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Pharmacotherapy in paediatric type 2 diabetes mellitus: a protocol for a systematic review and network meta-analysis of randomised trials

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ABSTRACT

Introduction The rates of type 2 diabetes mellitus (T2DM) in children and adolescents have risen globally over the past few years. While a few diabetes pharmacotherapies have been used in this population, their comparative benefits and harms are unclear. Thus, we will conduct a systematic review and network meta-analysis (NMA) of randomised controlled trials (RCTs) to compare the efficacy and safety of pharmacotherapies for managing paediatric T2DM.

Methods and analysis We will include RCTs that enrolled T2DM patients ≤18 years of age and who were randomised to monotherapy or combination pharmacotherapies with or without lifestyle interventions. Comparator groups will include placebo or non-pharmacological treatments including lifestyle interventions.

Treatment outcomes will include change from baseline in glycated haemoglobin A1c, body mass index z-score, weight, systolic/diastolic blood pressure, fasting plasma glucose, fasting insulin and lipid profiles, T2DM-related complications, as well as the incidence of treatment-related adverse events.

Literature searches will be conducted in Medline, Embase, CINAHL, CENTRAL and Web of Science. We will also search the grey literature and the reference list of included trials and relevant reviews. Two reviewers will assess the eligibility of articles identified through our searches and will extract data from eligible studies independently. We will use a modified Cochrane instrument to evaluate the risk of bias. Disagreements will be resolved through consensus or arbitration by a third reviewer.

A frequentist random-effects model will be used for conducting NMA. The quality of evidence will be assessed using the Confidence in Network Meta-Analysis platform. We will assess the effect modification through network meta-regression and subgroup analyses for sex, age at study inclusion, duration of T2DM, follow-up duration and risk of bias ratings.

Ethics and dissemination This study will not require ethics approval. We will disseminate our findings through publication in a peer-reviewed journal and conference presentations.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Network meta-analyses will enable the comparison and ranking between available pharmacotherapies for management of type 2 diabetes mellitus in children and adolescents.
⇒ Only randomised clinical trials will be included, which strengthens the confidence in study conclusions.
⇒ A priori subgroup and network meta-regression analyses can potentially explain sources of heterogeneity.
⇒ The relatively limited amount of available evidence may be a constraint to data interpretation.

INTRODUCTION

The paediatric obesity epidemic is impacting millions of children globally, representing a major health challenge with disproportionate burdens on the healthcare systems of low-income and middle-income countries.[1 2] The most common type of diabetes in children is type 1 diabetes mellitus (T1DM), whereby the immune-mediated pancreatic β-cell destruction leads to insulin deficiency and hyperglycaemia.[3 4] However, obesity has been a major driver of the emergence of type 2 diabetes mellitus (T2DM), an adult disease, in children.[5–8]

Paediatric T2DM is associated with comorbidities and complications that arise early in the course of the disease.[9–11] At presentation and within the first few years postdiagnosis, patients may develop hypertension, proteinuria, dyslipidaemia, obstructive sleep apnoea, non-alcoholic fatty liver disease and polycystic ovary syndrome.[12–15] Patients are also predisposed to retinopathy and neuropathy that occur more frequently and earlier in T2DM patients when compared with their T1DM counterparts.[16]

There is significant evidence demonstrating that tight glycaemic control improves diabetes

outcomes in adults and youth with T1DM.[17][18] While similar evidence is lacking in paediatric T2DM due to the limited natural history data, adequate glycemic control is crucial to attempt the mitigation of comorbidities and complications. Multiple pharmacotherapies have been approved to treat T2DM in adults, and the treatments for paediatric T2DM were limited to metformin and insulin, yet more recently some glucagon-like peptide-1 (GLP-1) receptor agonists were approved for use in the USA.[19–23]

However, these treatments have not been compared head-to-head to assess their efficacy and safety for management of T2DM in children.

The objective of the proposed systematic review and network meta-analysis (NMA) is to compare the efficacy and safety of current treatments in paediatric T2DM patients to provide treatment guidance and direct future research efforts.

METHODS AND ANALYSIS
Standardised reporting
The protocol for this review was registered in PROSPERO.[24] This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guideline.[25][26] We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of systematic reviews incorporating NMAs of healthcare interventions when reporting the findings of this review.[27] Any significant amendments to the protocol will be reported in the final review.

Information sources
We will include randomised controlled trials (RCTs) identified through search strategies developed in collaboration with a Senior Health Sciences Librarian. The databases will be searched from the date of inception of the database and up to 1 May 2022. The databases will include Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science. A sample of the proposed Medline search strategy is appended in **online supplemental table S1**. We will also search ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and the health sciences preprint server medRxiv. Reference lists of eligible primary papers and relevant reviews will be hand-searched to identify eligible articles. The searches will be restricted to human studies with no limitations on language or publication year.

