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Pharmacologic interventions for prevention of type 2 diabetes mellitus in people with prediabetes: a systematic review and network meta-analysis protocol

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Keywords:	diabetes, network meta-analysis, prevention, prediabetes, pharmacologic interventions, systematic review

Pharmacologic interventions for prevention of type 2 diabetes mellitus in people with prediabetes:

a systematic review and network meta-analysis protocol

Hai Zeng,[1] Junru Wen,[2,3] Guoxin He,[4] Meng Luo,[1] Zunjiang Li,[1] Yueling Jin,[3] Wenbin Fu [1,5*]

ABSTRACT

Introduction Type 2 diabetes mellitus (T2DM) is a substantial health problem worldwide. Prediabetic state is associated with increased risk for the development of diabetes. There are various pharmacologic therapies for diabetes prevention. Of those, most are being compared with placebo instead of active agents. The relative effects and safety of different pharmacologic interventions still remains uncertainty. To address this gap, we will conduct a systematic review and network meta-analysis to evaluate comparative efficacy and safety of pharmacologic therapies for T2DM prevention in patients with prediabetes to generate reliable evidence.

Methods and analysis PubMed, the Cochrane library, and EMBASE will be utilized to search for relevant RCTs of pharmacologic therapies for diabetes prevention in participants with prediabetes from inception until December 2018. Two reviewers working independently will screen titles, abstracts, and full papers. Data extraction will also be completed by two independent authors. Primary outcome will be incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include achievement of normoglycaemia, all-cause mortality, cardiovascular mortality, and hypoglycaemic event. Pairwise meta-analysis and network meta-analysis will be conducted for each outcome using a random-effects model within a frequentist approach. To evaluate the robustness of our findings, subgroup analyses and sensitivity analyses will also be performed. The comparison-adjusted funnel plot will be used to assess publication bias. The overall quality of evidence of estimates will be rated with the recommendations assessment, development and evaluation (GRADE) framework. Data analysis will be conducted using Stata V.14.0.

Ethics and dissemination Ethics approval is not required. We plan to submit results of this study to a peer-review journal.

PROSPERO registration number CRD42019119157.

Strengths and limitations of this study

► This is a comprehensive network meta-analysis to evaluate the effectiveness and safety of various pharmacologic therapies on diabetes prevention among people with prediabetic state.

► Where possible, network meta-analysis will combine direct evidence with indirect evidence, allowing comparisons of treatments without being compared to each other head-to-head in clinical trials.

► This research will generate clinically useful evidence to benefit patients, clinicians, and guideline-makers.

► The different frequencies, dosage, and routes of administration of pharmacological therapies may lead to considerable heterogeneity.

Keywords: diabetes, network meta-analysis, pharmacologic interventions, prediabetes, prevention, protocol, systematic review

INTRODUCTION

Type 2 diabetes is a chronic and complex disease related to insulin secretory defects frequently on the background of insulin resistance, and its progression is associated with genetic factors, metabolic stress, and inflammation.[1] The global prevalence of Type 2 diabetes mellitus (T2DM) has reached alarming proportions with an estimated 463 million people in 2017.[2] People with T2DM are at elevated risk for chronic kidney disease, heart failure, atherosclerotic cardiovascular disease, polyneuropathy, cognitive impairment, anxiety disorder, and depression.[1,3] The term prediabetes is used to describe a blood glucose level higher than is considered normal but below the cut-off value for T2DM.[4] Different glycaemic measurements to define the prediabetic stage exist, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and elevated glycosylated haemoglobin A1c (HbA1c).[1] According to standards of medical care in diabetes of American Diabetes Association (ADA), prediabetes is defined as a FBG of at least 5.6 mmol/L but lower than 6.9 mmol/L, a HbA1c of 5.7-6.4%, or IGT (a 2-hour plasma glucose value of 7.8-11.1 mmol/L during oral glucose tolerance test).[1] These measurements are considered to predict a different risk spectrum for progression of prediabetes to diabetes. The International Diabetes Federation (IDF) estimated that, in 2017, approximately 352 million persons globally had IGT, which is projected to exceed half a billion people before 2045.[5] Dysglycaemia is a well described risk factor for all-cause mortality, total numbers of all-age deaths attributed to high fasting plasma were 6 million people in 2017,[6] with type 2 diabetes accounting for 1 million deaths.[7] Moreover, the economic burden of diabetes is large, economic costs of which increased to 126% from 2012 to 2017 in the US, with a total estimated cost of $327 billion in 2017.[8,9] Diabetic patients incurred average medical expenditures of $16,750 yearly, with diabetes accounting for $9,600.[9] Thus, there is an urgent need to address huge burden of this worldwide disease with a growing number of suffers. Early interventions for preventing type 2 diabetes are warranted.[8] Persons diagnosed with prediabetes are thought to be at increased risk for developing T2DM, the approximated incidence rate of diabetes among people defined as “prediabetic stage” by measurements of IFG, IGT, or HbA1c in the following 10 years is more than one third.[10] These people are ideal candidates for T2DM prevention efforts. To prevent progression of prediabetes to type 2 diabetes, an intensive behavioral lifestyle intervention program is recommended, including individualized medical nutrition therapy, physical activity, and no tobacco use.[1] However, to date, whether any pharmacologic intervention should be recommended for persons with prediabetes or not has not yet to be clarified clearly.[11] Importantly, in recent years, an increasing number of clinical trials have investigated several groups of pharmacological therapies for T2DM prevention, including insulin secretagogues, glucagon-like peptide (GLP)-1 analogues, alpha-glucosidase inhibitors, dipeptidyl-peptidase (DPP)-4 inhibitors, biguanides, and thiazolidinediones. Some findings suggest that using these pharmacological agents could reduce or delay the progression to T2DM. Nevertheless, head-to-head comparisons of different pharmacologic therapies have rarely been performed by previous clinical trials. Evidence regarding the overall and comparative efficacy of these pharmacological interventions for T2DM prevention is limited, while important for clinical decision-making. Conventional pairwise meta-analyses are limited to pool the results

of trials comparing two interventions directly while a network meta-analysis (NMA) method is able to combine direct and indirect evidence and assess comparative efficacy and safety of various interventions.[12-14] Therefore, to bridge this knowledge gap, we plan to conduct a network meta-analysis to assess comparative effectiveness and safety of several medications for preventing T2DM in participants with prediabetes, which may provide beneficial information for clinical decision-making and further clinical trials.

