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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 antihyperglycaemic agent for type 2 diabetes (T2DM). In addition to glycaemic 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 the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 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 for randomised controlled trials and the Risk of Bias in Non-randomised Studies of Intervention for non-randomised 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 include 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 centred groups.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 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 first-line agent or as an adjunct with other therapy.
⇒ Using 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 antihyperglycaemic 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 patients with obesity.[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 activity, along with a 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 and cardiovascular protection, while remaining largely weight neutral.[3] As such, there is a guideline-based consensus among 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 antihyperglycaemic agents in this population.[6 7] Diabetes Canada states that 'there is not enough evidence to support specific recommendations regarding choice of antihyperglycaemic therapy' for post-transplant diabetes mellitus. Manufacturers and guidelines also list poor kidney function (eg, estimated glomerular filtration rate (eGFR) <30 mL/min) as a barrier to 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 chronic kidney disease (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 hyperglycaemia, and those without pre-existing diabetes may develop new-onset diabetes after transplantation, also called post-transplant diabetes mellitus (PTDM). Perioperative stress and diabetogenic effects of immunosuppressive medications (ie, prednisone, calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors), among other risk factors, such as coronary artery disease or smoking, can exacerbate the problem. Nevertheless, given the antihyperglycaemic 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 hyperglycaemia in the kidney transplant population may include insulin. Yet, there have been limited head-to-head studies that have examined such treatment strategies for glycaemic 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 glucagon like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors also have limited evidence in PTDM. For instance, a small placebo-controlled study showed a small reduction of 0.2% in hemoglobin A1C (HbA1C) with no difference in adverse events.[12] Another study involving dulaglutide showed no improvement in glycaemic control.[12]

Ideally, antihyperglycaemic 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 hyperglycaemia 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 SGLT-2 is limited by high cost and may require special authorisation 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 patients who are immunosuppressed, the risks of mycotic genitourinary infection with SGLT-2 inhibitors may be increased, especially in kidney transplant recipients on immunosuppressive medications.[13] Lastly, guidelines recommend that patients at increased risk for hypoglycaemia (eg, 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 who 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 hypoglycaemia 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 excreted drugs have also been reported).[15] As such, other classes of antihyperglycaemics 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[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 was registered with PROSPERO International Prospective Register of Systematic Reviews on 28 June 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 randomised 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. Paediatric patients may have distinct physiological and pharmacokinetic characteristics compared with 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. Kidney transplants can be of any type (living donor, deceased donor) and 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 interventions

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, SGLT-2 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 (eg, abdominal pain, time to metformin discontinuation) that patients may experience while on metformin therapy, as defined by the study authors. We aim to use 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 (online supplemental 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 PRISMA Statement. Studies or records identified by other sources, such as through references to other texts, will not be under consideration for review. The planned start date for the study is 1 April 2023, and the planned end date is 31 August 2024.

Data collection and analysis

Study selection

We intend to use a two-stage collaborative process for screening and study selection. First, two reviewers (FS and 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 used as an arbitrator to evaluate studies in the event of a disagreement between 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 use metformin as an intervention. Online supplemental figure 1 outlines the criteria of study selection (see online supplemental 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 (pancreas and kidney transplant, liver and kidney transplant, etc.)
- Patients with a clear diagnosis of type 1 diabetes (T1DM)
- Retransplants 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 (eg, cohort, case–control, RCTs), study characteristics (eg, country of publication, publication year), trial size, patient characteristics (age, gender), transplant types (eg, living donor, deceased donor), onset of diabetes (eg, PTDM or pre-existing T2DM), types of interventions used (eg, metformin, insulin, other oral antihyperglycaemics, lifestyle interventions), relevant parameters for subgroup analysis as outlined in this protocol (eg, 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-randomised Studies of Intervention (ROBINS-I) for non-randomised studies.[21] The ROB-2 uses signalling questions to assess five domains, which include risk of bias arising from randomisation, 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 judgement for an RCT-type study.

The ROBINS-I preliminarily urges to consider confounding domains and cointerventions that could be within a study and then proceeds to evaluate the study across seven 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 use standardised MD between the intervention and control groups. Finally, we will present the intervention effect of any time-to-event outcomes as HRs. The 95% CIs 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 summarised 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 summarise 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 summarise 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 antihyperglycaemics 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 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 organisation 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 organisations, patients and professional societies such as the International Diabetes Federation, International Society of Nephrology, Diabetes Canada, Kidney Foundation of Canada and related patient organisations and professional bodies.

DISCUSSION

Currently, there are no clinical care recommendations based on controlled studies on the approach to antihyperglycaemic 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 postoperative 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) minimising adverse effects of medications related to graft function, (2) maintaining adequate glycaemic 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 hypoglycaemia and weight gain. Insulin therapies also induce hypoglycaemia and weight gain, as well as require 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 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 antihyperglycaemic regiments, by conducting thorough subgroup analyses, which includes appraising the effects of metformin alone, metformin with other oral antihyperglycaemics and metformin with insulin. In addition, other parameters that are relevant to consider include accounting for graft failure from cardiovascular causes (eg, 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 transplant 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 hypoglycaemia, 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.

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Contributors 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, IO and 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 and 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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