Eligibility criteria
We will include RCT with any design (eg, parallel, crossover, cluster) that enrolled paediatric patients ≤18 years with T2DM diagnosed according to standard criteria,[20][22] and randomised to either monotherapy or combination pharmacotherapies. In addition, non-pharmacological interventions such as lifestyle programmes as add-ons or comparator and placebo arms will be included. Examples of acceptable pharmacotherapies include

biguanides (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, glitazones, dipeptidyl peptidase-4 inhibitors (gliptins), gliflozins, insulin and GLP-1 receptor agonists, as well as any other interventions that may be identified through the systematic literature searches.

We will include all sexes, races, geographical locations, pubertal stages and studies from any clinical setting in this review.

We will exclude patients diagnosed with T1DM, gestational diabetes mellitus, maturity-onset diabetes of the young and medication-induced diabetes. Complementary and alternative medicines, including traditional Chinese medicines, defined according to the National Center for Complementary and Integrative Health criteria[28][29] will also be excluded from this review.

Our main outcome of interest is the change in glycated haemoglobin A1c from baseline to the latest follow-up data reported. Other important outcomes include changes from baseline to latest follow-up of body mass index z-score, body weight, systolic and diastolic blood pressure, fasting plasma glucose, fasting insulin, fasting C-peptide, lipid profile (including cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein) and diabetes-related complications including nephropathy, retinopathy and neuropathy. We will also assess treatment-related side effects such as gastrointestinal manifestations as well as adverse events such as hypoglycaemia, diabetic ketoacidosis, and lactic acidosis and others reported in the literature.

Study selection and data abstraction
A pair of reviewers will independently screen the identified titles and abstracts in duplicate using the Rayyan platform (Rayyan Systems Inc., https://www.rayyan.ai).[30] Full-text of articles judged to be potentially eligible will be retrieved and their eligibility will be confirmed. We will conduct calibration exercises for the data abstraction to ensure consistency and accuracy of the extracted data. Data extraction will be performed in duplicate and independently. Reviewers will resolve any discrepancies by discussion to reach consensus or, if needed, by adjudication from a third reviewer.

For all included studies, reviewers will abstract data on study characteristics including bibliographic information, country, publication year, study setting and duration, funding source, the number of participating centres in multicenter trials, whether the analysis followed an intention-to-treat approach, and information about the design of cluster-randomised or crossover trials including data related to carry-over effect for crossover RCTs and intraclass correlation coefficients for cluster RCTs. Participant data collected will include screening and selection methods, mean age, mean duration of T2DM, sex, number of patients randomised and analysed for each outcome, and number of patients lost to follow-up. Data on the characteristics of interventions and comparators including treatment dose and duration,

length of follow-up, cointerventions, and data relating to our outcomes of interest and subgroup analyses will be abstracted.

Risk of bias assessment

Two reviewers will assess the risk of bias using the Cochrane risk-of-bias tool for randomised trials 2 (RoB 2).[31] Risk of bias will be assessed based on randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement and reporting bias. The overall risk of bias rating and that of each individual domain will be assessed.[32] The risk of bias assessments will be presented using a traffic light plot and a risk of bias summary bar graph.[33]

Missing data

For missing or unpublished data required for conducting the analyses, we will contact the study authors via e-mail to request the data.

For studies that present non-parametric statistics for continuous outcomes, such as medians with IQR or range, we will impute the mean and SD.[34]

For data available only in graphical form and unavailable from study authors, we will estimate the numerical values by pixel counting using WebPlotDigitizer.[35] For cross-over trials, if there is evidence of carry-over effect, we will only include the latest data from before the first crossover in the review.[36]

We will tabulate and narratively describe any relevant data that are deemed inappropriate to be quantitatively synthesised.

Methods for direct comparison

For direct comparisons, we will pool outcomes reported by at least two trials. For dichotomous outcomes, we will calculate the relative risk and the risk difference and the associated 95% CIs. For continuous outcomes, we will calculate the weighted mean differences and associated 95% CIs.

To account for interpatient variability, change scores from baseline to the end of follow-up will be used in the analysis. If change scores are not reported, we will calculate them using the baseline and end-of-study scores and the associated SD using a correlation coefficient derived from the largest trial at the lowest risk of bias that reported a change score.[37]

For any dichotomous outcomes with no events in at least one of the treatment arms, we will complete the meta-analysis by applying a continuity correction factor of 0.5.

