5. exp Organ Transplantation/ and exp Diabetes 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	<ol style="list-style-type: none"> 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

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

	#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

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only

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.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting 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
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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

1	Study records - data	#11c	Describe planned method of extracting data from reports (such as	10
2	collection process		piloting forms, done independently, in duplicate), any processes for	
3			obtaining and confirming data from investigators	
4				
5				
6	Data items	#12	List and define all variables for which data will be sought (such as	10-11
7			PICO items, funding sources), any pre-planned data assumptions	
8			and simplifications	
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11	Outcomes and	#13	List and define all outcomes for which data will be sought,	8
12	prioritization		including prioritization of main and additional outcomes, with	
13			rationale	
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16				
17	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	11
18	individual studies		studies, including whether this will be done at the outcome or study	
19			level, or both; state how this information will be used in data	
20			synthesis	
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24	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	12-13
25			synthesised	
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28	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned	12-13
29			summary measures, methods of handling data and methods of	
30			combining data from studies, including any planned exploration of	
31			consistency (such as I ² , Kendall's τ)	
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34	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or	13
35			subgroup analyses, meta-regression)	
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38	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of	13
39			summary planned	
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42	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	11
43			publication bias across studies, selective reporting within studies)	
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46	Confidence in	#17	Describe how the strength of the body of evidence will be assessed	11
47	cumulative		(such as GRADE)	
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None The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-078393.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2024
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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Renal transplantation < NEPHROLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Adult nephrology < NEPHROLOGY

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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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18 **Abstract Word Count:** 512
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20 **Manuscript Word Count:** 3523
21

22 **Running Title:** The Effect of Metformin Use on Graft and Patient Survival in Kidney Transplant
23 Recipients with Type 2 Diabetes: A Systematic Review Protocol
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26 **Keywords:** Metformin; Kidney Transplantation; Diabetes Mellitus, Type 2; Organ
27 Transplantation
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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 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-

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3 analysis cannot be performed, we will provide a narrative synthesis of included studies using the
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7 Synthesis Without Meta-Analysis Reporting Guideline.
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12 ***Ethics and Dissemination:***

14 Ethical approval will not be required for this review as the data used will be extracted
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16 from already published studies with publicly accessible data. As this study will assess the impact
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18 of metformin use on graft and patient survival in kidney transplant recipients, evidence gathered
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20 through it will be disseminated using traditional approaches that includes open-access peer-
21
22 reviewed publication, scientific presentations, and a report. We will also disseminate our
23
24 findings to appropriate academic bodies in charge of publishing guidelines related to T2DM and
25
26 transplantation, as well as patient and research centered groups.
27
28
29

30 **Article Summary:**

31 ***Strengths and Limitations:***

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34
35 • The focus on metformin as an exposure allows us to capture a wide range of patients with
36
37 diabetes, as it is commonly prescribed as a 1st-line agent or as an adjunct with other
38
39 therapy.
40
41
- 42 • Utilizing multiple reviewers when screening abstracts and full texts will allow us to
43
44 capture the most relevant studies.
45
46
- 47 • We will assess the quality of studies using a tool that incorporates assessments of risk of
48
49 bias across core study domains: sampling, sampling technique and size, outcome
50
51 measurement, response rate, and statistical reporting.
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- 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

1
2
3 atherogenesis) (3). The UKPDS study also demonstrated a reduction in myocardial infarctions in
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6
7 patients treated with metformin (3). Moreover, metformin also leads to a reduction in food
8
9
10 intake, related to changes in leptin levels and insulin sensitivity (4). Hence, metformin is thought
11
12
13 to have benefits related to metabolic syndrome, cardiovascular protection, while remaining
14
15
16 largely weight neutral (3). As such, there is guideline-based consensus amongst experts to use
17
18
19 metformin as a first line agent for T2DM, barring any contraindications. In kidney transplant
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21
22 recipients in whom cardiovascular mortality is the leading cause of death (5), metformin appears
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24
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26
27 to present itself as a reasonable cardioprotective option.
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29