METHODS

Study design and registration

This systematic review protocol is reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[15,16] This study will be performed in accordance with PRISMA extension statements for network meta-analysis.[12]

Eligibility criteria

Population

Adults (older than 18 years) who have prediabetes will be eligible for inclusion. In this study, prediabetic state involves separate impaired fasting glucose (IFG), separate impaired glucose tolerance (IGT), separate elevated glycosylated haemoglobin A1c (HbA1c) or combinations thereof. Diagnostic criteria for prediabetes should be established and described in eligible trials.

Intervention and comparator

This study will investigate comparisons of pharmacological interventions versus another active agent, lifestyle interventions (diet, exercise, or both), placebo or no intervention. Pharmacological therapies include alpha-glucosidase inhibitors, sulphonylureas, meglitinide analogues, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, biguanides, thiazolidinediones, alone or in combination.

Outcomes

Primary outcome will be incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include achievement of normoglycaemia, all-cause mortality, cardiovascular mortality, and hypoglycaemic event. Classification and definition of T2DM could be based on any recognised standard diagnosis criteria (ie, the American Diabetes Association guidelines).

Type of studies

All randomised controlled trials (RCTs) comparing pharmacological agents with other drugs, lifestyle interventions, placebo or no intervention for T2DM prevention in patients with prediabetes will be included in this study. Duration of intervention has to be with a minimum duration of 12 weeks.

Search strategy

Various databases will be utilized to search for RCTs of pharmacologic therapies for preventing diabetes among patients with prediabetes from inception date of databases until December 2018. The databases will include PubMed, Embase, and the Cochrane Library. In addition, the language of publication will be limited to English. Any potentially-relevant article will be retrieved for

review. Details of search strategy of PubMed database is shown in supplemental material. The literature search will be conducted using the following keywords: alpha-glucosidase inhibitors, sulphonylureas, glinide, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, biguanides, thiazolidinediones, diabetes, T2DM, prediabetes, prediabetic state, glucose intolerance, impaired glucose, diabetic, dysglycaemia, hyperglycaemia, conversion, delay, and prevent. Moreover, all drug names in each drug class will be included in key search terms, for instance, acarbose, voglibose, metformin, alogliptin, saxagliptin, liraglutide, and albiglutide. To identify other eligible studies, reference lists of relevant publications (including trials, reviews, and meta-analyses) will be reviewed for a manual search.

Selection of studies

In accordance with the prespecified inclusion criteria, two reviewers working independently will evaluate all titles and abstracts to eliminate papers deemed irrelevant. The remaining articles will be included in the further assessment. Reviewers will scrutinize full text for each potentially-relevant article. The study identification and exclusion process will be depicted using the PRISMA flow diagram. Discrepancies in study selection will be resolved by negotiation.

Data collection process

Two independent reviewers will use a standardized data form to extract trial information. All disagreements will be settled via discussion with the third reviewer. The data extracted will be as follows:

► Patient characteristics (age, gender, race, weight and glycemic parameters).

► trial characteristics (author, publication year, study design, country setting, and funding information).

►Details of intervention and control (dosage, frequency, and treatment duration).

►Outcome data for all endpoints of interest.

Assessment of methodological quality

The Cochrane risk of bias assessment tool will be used to assess risk of bias for individual studies. The method includes following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[17] Each item will be classified into one of three categories as follows: unclear, high or low risk. All discrepancies in quality assessment will be resolved after mutual agreement and discussion.

Data synthesis and statistical analysis

Initially, we will use a random-effects approach to pool effect estimates for all treatment comparisons in conventional pairwise meta-analyses. For categorical outcomes, the pooled estimates as risk ratios (RRs) with 95% confidence intervals (CIs) will be reported. Continuous data will be reported as mean differences (MDs) with their respective 95% CIs. Statistical heterogeneity across trials will be examined using the I^2 statistic. An I^2 statistic of 75%, 50%, or 25% indicates high, moderate, or low heterogeneity, separately.[18] Then, network meta-analyses will be carried out in a frequentist environment. Local inconsistency between direct and indirect evidence within each closed loop will be assessed using a node-splitting test.[19,20] In addition, a

"design-by-treatment" model will be applied to evaluate the assumption of consistency in the whole network.[19] We will generate the surface under the cumulative ranking curve (SUCRA) to assess probabilities of interventions in superiority regarding efficacy and safety outcomes, with higher SUCRA values indicating better effects or safety.[21] The level of significance will be set at an alpha of 0.05. All analyses will be performed with Stata version 14.0 (StataCorp, College Station, TX).

Sensitivity and subgroup analyses

We will perform additional sensitivity analyses. Where possible, analyses will be stratified by age (18-64 years and at least 65 years), gender, ethnicity, and BMI (25-29.9 kg/m^2 and ≥30 kg/m^2). Moreover, we will also perform subgroup analyses according to diagnostic criteria (IFG, IGT, and HbA1c).

Publication bias

We will employ the comparison-adjusted funnel plot to assess small study effects including publication bias at the network level.[22]

Quality of evidence

The quality of evidence of estimates derived from NMA will be rated using the recommendations assessment, development and evaluation (GRADE) framework. The GRADE approach characterises the quality of evidence according to publication bias, study limitations, inconsistency, imprecision, and indirectness.[23] Evidence of efficacy outcomes will be rated from high quality to very low quality.

Patient and public involvement

No patients or public will participate in the study.

Ethics and dissemination

Since confidential patient data will not be involved in this study, formal ethics approval is not required. The framework of the PRISMA statements for NMA will be applied to guide review authors to perform this study. The results will be disseminated by a peer-reviewed publication.

DISCUSSION

This study is a comprehensive NMA comparing and ranking a variety of pharmacological interventions for preventing T2DM in patients at high risk for the development of T2DM. Our study will provide a summary of the best available evidence concerning pharmacological therapies for T2DM prevention in patients with prediabetic state, benefitting for clinicians, guideline-makers, and policy-makers to generate higher quality recommendations for these patients. Although a relevant NMA[24] published, the study was based on clinical trials before 2014. Additionally, included pharmacological interventions in the study were limited, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, and some other glucose-lowering drugs that have been tested by later trials clinically were not involved. It is essential to contain these commonly prescribed agents in multiple comparisons of medications for the prevention of T2DM. Moreover, the definition of adults at high risk for T2DM was based on

IFG and IGT, excluding people identified by HbA1c. Importantly, HbA1c is a biomarker of long-term glycemic control when compared IFG and IGT, representing average blood glucose levels during the preceding two to three months.[25] Several strengths can be foreseen of this review, but our network meta-analysis may have some possible limitations. The different frequencies, dosage, and routes of administration of pharmacological therapies may result in considerable heterogeneity. Differences in inclusion criteria of participants and definition of end-point events may influence the quality of evidence.