To account for potential heterogeneity due to differences in methodologies and settings, we will use DerSimonian-Laird random-effects models for meta-analysis of all direct comparisons.[38]

Methods for NMA

We will perform a frequentist random-effects model using multivariate meta-analysis.[39 40] We will use the 'design-by-treatment' model as a global test to assess the coherence

assumption for each outcome network.[39] We will use the side-splitting method to evaluate local loop-specific incoherence in each closed loop of the network as the difference between direct and indirect evidence.[41 42]

We will estimate ranking probabilities among competing therapies and rank interventions for the NMA using the surface under the cumulative ranking curve (SUCRA) or mean ranks. An intervention with a SUCRA value of 100 is considered the most effective, whereas a value of 0 indicate that the intervention is the least effective. However, to estimate probability rankings and the SUCRA values, the point estimates of effect are considered, but not the associated precision or the certainty of evidence. Thus, we will instead apply a minimally contextualised approach to convey the relative benefits and harms of eligible interventions and will categorise them from most to least effective/harmful, based on the treatment effect estimates, obtained from NMA and their associated certainty of evidence.[43]

We will use STATA V.16.0 (StataCorp) for all analyses. All comparisons will be two-tailed using a threshold $p \leq 0.05$.

Subgroup analyses and network meta-regressions

We will conduct subgroup analyses by sex, race, risk of bias ratings and diabetes duration for each outcome if the data allow such analyses. Additionally, we will also conduct network meta-regressions based on age at study inclusion, sex, race and duration of T2DM.

Heterogeneity and small-study effect assessment

Heterogeneity between studies for each direct comparison will be investigated using visual inspection of the forest plots and the I^2 statistic. For direct comparisons, we will consider $\leq 25\%$ as low, $>25\% - <50\%$ as moderate and $\geq 50\%$ as substantial heterogeneity.[37] For all direct comparisons, where there are ≥ 10 trials for the meta-analysis, we will assess small-study effects using Harbord's test for binary outcomes and Egger's test for continuous outcomes.[44 45]

Assessing the quality of evidence

We will use the Confidence in Network Meta-Analysis (CINeMA) web application to assess the certainty of the direct, indirect and the network estimate for all outcomes. CINeMA evaluates certainty of the evidence based on six domains including within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.[46 47] The first five domains correspond to the risk of bias, publication bias, indirectness, imprecision and inconsistency domains evaluated by the Grading of Recommendations, Assessment, Development and Evaluations approach for assessing certainty of the evidence.[48] Incoherence is a NMA-exclusive domain that is assessed in CINeMA, representing the inconsistency between direct and indirect evidence in a closed-loop of evidence within the network.[49]

Minimally contextualised approach

Once certainty of evidence is assessed for each outcome, we will create groups of interventions as follows: (1) the reference intervention and interventions no different from the reference, which we refer to as 'among the least effective'; (2) interventions superior to the reference treatment but not superior to other intervention(s), which we describe as 'inferior to the most effective, but superior to the least effective' (category 2 interventions) and (3) interventions that prove superior to at least one intervention in the category 2 interventions (which we defined as 'among the most effective'). The same approach will be used for the safety outcomes, but we will create groups of interventions as follows: (1) no more harmful than the reference treatment; (2) less harmful than some alternatives, but more harmful than the reference and (3) among the most harmful. We will then categorise interventions as those with moderate or high certainty, and those with low or very low certainty of evidence.[43 50]

Patient and public involvement

There was no patient or family involvement in posing the research question, establishing the study design and methods, and the plan for data analysis. The findings from this report will be disseminated to Healthcare providers and organisations supporting children and their families with T2DM.

DISCUSSION

The paediatric obesity epidemic has propelled several other paediatric chronic diseases, including T2DM. The emergence of T2DM in children heralded a new era in paediatric diabetes care. Multidisciplinary care approaches to manage paediatric diabetes have been in place for the past three decades.[20] However, these care systems are predominantly designed for children and adolescents with T1DM, and care for T2DM patients require significant modifications and new resources as the patient characteristics and healthcare needs in T2DM are quite different from T1DM patients.[51 52] T2DM is a predominantly an adolescent disease, and these patients need special consideration in terms of managing a multicomorbidity disease such as T2DM.[5 20 53]

Family-centred and culturally appropriate multidisciplinary programmes for T2DM management are essential and need to combine comprehensive lifestyle interventions with pharmacotherapies, and with focus on mental and emotional health needs of this population.

This systematic review and NMA will investigate the efficacy and safety of pharmacotherapies used in the management of T2DM in children and adolescents. The NMA approach will allow more precise estimates and provide relative ranking of interventions based on direct and indirect evidence. This approach will enable the examination of all available interventions for paediatric T2DM to offer a comprehensive overview of the current gaps in clinical care and research.

Ethics and dissemination

Ethical approval is not required for the proposed review, as only published, aggregate patient data will be used for analysis. The final review will be submitted to peer-reviewed journals for dissemination and will be presented in scientific meetings.

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