30
31 Nevertheless, there is some uncertainty surrounding the use of metformin – for new or
32
33
34 pre-existing diabetes in kidney transplant recipients – given the lack of evidence regarding
35
36
37 optimal regimens of anti-hyperglycemic agents in this population (6, 7). Diabetes Canada states
38
39
40 that “there is not enough evidence to support specific recommendations regarding choice of
41
42
43 antihyperglycemic therapy” for post-transplant diabetes mellitus. Manufacturers and guidelines
44
45
46 also list poor kidney function (e.g., eGFR<30mls/min) as a barrier for its use (8). This stems
47
48
49
50 from the concern of lactic acidosis, which arose partly due to case reports of metformin-
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53 associated lactic acidosis in patients with CKD (8). Furthermore, there are limited controlled
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2
3 studies have been undertaken to elucidate optimal management for transplant recipients with pre-
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6
7 existing diabetes (9). Early after kidney transplantation, patients with pre-existing T2DM may
8
9
10 often experience difficult to manage hyperglycemia, and those without pre-existing diabetes may
11
12
13 develop New Onset Diabetes After Transplantation (NODAT), also called Post Transplant
14
15
16 Diabetes Mellitus (PTDM). Peri-operative stress and diabetogenic effects of immunosuppressive
17
18
19 medications (i.e., prednisone, calcineurin inhibitors and mTOR inhibitors), among other risk
20
21
22 factors, such as coronary artery disease or smoking, can exacerbate the problem. Nevertheless,
23
24
25 given the anti-hyperglycemic and cardioprotective effects of metformin, it is important to
26
27
28 ascertain its place in therapy for the treatment of T2DM in this population.
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33
34 Management of T2DM or hyperglycemia in the kidney transplant population may include
35
36
37 insulin. Yet, there have been limited head-to-head studies that have examined such treatment
38
39
40 strategies for glycaemic management after transplantation. Researchers have evaluated the use of
41
42
43 dipeptidyl peptidase (DPP)-4 inhibitors in PTDM, and they have found them to be safe and
44
45
46 beneficial with respect to lowering blood glucose levels in the short term, as well as mitigating
47
48
49 weight gain (10, 11). Nevertheless, these studies included a very small number of participants,
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52
53 and did not study clinically relevant outcomes of graft survival or patient mortality. Furthermore,
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4 newer agents such as GLP-1 agonists and SGLT-2 inhibitors also have limited evidence in
5
6
7 PTDM. For instance, a small placebo-controlled study showed a small reduction of 0.2% in
8
9
10 HbA1C with no difference in adverse events (12). Another study involving dulaglutide showed
11
12
13 no improvement in glycaemic control (12).
14
15

16
17 Ideally, antihyperglycemic agents used to treat T2DM in a transplant population should
18
19
20 preferably not promote weight gain, nor increase the risk of metabolic syndrome and
21
22
23 cardiovascular disease. In addition to this, corticosteroid use as part of post-transplant
24
25
26 management is an important risk factor to consider, as it can lead to hyperglycemia and worsen
27
28
29 or cause PTDM. Therefore, metformin, which appears protective against the aforementioned risk
30
31
32 factors, appears to be a reasonable first-line agent assuming well reserved kidney and liver
33
34
35 function. GLP-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT2) are limited by
36
37
38 high cost, and may require special authorization for coverage, as is the case in Canada. In
39
40
41 contrast, metformin presents itself as an economical option, covered through nearly all public
42
43
44 and private plans. Furthermore, in immunosuppressed patients, the risks of mycotic genitourinary
45
46
47 infection with SGLT2 inhibitors may be increased, especially in kidney transplant recipients on
48
49
50 immunosuppressive medications (13). Lastly, guidelines recommend that patients at increased
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2
3 risk for hypoglycemia (e.g., transplant recipients with impaired hepatic or kidney function) or
4
5
6 pancreas transplant recipients with graft dysfunction avoid using insulin secretagogues agents. It
7
8
9
10 is also worth considering that patients with PTDM or those that had pre-existing diabetes prior to
11
12
13 transplant will likely require insulin for diabetes control, given that their diabetic control
14
15
16 eventually led to diabetic nephropathy, which necessitated a transplant. In this context, the
17
18
19 addition of metformin could serve to limit incremental insulin dosing and limit its adverse effects
20
21
22
23 of hypoglycemia and weight gain.
24
25
26
27