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Contributors HZ conceived the review. JRW, GXH, and HZ wrote the first draft of this protocol. WBF, ZJL, ML, and YLJ were responsible for revising the draft. HZ, ML and JRW contributed to developing the search strategy and registering the protocol. WBF and YLJ were the guarantors. All authors scrutinized and approved the final manuscript.

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Provenance and peer review Not commissioned; externally peer review.

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Search strategy in PubMed.

Block 1: Prediabetes
#1 "Prediabetic state" [Mesh]
#2 "Glucose Intolerance" [Mesh]
#3 (prediabet* OR pre diabet*) [tiab]
#4 intermediate hyperglyc?emi* [tiab]
#5 ((impaired fasting adj2 glucose) OR IFG or impaired FPG) [tiab]
#6 ((impaired glucose adj (tolerance OR metabolism)) OR IGT) [tiab]
#7 ("dysglycaemia" OR "hyperglycaemia") [tiab]
#8 ((risk OR progress* OR prevent* OR inciden* OR conversion OR develop* OR delay*) adj4 (diabetes OR T2D* OR NIDDM OR "type 2" OR "type II")) [tiab]
#9 OR #1-8

Block 2: Alpha-glucosidase inhibitors
#10 "Acarbose" [Mesh]
#11 (acarbos* OR glucobay OR precose OR prandase OR "bay g 5421" OR BAYG5421) [tiab]
#12 (voglibos* OR glustat OR basen) [tiab]
#13 (miglitol* OR glyset) [tiab]
#14 (glucosidase* adj3 inhibitor*) [tiab]
#15 OR #11-14

Block 3: DPP-4 inhibitors
16# "Dipeptidyl-Peptidase IV Inhibitors" [Mesh]
17# "gliptin*"[tiab]
18# ((dipeptidyl peptidase or dipeptidylpeptidase or dpp) adj ("4" or IV) adj inhibitor?) [tiab]
19# (alogliptin OR anagliptin OR bisegliptin OR carmegliptin OR denagliptin OR dutogliptin OR evogliptin OR gemigliptin OR gosogliptin OR linagliptin OR melogliptin OR omarigliptin OR sitagliptin OR saxagliptin OR teneligliptin OR trelagliptin OR vildagliptin) [tiab]
#20 OR #16-19

Block 4: GLP-1 analogue
#21 "Glucagon-Like Peptide 1" [Mesh]
#22 ((glucagon like peptide* or GLP 1 or GLP1) adj3 (analog* or agonist*))[tiab]
#23 (exenatide OR liraglutide OR albiglutide OR elsiglutide OR lixisenatide OR dulaglutide OR taspoglutide OR semaglutide OR teduglutide) [tiab]
#24 OR #21-23

Block 5: Sulfonylurea
#25 "Sulfonylurea Compounds" [Mesh]

#26 (sulfon?lurea* OR sulphon?lurea*)[tiab]
#27 (gl?benclamid* OR glyburid*)[tiab]
#28 (gl?bornurid* OR gluborid*)[tiab]
#29 (glipizid* OR gl?diazinamide OR glypidizine OR melizide OR napizide)[tiab]
#30 (gliquidon* OR glisoxepid* OR gl?clopyramid* OR glimepirid* OR gl?clazid* OR gl?cazid*)[tiab]
#31 OR #25-30

Block 6: Glinide
#32 (glinide OR glinides) [tiab]
#33 (nateglinid* or senaglinid* OR repaglinid* OR mitiglinid*) [tiab]
#34 OR #32-33

Block 7: Biguanides
#35 “Biguanides” [Mesh]
#36 (buformi* OR chloroguani* OR metformi* OR phenformi*) [tiab]
#37 OR #35-36

Block 8: Thiazolidinediones
#38 “Thiazolidinediones” [Mesh]
#39 (thiazolidinedione OR TZD OR glitazone OR glitazones) [tiab]
#40 (pioglit* OR rosiglit* OR troglit*) [tiab]
#41 OR #38-40

Block 9: RCT-filter
#42 "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]

#43
#9 AND #15 AND #20 AND #24 AND #31 AND #34 AND #37 AND #41 AND #42

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2, 3
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	3
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	3, 4
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	3, 4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
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)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	4
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	4
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	4, 5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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ABSTRACT

Introduction Type 2 diabetes mellitus (T2DM) is a substantial health problem worldwide. Prediabetic state is associated with increased risk for the development of diabetes. There are various pharmacologic therapies with glucose-lowering activity for diabetes prevention. Of those, most are being compared with placebo instead of active agents. The relative effects and safety of different glucose-lowering drugs still remain uncertain. To address this gap, we will conduct a systematic review and network meta-analysis (NMA) to evaluate comparative efficacy and safety of glucose-lowering agents for T2DM prevention in patients with prediabetes.

Methods and analysis PubMed, the Cochrane library, and Embase will be searched from inception to December 2019 for relevant randomized controlled trials (RCTs) that examined anti-diabetic drugs for diabetes prevention in patients with prediabetes. Two reviewers working independently will screen titles, abstracts, and full papers. Data extraction will also be completed by two independent authors. The primary outcome will be the incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include the achievement of normoglycemia, all-cause mortality, cardiovascular mortality, and hypoglycemic event. Pairwise meta-analysis and NMA will be conducted for each outcome using a frequentist random-effects model. Additionally, subgroup analyses will also be performed. The comparison-adjusted funnel plot will be used to assess publication bias. The overall quality of evidence will be rated with the recommendations assessment, development and evaluation (GRADE) framework. Data analysis will be conducted using Stata V.14.0.

Ethics and dissemination Ethics approval is not required. We plan to submit the results of this study to a peer-review journal.

PROSPERO registration number CRD42019119157.

Strengths and limitations of this study

► This is a comprehensive systematic review and network meta-analysis to evaluate the effectiveness and safety of various glucose-lowering medications on diabetes prevention among people with prediabetic state.

► Where possible, a NMA will combine direct evidence with indirect evidence, allowing comparisons of treatments without being compared to each other head-to-head in clinical trials.

► This research will generate clinically useful evidence to benefit patients, clinicians, and guideline-makers.

► The different frequencies, dosages, and routes of administration of pharmacological therapies may lead to considerable heterogeneity.