28
29 Despite the noted advantages, the hesitation to use metformin for the kidney transplant
30
31 population may stem from the tolerability or safety of metformin when used in conjunction with
32
33 multiple medications indicated for post-transplant care (14). Furthermore, concerns regarding
34
35 lactic acidosis with metformin when used in patients with impaired renal function (reflecting
36
37 decreased ability to renally excrete drugs have also been reported (15). As such, other classes of
38
39 antihyperglycemics such as meglitinides can be used due to the perceived relative safety (14).
40
41
42 Nevertheless, it is important to consider the role of metformin in type 2 diabetic kidney
43
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45 transplant recipients. Metformin can provide cardiovascular benefits through mechanisms
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3 detailed earlier, which may help decrease death with graft function (DWGF) (16) - a significant
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6
7 cause of mortality in kidney transplant recipients (17).
8
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10 Given the paucity of knowledge regarding metformin use in kidney transplant recipients,
11
12
13 as well as the safety concerns with polypharmacy, we aim to conduct a systematic review of the
14
15
16
17 literature on the use of metformin and its potential effect on graft and patient survival in kidney
18
19
20 transplant recipients with T2DM.
21
22

23 **Objective:**

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25
26
27 Given that multiple observational studies (9, 18) have shown promise with metformin use
28
29
30 in kidney transplant recipients with T2DM, we aim to assess the effect of metformin on graft and
31
32
33
34 patient survival in kidney transplant recipients with T2DM.
35
36

37 **Methods and Analysis:**

38
39
40 This protocol was guided by the Preferred Reporting Items for Systematic reviews and
41
42
43 Meta-Analyses for Protocols 2015 (PRISMA-P 2015) (19). As recommended by the PRISMA-P
44
45
46 guidelines, this review protocol is registered with PROSPERO International Prospective Register
47
48
49 of Systematic Reviews on June 28, 2023: registration number CRD42023421799. For protocol
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3 amendments, we will report the date, description of the change, and rationale in a tabular format.
4
5

6
7 These changes will not be incorporated into the protocol.
8
9

10 Criteria for Considering Studies for Review

11 *Types of Studies*

12
13
14
15
16
17 We aim to include observational studies and randomized control trials (RCTs) that
18
19
20 evaluated graft survival and mortality in kidney transplant recipients using metformin. We
21
22
23 restricted the study to articles published in the English language only, as our preliminary
24
25
26 research on the topic revealed a paucity of studies regardless of the language.
27
28
29

30 *Study Population*

31
32
33
34 We will include studies that have kidney transplant only recipients over the age of 18,
35
36
37 regardless of sex and ethnicity. We excluded children and adolescents from our study, as we
38
39
40 intended to focus solely on the adult population. Pediatric patients may have distinct
41
42
43 physiological and pharmacokinetic characteristics compared to adults. By focusing on adult
44
45
46 populations, the review aims to provide more relevant and specific findings for the target
47
48
49 population of adult kidney transplant recipients. The kidney transplants can be of any type
50
51
52 (living donor, deceased donor) and of any duration. We excluded any dual organ transplants as
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2
3 limiting the scope to kidney transplantation allows for a more focused and specific analysis of
4
5
6 the effects of metformin in this context. Dual organ transplants involve additional complexities
7
8
9 and variations in patient outcomes, which could introduce heterogeneity into the review. To
10
11
12 maintain clarity and specificity, the decision was made to concentrate solely on kidney transplant
13
14 recipients. Finally, the participants in these studies must also have a diagnosis of type 2 diabetes
15
16
17 (as defined in the published studies to be reviewed) either before or after the receipt of kidney
18
19
20 transplantation.
21
22
23
24
25

26 27 *Types of Intervention*

28
29
30 The intervention of interest will be metformin, at any dose, for the treatment of pre-
31
32
33 existing T2DM or PTDM in kidney transplant recipients. To be eligible, patients must be
34
35
36 receiving treatment with metformin at any defined daily dose for any length of time. Metformin
37
38
39 usage may be demonstrated by (but not limited to) a history of metformin fills, prescriptions
40
41
42 rendered, pharmacy claims data, and hospital records. Studies must have also reported on at least
43
44
45 one outcome measure to be included. Comparators may include no medication, lifestyle
46
47
48 interventions, insulin, GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas,
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4 meglitinides, and thiazolidinediones. Where comparators are not included, we will report the
5
6
7 outcomes of studies based on metformin alone.
8
9

10 *Types of Outcome Measures*

11
12
13 The primary outcomes will include graft survival (defined as survival time from the onset
14
15
16 of kidney transplantation) and all-cause patient mortality. Secondary outcomes may include
17
18
19 effects of metformin toxicity (e.g., abdominal pain, time to metformin discontinuation) that
20
21
22 patients may experience while on metformin therapy, as defined by study authors. We aim to
23
24
25
26
27 utilize the definitions for these parameters as they are defined in the selected published studies
28
29
30 for review.
31
32

33 Methods

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35
36
37 The medical librarian (JYK) will develop and execute comprehensive searches in Ovid
38
39
40 MEDLINE, Ovid Embase, CINAHL, Cochrane Library (via Wiley), and Web of Science Core
41
42
43 Collection, from inception to present. Both qualitative and quantitative studies will be sought,
44
45
46
47 with no limitations on study types. Searches will be limited to English language. To capture all
48
49
50 relevant literature pertaining to metformin use and associations with adverse health outcomes in
51
52
53 patients after undergoing kidney transplantation, relevant keywords and controlled vocabulary
54
55
56
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1
2
3 will be carefully selected (Supplementary Table S1). Literature search results will be uploaded to
4
5
6
7 Covidence (www.covidence.org), a web-based tool, which will be used for abstract and full text
8
9
10 screening. The reporting of this systematic review will be guided by the standards of the
11
12
13 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.
14
15
16
17 Studies or records identified by other sources, such as through references of other texts, will not
18
19
20 be under consideration for review. The planned start date for the study is April 1, 2023, and the
21
22
23
24 planned end date is August 31, 2024.
25

26 **Data Collection and Analysis**

27 ***Study selection***

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33
34 We intend to use a two-stage collaborative process for screening and study selection.
35
36
37 Firstly, two reviewers (FS & ST) will independently assess and evaluate the titles and abstracts
38
39
40 of the retrieved studies to ensure that the population studied was kidney transplant recipients
41
42
43 with pre-existing or PTDM. The selected articles will then be included for full-text review. In the
44
45
46
47 second stage, reviewers will assess the full-text articles to ensure that metformin was used as an
48
49
50 intervention, and that one of the primary outcomes of graft survival or patient mortality was
51
52
53 reported. An independent third reviewer will be utilized as an arbitrator to evaluate studies in the
54
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1
2
3 event of a disagreement of the two reviewers. In such cases, the final decision to select a study
4
5
6
7 will then lie with the independent reviewer. We will also include reasons for exclusion of studies
8
9
10 and will exclude any studies that do not utilize metformin as an intervention. Supplementary
11
12
13 Figure 1 outlines the criteria of study selection (see Appendix).
14
15