Keywords: anti-diabetic agents, diabetes, network meta-analysis, prediabetes, prevention, systematic review

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and complex disease, related to insulin secretory defects frequently on the background of insulin resistance; the progression of the disease is associated with genetic factors, metabolic stress, and inflammation.[1] The global prevalence of T2DM was estimated to be 463 million people in 2017.[2] People with T2DM are at elevated risk for chronic kidney disease, heart failure, atherosclerotic cardiovascular disease, polyneuropathy, cognitive impairment, anxiety disorder, and depression.[3-5] The term prediabetes is used to describe a blood glucose level higher than the normal range but below the cut-off value for T2DM.[6] Different glycemic measurements to define the prediabetic stage exist, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and elevated glycosylated haemoglobin A1c (HbA1c).[1] According to the standards of medical care in diabetes of the American Diabetes Association (ADA), prediabetes is defined as a fasting plasma glucose of at least 5.6 mmol/L but lower than 6.9 mmol/L, a HbA1c of 5.7-6.4%, or IGT (a 2-hour plasma glucose value of 7.8-11.1 mmol/L during oral glucose tolerance test).[1] These measurements are considered to predict a different risk spectrum for the progression of prediabetes to diabetes. The International Diabetes Federation (IDF) estimated that, in 2017, approximately 352 million persons globally had IGT, which is projected to exceed half a billion people before 2045.[7] Hyperglycemia is a well described risk factor for all-cause mortality, total number of all-age deaths attributable to high fasting plasma was 6.5 million people in 2017,[8] with T2DM accounting for 1 million deaths.[9] Moreover, the economic burden of diabetes is large; in 2017, the ADA estimated the total economic costs attributable to diabetes in the U.S. to be $327 billion.[10,11] Diabetic patients incurred average medical expenditures of $16,750 yearly, with diabetes accounting for $9,600.[11] Thus, there is an urgent need to address huge burden of this worldwide disease with a growing number of suffers. Early interventions for preventing type 2 diabetes are warranted.[10] Persons diagnosed with prediabetes are thought to be at increased risk for developing T2DM, the estimated incidence rate of diabetes among people defined as "prediabetic stage" by measurements of IFG, IGT, or HbA1c in the following 10 years exceeds one-third.[12] These people are ideal candidates for diabetes prevention efforts.

To prevent the progression of prediabetes to T2DM, an intensive behavioral lifestyle intervention program is recommended in the ADA guidelines, including individualized medical nutrition therapy, physical activity, and no tobacco use.[13] Besides lifestyle modification, a variety of anti-diabetic agents have been investigated in clinical trials for diabetes prevention, including insulin secretagogues, glucagon-like peptide (GLP)-1 analogues, alpha-glucosidase inhibitors, dipeptidyl-peptidase (DPP)-4 inhibitors, biguanides, and thiazolidinediones. These pharmacologic approaches with intrinsic glucose-lowering activity (e.g., improve the insulin resistance and preserve pancreatic β -cell function) are recommended for glycemic treatment in patients with T2DM in the ADA guidelines.[14] Of these pharmacologic medications, only metformin therapy for diabetes prevention is recommended as an option for patients with prediabetes.[13] However, to date,

whether other glucose-lowering agents should be considered in those patients or not has not yet to be clarified clearly, even though some findings of recent studies have demonstrated that these pharmacological agents could also exert benefits to prevent or delay the progression to T2DM. In addition, head-to-head comparisons of different anti-diabetic agents have rarely been performed by previous clinical trials. Evidence regarding the overall and comparative efficacy of these anti-hyperglycemia agents for T2DM prevention is limited, while it is important for clinical decision-making. Conventional pairwise meta-analyses are limited to pool the results of trials comparing two interventions directly while a network meta-analysis (NMA) method is able to combine direct and indirect evidence and assess comparative efficacy and safety of various interventions.[15-17] Therefore, to bridge this knowledge gap, we plan to conduct the systematic review and NMA to assess comparative effects and safety of various anti-diabetic medications in preventing T2DM in patients with prediabetes, which may provide beneficial information for clinical decision-making and further clinical trials.

METHODS

Study design and registration

This systematic review protocol is reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[18,19] This study will be performed in accordance with the PRISMA extension statements for NMA.[15]

Eligibility criteria

Population

Adults (older than 18 years) who have prediabetes will be eligible for inclusion. In this study, prediabetic state involves separate IFG, separate IGT, separate elevated HbA1c or combinations thereof. Diagnostic criteria for prediabetes should be established and described in eligible trials.

Intervention and comparator

This study will investigate comparisons of anti-diabetic drugs versus another anti-diabetic agent, lifestyle interventions (diet, exercise, or both), placebo or no intervention. Anti-diabetic agents include alpha-glucosidase inhibitors (e.g., acarbose and voglibose), sulphonylureas (e.g., glipizide and glimepiride), meglitinide analogues (e.g., nateglinide), dipeptidyl-peptidase (DPP)-4 inhibitors (e.g., linagliptin and vildagliptin), glucagon-like peptide (GLP)-1 analogues (e.g., exenatide and liraglutide), biguanides (e.g., metformin), thiazolidinediones (e.g., rosiglitazone and pioglitazone), alone or in combination. In addition, studies using vitamins, traditional Chinese medicines, or alternative/herbal supplements will be excluded.

Outcomes

The primary outcome will be the incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include the achievement of normoglycemia, all-cause mortality, cardiovascular mortality, and hypoglycemic event. Classification and definition of T2DM could be based on any recognized standard diagnosis criteria (e.g., the ADA guidelines).

Type of studies

All randomized controlled trials (RCTs) comparing anti-diabetic drugs with another anti-diabetic

agent, lifestyle interventions, placebo or no intervention for T2DM prevention in patients with prediabetes will be included in this study. Duration of intervention has to be with a minimum of 12 weeks.

Search strategy

Several databases will be searched from inception to December 2019 for RCTs that investigated anti-diabetic agents for prevention of diabetes among patients with prediabetes. The databases will include PubMed, Embase, and the Cochrane Library. In addition, the language of publication will be limited to English. Any potentially-relevant article will be retrieved for review. Details of search strategy of PubMed database are shown in the supplemental material. The literature search will be conducted using the following keywords: alpha-glucosidase inhibitors, sulphonylureas, glinides, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, biguanides, thiazolidinediones, diabetes, T2DM, prediabetes, prediabetic state, glucose intolerance, impaired glucose, conversion, delay, and prevent. Moreover, all drug names in each drug class will be included in key search terms, for instance, acarbose, voglibose, metformin, glipizide, glimepiride, linagliptin, vildagliptin, nateglinide, liraglutide, exenatide, rosiglitazone, and pioglitazone. To identify other eligible studies, reference lists of relevant publications (including trials, reviews, and meta-analyses) will be reviewed for a manual search.

Selection of studies

In accordance with the prespecified inclusion criteria, two reviewers working independently will evaluate all titles and abstracts to eliminate papers that were deemed irrelevant. The remaining articles will be included in the further assessment. Reviewers will scrutinize full text for each potentially-relevant article. The study identification and exclusion process will be depicted using the PRISMA flow diagram. Discrepancies in study selection will be resolved by negotiation.