16 ***Inclusion Criteria***

- 17
- 18
- 19
- 20 - Studies conducted in kidney transplant recipients (deceased or living donor) with pre-
- 21 existing diabetes or PTDM
- 22
- 23
- 24
- 25 - Studies using any metformin use as the intervention
- 26
- 27
- 28
- 29 - Studies reporting any primary outcome of graft survival or patient mortality
- 30
- 31
- 32 - Any study design (except exclusions listed below)
- 33
- 34
- 35 - From inception through to 2023 when the search will be conducted
- 36
- 37
- 38
- 39 - Languages limited to English
- 40
- 41
- 42 - Patients \geq 18 years old
- 43
- 44

45 ***Exclusion Criteria***

- 46
- 47
- 48
- 49 - Studies in which specific outcome of interest cannot be identified or extrapolated
- 50
- 51
- 52 - Age <18 years old
- 53
- 54
- 55
- 56
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- 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

1
2
3 mortality) and conclusions. When multiple outcome times are reported, the longer outcome time
4
5
6 will be extracted. Reviewers will resolve any conflicts in data extraction by discussion. The
7
8
9 independent reviewer will be responsible for the adjudication of any unresolved conflicts. The
10
11
12 quality of the evidence will be assessed by the Grading of Recommendations Assessment,
13
14
15 Development and Evaluation working group methodology.
16
17
18
19

20 *Assessment of Risk of Bias in Included Studies*

21
22

23
24 For the assessment of the risk of bias, we will employ the Cochrane Risk of Bias Tool 2
25
26 (ROB-2) (20) for RCTs and the Risk of Bias in Non-randomized Studies of Intervention
27
28 (ROBINS-I) for non-randomized studies (21). The ROB-2 uses signalling questions to assess 5
29
30
31 domains, which include risk of bias arising from randomization, risk of bias arising from
32
33
34 deviations from intended interventions, missing outcome data, risk of bias in measurement of
35
36
37 outcomes, and risk of bias in selection of the reported results. This helps elicit an overall risk of
38
39
40 bias judgment for an RCT-type study.
41
42
43
44
45

46
47 The ROBINS-I preliminarily urges to consider confounding domains and co-
48
49
50 interventions that could be within a study, and then proceeds to evaluate the study across 7
51
52
53 domains: bias due to confounding, bias due to participant selection, bias in classification of
54
55
56
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1
2
3 interventions, bias due to deviations from intended interventions, bias from missing data, bias in
4
5
6 measurement outcomes, and bias in selection of the reported result.
7
8
9

10 We will also present the overall risk of bias per study in a summary table. If there is
11
12 insufficient information to assess bias, we will assign it as 'unclear'. Finally, we will assess the
13
14 possibility of any publication bias using a regression-based test and by the examination of the
15
16 resultant funnel plots.
17
18
19
20
21
22

23 *Measures of Treatment Effect*

24
25 We will present dichotomous outcomes as risk ratios, and continuous outcomes as mean
26
27 differences (MD) between the intervention and control groups. If any continuous outcomes have
28
29 been measured in different ways across studies, we will utilize standardized MD between the
30
31 intervention and controlled groups. Finally, we will present the intervention effect of any time-
32
33 to-event outcomes as hazard ratios. The 95% confidence intervals for all outcomes will be
34
35 reported.
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46 *Dealing with Missing Data*

47
48
49 When we encounter missing or unclear data, we will attempt to contact the authors of the
50
51 relevant study to seek data or clarify information. Further, attempts will be made to calculate any
52
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3
4 required parameters from the given data, as necessary and appropriate. All missing data will be
5
6
7 reported in our data extraction sheet and the risk of bias assessments.
8
9

10 *Assessment of Heterogeneity*

11
12
13 We will assess heterogeneity between studies with respect to participant characteristics,
14
15
16
17 intervention types, duration of intervention, donor types, and outcomes. We will test statistical
18
19
20 heterogeneity using the χ^2 test and estimate the amount of heterogeneity using the I^2 value.
21
22

23 *Data Synthesis*

24
25
26
27 The data and study characteristics will be summarized in a table, and we will determine if
28
29
30 a meta-analysis can be performed by clinical and methodological heterogeneity. Statistical
31
32
33 heterogeneity will be quantified using I^2 statistics in each analysis (22). If the extent of
34
35
36 heterogeneity is deemed acceptable ($I^2 < 50\%$) based on previous works, we will perform a meta-
37
38
39 analysis to summarize pooled results using a random effects model (23). If the study
40
41
42 characteristics display excessive heterogeneity ($I^2 > 50\%$), then we will report the data
43
44
45 descriptively, and we will provide a narrative synthesis of included studies using the Synthesis
46
47
48 Without Meta-Analysis Reporting Guideline as a framework (24). If quantitative synthesis of
49
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3
4 data is not possible, we will present a narrative synthesis in a table format to summarize the
5
6
7 findings of the appropriate studies.
8
9

10 *Subgroup Analysis*

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12
13 Subgroup analysis will be performed for the following parameters: study duration, donor
14
15
16 type (living vs. deceased), PTDM, pre-existing T2DM, blood pressure, blood glucose, statin use,
17
18
19 steroid use, metformin alone, metformin with other oral antihyperglycemics, and metformin with
20
21
22 insulin.
23
24
25

26 *Patient and Public Involvement*

27
28
29 We will be providing our findings to a Canadian research initiative known as CanSOLVE
30
31
32
33 CKD, which comprises of patients, healthcare providers, and researchers collaborating to
34
35
36
37 transform the care received by patients affected by chronic kidney disease. In addition, we will
38
39
40 also share our results with Diabetes Action Canada, a non-profit organization made of patient-
41
42
43 partners, researchers and healthcare providers that execute research projects benefiting patients
44
45
46 living with diabetes.
47
48
49

50 *Ethics and Dissemination*

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2
3
4 Ethics approval will not be required for this study, as it is entirely based on pre-existing
5
6
7 data from published studies. Our dissemination strategy will consist of peer reviewed
8
9
10 publications, presentations, and a report. We will disseminate our findings to major
11
12
13 organizations, patients, and professional societies such as the International Diabetes Federation
14
15
16 (IDF), International Society of Nephrology (ISN), Diabetes Canada, Kidney Foundation of
17
18
19 Canada and related patient organizations and professional bodies.
20
21
22

23 Discussion

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27 Currently, there are no clinical care recommendations based upon controlled studies on
28
29
30 the approach to anti-hyperglycemic medication management in kidney transplant recipients with
31
32
33 T2DM (9). As mentioned, patients who have pre-existing T2DM prior to their transplant, or
34
35
36 those who develop it after their transplant face numerous challenges. Transplant recipients are
37
38
39 predisposed to developing diabetes due to various risk factors such as post-operative stress, use
40
41
42 of corticosteroids, and use of calcineurin inhibitors (25). Presently, the guidelines do not favour
43
44
45 one pharmacological therapy over another in the setting of T2DM following kidney
46
47
48 transplantation (26). Although some studies have shown promise regarding a glucose lowering
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3 effect, they have been limited by sample size, and did not study clinically relevant outcomes
4
5
6
7 such as graft rejection or mortality (10, 11).
8
9