Data collection process

Two independent reviewers will use a standardized data form to extract trial information. All disagreements will be settled via discussion with the third reviewer. The data extracted will be as follows:

- Patient characteristics (age, gender, race, and glycemic parameters).
- Trial characteristics (author, year of publication, study design, number of participants, country setting, and funding information).
- Details of intervention and control (dosage, frequency, and treatment duration).
- Data on the outcomes mentioned above.

Assessment of methodological quality

The Cochrane risk of bias assessment tool will be used to assess risk of bias for individual studies. This method includes the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[20] Each item will be classified into one of three categories as follows: unclear, high, or low risk. All discrepancies in quality assessment will be resolved after mutual agreement and discussion.

Data synthesis and statistical analysis

Initially, we will use a random-effects approach to pool effect estimates for all treatment comparisons in conventional pairwise meta-analyses. For categorical outcomes, the pooled estimates as risk ratios (RRs) with 95% confidence intervals (CIs) will be reported. When data is available, to observe whether the effects of medications on diabetes prevention remain after intervention withdrawn, the pooled RRs for diabetes of the intervention and wash-out or follow-up periods, respectively, will be estimated. Continuous data will be reported as mean differences (MDs) with their respective 95% CIs. Statistical heterogeneity across trials will be examined using the I^2 statistic. The I^2 statistic of 75%, 50%, or 25% indicates high, moderate, or low heterogeneity, separately.[21] Then, a NMA will be conducted with a frequentist random-effects model. Local inconsistency between direct and indirect evidence within each closed loop will be assessed using a node-splitting test.[22,23] In addition, a "design-by-treatment" model will be applied to evaluate the assumption of consistency in the whole network.[22] We will generate the surface under the cumulative ranking curve (SUCRA) to assess probabilities of interventions in superiority regarding efficacy and safety outcomes, with higher SUCRA values indicating better effects or safety.[24] The level of significance will be set at an alpha of 0.05. All analyses will be performed with Stata version 14.0 (StataCorp, College Station, TX).

Subgroup analyses

Where possible, analyses will be stratified by age (18-45 years and at least 45 years), gender, ethnicity, and BMI (25-29.9 kg/m^2 and ≥30 kg/m^2). Moreover, we will also perform subgroup analyses according to diagnostic criteria of prediabetes (IFG, IGT, and HbA1c).

Publication bias

We will use the comparison-adjusted funnel plot to assess small study effects including publication bias at the network level.[25]

Quality of evidence

The quality of evidence of estimates derived from this study will be rated using the grading of recommendations assessment, development and evaluation (GRADE) framework. The GRADE approach characterises the quality of evidence according to publication bias, study limitations, inconsistency, imprecision, and indirectness.[26] Evidence of efficacy outcomes will be rated from high quality to very low quality.

Patient and public involvement

No patients or public will participate in the study.

Ethics and dissemination

Since confidential patient data will not be involved in this study, formal ethics approval is not required. The framework of the PRISMA statements for NMA will be applied to guide review authors to perform this study. The results will be disseminated by a peer-reviewed publication.

DISCUSSION

This study is a comprehensive systematic review and NMA to compare and rank a variety of

anti-diabetic agents for preventing the development of T2DM in patients with prediabetes. Our study will provide a summary of available evidence concerning various anti-hyperglycemia agents for T2DM prevention in patients with prediabetic state, benefiting for clinicians and guideline-makers to generate high quality recommendations for these patients. Although a relevant NMA[27] published, the study was based on clinical trials before 2014. Additionally, included types anti-diabetic agents in the study were limited, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, and some other glucose-lowering drugs that have been tested by later trials clinically were not involved. It is essential to contain these commonly prescribed medications in multiple comparisons of glucose-lowering agents for the prevention of T2DM. Moreover, the definition of adults at high risk for T2DM was based on IFG and IGT, excluding people identified by HbA1c. Importantly, HbA1c is a biomarker of long-term glycemic control when compared with IFG and IGT, representing average blood glucose levels during the preceding two to three months.[28] However, our network meta-analysis may have several possible limitations. Firstly, the different frequencies, dosages, and routes of administration of pharmacological therapies may result in considerable heterogeneity. Secondly, differences in the inclusion criteria of participants and definition of the primary end-point events may influence the quality of evidence. Finally, study level data will be used rather than data on individuals.

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Contributors HZ conceived the review. JRW, GXH, YLJ, and HZ wrote the first draft of this protocol. WBF, ZJL, ML, and PZ were responsible for revision of the draft. HZ, ML and JRW contributed to developing the search strategy and registering the protocol. WBF and PZ were the guarantors. All authors scrutinized and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer review.

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Search strategy in PubMed.

Block 1: Prediabetes
#1 “Prediabetic state” [Mesh]
#2 “Glucose Intolerance” [Mesh]
#3 prediabet*[tiab] OR pre diabet*[tiab]
#4 (“impaired fasting”[tiab] AND glucose[tiab]) OR IFG[tiab] OR “impaired FPG”[tiab]
#5 “glucose intolerance”[tiab] OR “impaired glucose”[tiab] AND (tolerance[tiab] OR metabolism[tiab]) OR IGT[tiab]
#6 (risk[tiab] OR progress*[tiab] OR prevent*[tiab] OR inciden*[tiab] OR conversion[tiab] OR develop*[tiab] OR delay*[tiab]) AND (diabetes[tiab] OR T2D*[tiab] OR NIDDM[tiab] OR “type 2”[tiab] OR “type II”[tiab])
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

Block 2: Alpha-glucosidase inhibitors
#8 “Acarbose” [Mesh]
#9 acarbos*[tiab] OR glucobay[tiab] OR precose[tiab] OR prandase[tiab] OR “bay g 5421”[tiab] OR BAYG5421 [tiab]
#10 voglibos*[tiab] OR glustat[tiab] OR basen[tiab]
#11 miglitol*[tiab] OR glyset[tiab]
#12 glucosidase*[tiab] AND inhibitor*[tiab]
#13 #8 OR #9 OR #10 OR #11 OR #12

Block 3: DPP-4 inhibitors
14# “Dipeptidyl-Peptidase IV Inhibitors” [Mesh]
15# “gliptin*”[tiab] OR “dipeptidyl peptidase 4” OR “DPP 4” OR DPP4[tiab] OR “dipeptidyl peptidase IV”[tiab] OR “DPP IV”[tiab]
16# alogliptin[tiab] OR anagliptin[tiab] OR bisegliptin[tiab] OR carmegliptin[tiab] OR denagliptin[tiab] OR dutogliptin[tiab] OR evogliptin[tiab] OR gemigliptin[tiab] OR gosogliptin[tiab] OR linagliptin[tiab] OR melogliptin[tiab] OR omarigliptin[tiab] OR sitagliptin[tiab] OR saxagliptin[tiab] OR teneligliptin[tiab] OR trelagliptin[tiab] OR vildagliptin [tiab]
#17 #14 OR #15 OR #16