10 Ideally, the choice of therapy in T2DM affecting kidney transplant recipients should
11
12 focus on: (1) minimizing adverse effects of medications related to graft function, (2) maintaining
13
14 adequate glycemic control, and (3) demonstrating a cardiovascular or overall mortality benefit.
15
16
17 DPP-4 inhibitors and GLP-1 agonists show promise with a glucose lowering effect in this
18
19 population (10, 11, 27), but they have not been studied for a mortality benefit. In addition, they
20
21 are expensive agents and can be limited by cost (28). Furthermore, other options such as
22
23
24 sulfonylureas may not be appropriate due to the risks of hypoglycemia and weight gain. Insulin
25
26
27 therapies also induce hypoglycemia and weight gain, as well as requiring subcutaneous
28
29
30 injections that may be inconvenient for patients. As such, metformin may be a favourable option
31
32
33 in this setting. Metformin has been used for treatment of patients with T2DM patients in various
34
35
36 settings, owing to its effectiveness and other metabolic and cardiovascular benefits. However,
37
38
39 due to purported concerns about lactic acidosis, especially in patients with reduced kidney
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41
42 function, there is apprehension surrounding its use in kidney transplant recipients. We aim to
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54 evaluate the effects of metformin in kidney transplant recipients with T2DM, who are likely to
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3 be on advanced antihyperglycemic regimens, by conducting thorough subgroup analyses, which
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5
6 includes appraising the effects of metformin alone, metformin with other oral
7
8
9 antihyperglycemics and metformin with insulin. In addition, other parameters that are relevant to
10
11
12 consider include accounting for graft failure from cardiovascular causes (e.g., blood pressure,
13
14
15 steroid use, blood glucose), which may be responsible for the majority of kidney transplant
16
17
18 failures. As such, this will also be included in our subgroup analysis in order to separate the
19
20
21 effects of metformin use alone.
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26
27 Overall, this work will aim to provide much needed information on the effects of
28
29
30 metformin use in kidney transplant recipients and determine its place in the pharmacologic
31
32
33 management of kidney transplant recipients with T2DM. Currently, there are limited studies on
34
35
36 this topic in the literature. An evaluation of the literature via a systematic review will be helpful
37
38
39 in assessing their overall conclusions. This would be invaluable for such patients and clinicians,
40
41
42 no matter the outcome. If metformin is beneficial to positively impact patient-relevant outcomes
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44
45 in the study, the information may inform guideline recommendations for the use of this agent as
46
47
48 an inexpensive option for clinicians to consider for their patients with diabetes and kidney
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51 transplant. In addition, its other benefits, such as weight loss or minimal hypoglycemia, could
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3 also be leveraged in its favour. On the other hand, if we find metformin to be detrimental in
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6
7 kidney transplant recipients, clinicians may need to pursue other treatment options, as metformin
8
9
10 is currently often prescribed for patients with T2DM.
11
12