Block 4: GLP-1 analogue
#18 “Glucagon-Like Peptide 1” [Mesh]
#19 “glucagon like peptide*”[tiab] OR “GLP 1”[tiab] OR GLP1[tiab]
#20 exenatide[tiab] OR liraglutide[tiab] OR albiglutide[tiab] OR elsiglutide[tiab] OR lixisenatide[tiab] OR dulaglutide[tiab] OR taspoglutide[tiab] OR semaglutide[tiab] OR teduglutide[tiab]
#21 #18 OR #19 OR #20

Block 5: Sulfonylurea
#22 "Sulfonylurea Compounds"[Mesh]
#23 glyburid*[tiab] OR gluborid*[tiab] OR glipizid*[tiab] OR glypidizine[tiab] OR melizide[tiab] OR napizide[tiab] OR gliquidon*[tiab] OR glisoxepid*[tiab] OR glimepirid*[tiab]
#24 #22 OR #23

Block 6: Glinide
#25 glinide[tiab] OR glinides[tiab]
#26 nateglinid*[tiab] OR senaglinid*[tiab] OR repaglinid*[tiab] OR mitiglinid*[tiab]
#27 #25 OR #26

Block 7: Biguanides
#28 Biguanides[Mesh]
#29 buformi*[tiab] OR chloroguani*[tiab] OR metformi*[tiab] OR phenformi*[tiab]
#30 #28 OR #29

Block 8: Thiazolidinediones
#31 Thiazolidinediones[Mesh]
#32 thiazolidinedione[tiab] OR TZD[tiab] OR glitazone[tiab] OR glitazones[tiab]
#33 pioglit*[tiab] OR rosiglit*[tiab] OR troglit*[tiab]
#34 #31 OR #32 OR #33

Block 9: All medications
#35
#13 OR #17 OR #21 OR #24 OR #27 OR #30 OR #34

Block 10: RCT-filter
#36 "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]

Block 11:
#37
#7 AND #35 AND #36

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2, 3
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	3, 4
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	4
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	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
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)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4, 5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Anti-diabetic agents for prevention of type 2 diabetes mellitus in people with prediabetes: a systematic review and network meta-analysis protocol

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	diabetes, network meta-analysis, prevention, prediabetes, anti-diabetic agents, systematic review

Anti-diabetic agents for prevention of type 2 diabetes mellitus in people with prediabetes: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction Type 2 diabetes mellitus (T2DM) is a substantial health problem worldwide. Prediabetic state is associated with increased risk for the development of diabetes. There are various pharmacologic therapies with glucose-lowering activity for diabetes prevention. Of those, most are being compared with placebo instead of active agents. The relative effects and safety of different glucose-lowering drugs still remain uncertain. To address this gap, we will conduct a systematic review and network meta-analysis (NMA) to evaluate comparative efficacy and safety of glucose-lowering agents for T2DM prevention in patients with prediabetes.

Methods and analysis PubMed, the Cochrane library, and Embase will be searched from inception to December 2019 for relevant randomized controlled trials (RCTs) that examined anti-diabetic drugs for diabetes prevention in patients with prediabetes. Two reviewers working independently will screen titles, abstracts, and full papers. Data extraction will also be completed by two independent authors. The primary outcome will be the incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include the achievement of normoglycemia, all-cause mortality, cardiovascular mortality, and hypoglycemic event. Pairwise meta-analysis and NMA will be conducted for each outcome using a frequentist random-effects model. Additionally, subgroup analyses will also be performed. The comparison-adjusted funnel plot will be used to assess publication bias. The overall quality of evidence will be rated with the recommendations assessment, development and evaluation (GRADE) framework. Data analysis will be conducted using Stata V.14.0.

Ethics and dissemination Ethics approval is not required. We plan to submit the results of this study to a peer-review journal.

PROSPERO registration number CRD42019119157.

Strengths and limitations of this study

► This is a comprehensive systematic review and network meta-analysis to evaluate the effectiveness and safety of various glucose-lowering medications on diabetes prevention among people with prediabetic state.

► Where possible, a NMA will combine direct evidence with indirect evidence, allowing comparisons of treatments without being compared to each other head-to-head in clinical trials.

► This research will generate clinically useful evidence to benefit patients, clinicians, and guideline-makers.

► The different frequencies, dosages, and routes of administration of pharmacological therapies may lead to considerable heterogeneity.

Keywords: anti-diabetic agents, diabetes, network meta-analysis, prediabetes, prevention, systematic review

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and complex disease, related to insulin secretory defects frequently on the background of insulin resistance; the progression of the disease is associated with genetic factors, metabolic stress, and inflammation.[1] The global prevalence of T2DM was estimated to be 463 million people in 2017.[2] People with T2DM are at elevated risk for chronic kidney disease, heart failure, atherosclerotic cardiovascular disease, polyneuropathy, cognitive impairment, anxiety disorder, and depression.[3-5] The term prediabetes is used to describe a blood glucose level higher than the normal range but below the cut-off value for T2DM.[6] Different glycemic measurements to define the prediabetic stage exist, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and elevated glycosylated haemoglobin A1c (HbA1c).[1] The International Diabetes Federation (IDF) estimated that, in 2017, approximately 352 million persons globally had IGT, which is projected to exceed half a billion people before 2045.[7] Hyperglycemia is a well described risk factor for all-cause mortality, total number of all-age deaths attributable to high fasting plasma was 6.5 million people in 2017,[8] with T2DM accounting for 1 million deaths.[9] Moreover, the economic burden of diabetes is large; in 2017, the American Diabetes Association (ADA) estimated the total economic costs attributable to diabetes in the U.S. to be $327 billion.[10,11] Thus, there is an urgent need to address huge burden of this worldwide disease with a growing number of suffers. Early interventions for preventing T2DM are warranted.[10] Persons diagnosed with prediabetes are thought to be at increased risk for developing T2DM, the estimated incidence rate of diabetes among patients with prediabetes in the following 10 years exceeds one-third.[12] These people are ideal candidates for diabetes prevention efforts.