13 **Author contributions:** FS and AKB conceived the idea of the study. FS drafted the protocol
14
15
16 manuscript. AKB serves as the guarantor and supervisor of the research. All authors contributed
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18
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23
24
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26
27
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31 data extraction, and thoroughly proofread the study. All authors reviewed and approved the final
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3 None
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5 **Patient consent:**
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7 Not required
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10 **Data sharing statement:**
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12 We will make data available on request.
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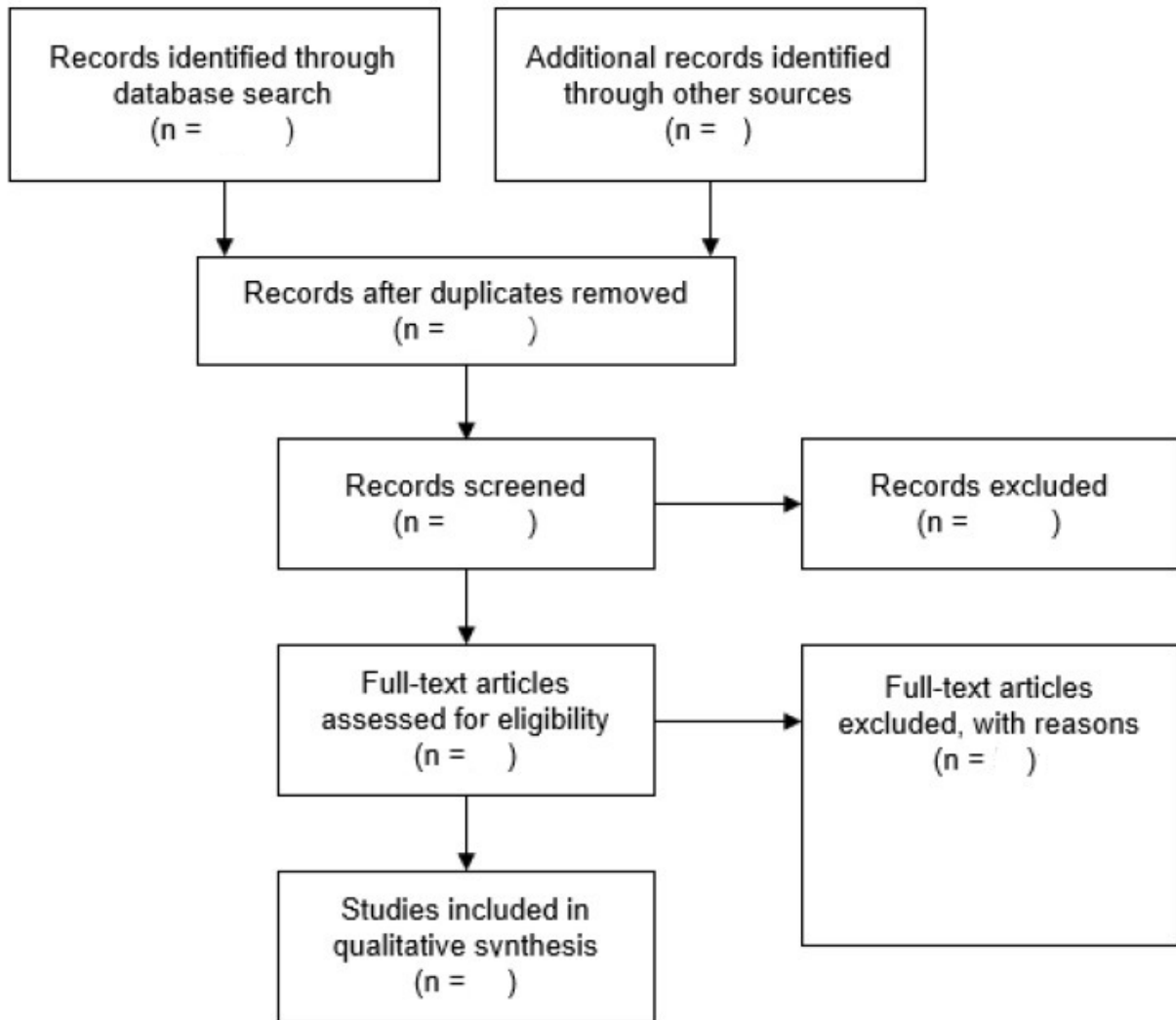
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For peer review only

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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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

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

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.

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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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
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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

1	Study records - data	#11c	Describe planned method of extracting data from reports (such as	10
2	collection process		piloting forms, done independently, in duplicate), any processes for	
3			obtaining and confirming data from investigators	
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6	Data items	#12	List and define all variables for which data will be sought (such as	10-11
7			PICO items, funding sources), any pre-planned data assumptions	
8			and simplifications	
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11	Outcomes and	#13	List and define all outcomes for which data will be sought,	8
12	prioritization		including prioritization of main and additional outcomes, with	
13			rationale	
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17	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	11
18	individual studies		studies, including whether this will be done at the outcome or study	
19			level, or both; state how this information will be used in data	
20			synthesis	
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24	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	12-13
25			synthesised	
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27				
28	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned	12-13
29			summary measures, methods of handling data and methods of	
30			combining data from studies, including any planned exploration of	
31			consistency (such as I ² , Kendall's τ)	
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34	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or	13
35			subgroup analyses, meta-regression)	
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38	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of	13
39			summary planned	
40				
41				
42	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	11
43			publication bias across studies, selective reporting within studies)	
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46	Confidence in	#17	Describe how the strength of the body of evidence will be assessed	11
47	cumulative		(such as GRADE)	
48	evidence			
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