To prevent the progression of prediabetes to T2DM, an intensive behavioral lifestyle intervention program (e.g., medical nutrition therapy and physical activity) is recommended in the ADA guidelines.[13] Besides lifestyle modification, a variety of anti-diabetic agents (e.g., glucagon-like peptide (GLP)-1 analogues, metformin, and thiazolidinediones) have been investigated in clinical trials for diabetes prevention. These pharmacologic approaches with intrinsic glucose-lowering activity (e.g., improve the insulin resistance and preserve pancreatic β -cell function) are recommended for glycemic treatment in patients with T2DM.[14] Of these

medications, only metformin therapy for diabetes prevention is recommended as an option for patients with prediabetes.[13] However, to date, whether other glucose-lowering agents should be considered in those patients or not has not yet to be clarified clearly, even though some findings of recent studies have demonstrated that these pharmacological agents could also exert benefits to prevent or delay the progression to T2DM. In addition, head-to-head comparisons of different anti-diabetic agents have rarely been performed by previous clinical trials. A network meta-analysis (NMA) method is able to combine direct and indirect evidence and assess comparative efficacy and safety of various interventions.[15-17] Therefore, we plan to conduct the systematic review and NMA to assess comparative effects and safety of various anti-diabetic medications in preventing T2DM in patients with prediabetes.

METHODS

Study design and registration

This systematic review protocol is reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[18,19] This study will be performed in accordance with the PRISMA extension statements for NMA.[15]

Eligibility criteria

Population

Adults (older than 18 years) who have prediabetes will be eligible for inclusion. In this study, prediabetic state involves separate IFG, separate IGT, or both. Diagnostic criteria for prediabetes should be established and described in eligible trials.

Intervention and comparator

This study will investigate comparisons of anti-diabetic drugs versus another anti-diabetic agent, lifestyle interventions (diet, exercise, or both), placebo or no intervention. Anti-diabetic agents include alpha-glucosidase inhibitors (e.g., acarbose and voglibose), sulphonylureas (e.g., glipizide and glimepiride), meglitinide analogues (e.g., nateglinide), dipeptidyl-peptidase (DPP)-4 inhibitors (e.g., linagliptin and vildagliptin), glucagon-like peptide (GLP)-1 analogues (e.g., exenatide and liraglutide), biguanides (e.g., metformin), thiazolidinediones (e.g., rosiglitazone and pioglitazone), alone or in combination. In addition, studies using vitamins, traditional Chinese medicines, and alternative therapies will be excluded.

Outcomes

The primary outcome will be the incidence of T2DM in patients with prediabetes at baseline. Secondary outcomes will include the achievement of normoglycemia, all-cause mortality, cardiovascular mortality, and hypoglycemic event. Classification and definition of T2DM could be based on any recognized standard diagnosis criteria (e.g., the ADA guidelines).

Type of studies

All randomized controlled trials (RCTs) comparing anti-diabetic drugs with another anti-diabetic agent, lifestyle interventions, placebo or no intervention for T2DM prevention in patients with prediabetes will be included in this study. Duration of intervention has to be with a minimum of 12 weeks.

Search strategy

Several databases will be searched from inception to December 2019 for RCTs that investigated anti-diabetic agents for prevention of diabetes among patients with prediabetes. The databases will include PubMed, Embase, and the Cochrane Library. In addition, the language of publication will be limited to English. Any potentially-relevant article will be retrieved for review. Details of search strategy of PubMed database are shown in the supplemental material. The literature search will be conducted using the following keywords: alpha-glucosidase inhibitors, sulphonylureas, glinides, dipeptidyl-peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, biguanides, thiazolidinediones, diabetes, T2DM, prediabetes, prediabetic state, glucose intolerance, impaired glucose, conversion, delay, and prevent. Moreover, all drug names in each drug class will be included in key search terms, for instance, acarbose, voglibose, metformin, glipizide, glimepiride, linagliptin, vildagliptin, nateglinide, liraglutide, exenatide, rosiglitazone, and pioglitazone. To identify other eligible studies, reference lists of relevant publications (including trials, reviews, and meta-analyses) will be reviewed for a manual search.

Selection of studies

In accordance with the prespecified inclusion criteria, two reviewers working independently will evaluate all titles and abstracts to eliminate papers that were deemed irrelevant. The remaining articles will be included in the further assessment. Reviewers will scrutinize full text for each potentially-relevant article. The study identification and exclusion process will be depicted using the PRISMA flow diagram. Discrepancies in study selection will be resolved by negotiation.

Data collection process

Two independent reviewers will use a standardized data form to extract trial information. All disagreements will be settled via discussion with the third reviewer. The data extracted will be as follows:

- Patient characteristics (age, gender, race, and glycemic parameters).
- Trial characteristics (author, year of publication, study design, number of participants, country setting, and funding information).
- Details of intervention and control (dosage, frequency, and treatment duration).
- Data on the outcomes mentioned above.

Assessment of methodological quality

The Cochrane risk of bias assessment tool will be used to assess risk of bias for individual studies. This method includes the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[20] Each item will be classified into one of three categories as follows: unclear, high, or low risk. All discrepancies in quality assessment will be resolved after mutual agreement and discussion.

Data synthesis and statistical analysis

Initially, we will use a random-effects approach to pool effect estimates for all treatment comparisons in conventional pairwise meta-analyses. For categorical outcomes, the pooled

estimates as risk ratios (RRs) with 95% confidence intervals (CIs) will be reported. When data is available, to observe whether the effects of medications on diabetes prevention remain after intervention withdrawn, the pooled RRs for diabetes of the intervention and wash-out or follow-up periods, respectively, will be estimated. Continuous data will be reported as mean differences (MDs) with their respective 95% CIs. Statistical heterogeneity across trials will be examined using the I^2 statistic. The I^2 statistic of 75%, 50%, or 25% indicates high, moderate, or low heterogeneity, separately.[21] Then, a NMA will be conducted with a frequentist random-effects model. Local inconsistency between direct and indirect evidence within each closed loop will be assessed using a node-splitting test.[22,23] In addition, a "design-by-treatment" model will be applied to evaluate the assumption of consistency in the whole network.[22] We will generate the surface under the cumulative ranking curve (SUCRA) to assess probabilities of interventions in superiority regarding efficacy and safety outcomes, with higher SUCRA values indicating better effects or safety.[24] The level of significance will be set at an alpha of 0.05. All analyses will be performed with Stata version 14.0 (StataCorp, College Station, TX).

Subgroup analyses

Where possible, analyses will be stratified by age (18-45 years and at least 45 years), gender, ethnicity, and BMI (25-29.9 kg/m^2 and ≥30 kg/m^2). Moreover, we will also perform subgroup analyses according to diagnostic criteria of prediabetes (IFG and IGT).

Publication bias

We will use the comparison-adjusted funnel plot to assess small study effects including publication bias at the network level.[25]

Quality of evidence

The quality of evidence of estimates derived from this study will be rated using the grading of recommendations assessment, development and evaluation (GRADE) framework. The GRADE approach characterises the quality of evidence according to publication bias, study limitations, inconsistency, imprecision, and indirectness.[26] Evidence of efficacy outcomes will be rated from high quality to very low quality.

Patient and public involvement

No patients or public will participate in the study.

Ethics and dissemination

Since confidential patient data will not be involved in this study, formal ethics approval is not required. The framework of the PRISMA statements for NMA will be applied to guide review authors to perform this study. The results will be disseminated by a peer-reviewed publication.

DISCUSSION

This study is a comprehensive systematic review and NMA to compare a variety of anti-diabetic agents for preventing the development of T2DM in patients with prediabetes. Our study will provide a summary of available evidence concerning various anti-hyperglycemia agents for T2DM prevention in patients with prediabetic state, benefiting for clinicians and guideline-makers.

Previous relevant reviews and meta-analyses[27-29] only included clinical trials published before 2015. Importantly, recent large-scale RCTs (e.g., the ACE and IRIS trials) [30,31] have provided substantial data with respect to this topic. Additionally, dipeptidyl-peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 analogues are not involved in previous studies. It is essential to contain these commonly prescribed medications in multiple comparisons of glucose-lowering agents for the prevention of T2DM. Moreover, the influence of different diagnostic criteria for prediabetes (IFG and IGT) on the prevention efficacy of anti-diabetic agents remains uncertain.[28] Thus, we plan to conduct this study to investigate various anti-diabetic agents for diabetes prevention. The findings of our study will generate high quality recommendations regarding the optimal anti-diabetic agent to reduce risk of diabetes for patients with prediabetes. This study will combine data of all glucose-lowering drugs that have been tested for diabetes prevention by clinical trials. To develop better individualized strategies for diabetes prevention, intervention efficacy according to diagnostic criteria for prediabetes (IFG and IGT) will also be explored. However, our study may have several possible limitations. Firstly, the different frequencies, dosages, and routes of administration of pharmacological therapies may result in considerable heterogeneity. Secondly, differences in the inclusion criteria of participants and definition of the primary end-point events may influence the quality of evidence. Finally, study level data will be used rather than data on individuals.

Contributors: HZ and XZW conceived the review. BLN, GXH, JBL, and XZW wrote the first draft of this protocol. WBF, LC, LJH, and RM were responsible for revision of the draft. HZ, LJH, and JBL contributed to developing the search strategy and registering the protocol. WBF and HZ were the guarantors. All authors scrutinized and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer review.

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Search strategy in PubMed.

Block 1: Prediabetes
#1 “Prediabetic state” [Mesh]
#2 “Glucose Intolerance” [Mesh]
#3 prediabet*[tiab] OR pre diabet*[tiab]
#4 (“impaired fasting”[tiab] AND glucose[tiab]) OR IFG[tiab] OR “impaired FPG”[tiab]
#5 “glucose intolerance”[tiab] OR “impaired glucose”[tiab] AND (tolerance[tiab] OR metabolism[tiab]) OR IGT[tiab]
#6 (risk[tiab] OR progress*[tiab] OR prevent*[tiab] OR inciden*[tiab] OR conversion[tiab] OR develop*[tiab] OR delay*[tiab]) AND (diabetes[tiab] OR T2D*[tiab] OR NIDDM[tiab] OR “type 2”[tiab] OR “type II”[tiab])
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

Block 2: Alpha-glucosidase inhibitors
#8 “Acarbose” [Mesh]
#9 acarbos*[tiab] OR glucobay[tiab] OR precose[tiab] OR prandase[tiab] OR “bay g 5421”[tiab] OR BAYG5421 [tiab]
#10 voglibos*[tiab] OR glustat[tiab] OR basen[tiab]
#11 miglitol*[tiab] OR glyset[tiab]
#12 glucosidase*[tiab] AND inhibitor*[tiab]
#13 #8 OR #9 OR #10 OR #11 OR #12

Block 3: DPP-4 inhibitors
14# “Dipeptidyl-Peptidase IV Inhibitors” [Mesh]
15# “gliptin*”[tiab] OR “dipeptidyl peptidase 4” OR “DPP 4” OR DPP4[tiab] OR “dipeptidyl peptidase IV”[tiab] OR “DPP IV”[tiab]
16# alogliptin[tiab] OR anagliptin[tiab] OR bisegliptin[tiab] OR carmegliptin[tiab] OR denagliptin[tiab] OR dutogliptin[tiab] OR evogliptin[tiab] OR gemigliptin[tiab] OR gosogliptin[tiab] OR linagliptin[tiab] OR melogliptin[tiab] OR omarigliptin[tiab] OR sitagliptin[tiab] OR saxagliptin[tiab] OR teneligliptin[tiab] OR trelagliptin[tiab] OR vildagliptin [tiab]
#17 #14 OR #15 OR #16

Block 4: GLP-1 analogue
#18 “Glucagon-Like Peptide 1” [Mesh]
#19 “glucagon like peptide*”[tiab] OR “GLP 1”[tiab] OR GLP1[tiab]
#20 exenatide[tiab] OR liraglutide[tiab] OR albiglutide[tiab] OR elsiglutide[tiab] OR lixisenatide[tiab] OR dulaglutide[tiab] OR taspoglutide[tiab] OR semaglutide[tiab] OR teduglutide[tiab]
#21 #18 OR #19 OR #20

Block 5: Sulfonylurea
#22 "Sulfonylurea Compounds"[Mesh]
#23 glyburid*[tiab] OR gluborid*[tiab] OR glipizid*[tiab] OR glypidizine[tiab] OR melizide[tiab] OR napizide[tiab] OR gliquidon*[tiab] OR glisoxepid*[tiab] OR glimepirid*[tiab]
#24 #22 OR #23

Block 6: Glinide
#25 glinide[tiab] OR glinides[tiab]
#26 nateglinid*[tiab] OR senaglinid*[tiab] OR repaglinid*[tiab] OR mitiglinid*[tiab]
#27 #25 OR #26

Block 7: Biguanides
#28 Biguanides[Mesh]
#29 buformi*[tiab] OR chloroguani*[tiab] OR metformi*[tiab] OR phenformi*[tiab]
#30 #28 OR #29

Block 8: Thiazolidinediones
#31 Thiazolidinediones[Mesh]
#32 thiazolidinedione[tiab] OR TZD[tiab] OR glitazone[tiab] OR glitazones[tiab]
#33 pioglit*[tiab] OR rosiglit*[tiab] OR troglit*[tiab]
#34 #31 OR #32 OR #33

Block 9: All medications
#35
#13 OR #17 OR #21 OR #24 OR #27 OR #30 OR #34

Block 10: RCT-filter
#36 "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]

Block 11:
#37
#7 AND #35 AND #36

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2, 3
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	3, 4
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	4
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	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
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)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4, 5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.