The Efficacy and Tolerability of Sitagliptin, Saxagliptin, Vildagliptin, Lindagliptin, Alogliptin, Omarigliptin and Trelagliptin in Patients with Type 2 Diabetes: Protocol for a Network Meta-Analysis of Randomized Control Trials

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Protocol

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Abstract

Background: Type 2 diabetes mellitus remains a major public health challenge in the worldwide. The control of blood glucose is essential in the metabolic management of diabetes. Dipeptidyl peptidase-4 (DPP-4) inhibitors are new hypoglycemic agents with good hypoglycemic effect. However, the difference of efficacy and tolerability among different kinds of DPP-4 inhibitors remains unclear and no network meta-analysis(NMA) has been performed yet to compare different kinds of DPP-4 inhibitors comprehensively. Our research aims to investigate and rank different kinds of DPP-4 inhibitors on efficacy and tolerability.

Methods/design: English language studies will be searched in the electronic databases(PubMed, the Cochrane Library and EMBASE), without time restriction. Parallel-group randomized controlled trials (RCTs) meeting the following criteria will be included, regardless of the blinding design: (1) T2DM patients aged over 18, pregnant or breastfeeding female patients and patients with T2DM on Maintenance Hemodialysis will be excluded, (2) interventions with DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, lindagliptin, alogliptin, omarigliptin and trelagliptin), traditional antidiabetic agents includes α -glucosidase inhibitors, sulphonylureas, non-sulphonylureas and thiazolidinediones, or placebo and (3) change in HbA1c concentration, weight and FPG from baseline to the end of treatment and proportions of patients in achieving HbA1c < 7.0%, patients with treatment-emergent adverse events leading to treatment discontinuation and patients with hypoglycaemia. Random effects pairwise and Bayesian NMA will be performed for these outcomes. Subgroup analyses are carried out for race and dosing frequency.

Discussion: Our NMA will be the first to systematically summarize, compare and rank the efficacy and tolerability of different kinds of DPP-4 inhibitors in T2DM patients. We are confident that our research project will significantly contribute to optimizing hypoglycemic therapy.

Systematic review registration:PROSPERO:CRD42021253822

Background

The prevalence of diabetes mellitus has increased rapidly in recent decades, making it the ninth major cause of death. Asia^[1] has emerged as the major area with a rapidly developing T2DM epidemic. Type 2 diabetes mellitus(T2DM) and its complications have contributed tremendously to the burden of mortality and disability worldwide. The number of patients with diabetes worldwide is expected to increase to 642 million in 2040^[2]. The control of blood glucose plays an important role in the metabolic management of diabetes. Hemoglobin A1c (HbA1c) is the most important indicator of blood glucose control. The results of the UK Prospective Diabetes Study (UKPDS) showed that a 1% decrease in HbA1c can reduce the risk of all diabetes-related endpoints and the risk of diabetes-related death by 21% ($P < 0.01$)^[3]. T2DM is a progressive disease. As the course of the disease progresses, glucose control is gradually substandard. The intensity of treatment to control hyperglycemia should be strengthened. Metformin is

the most commonly used hypoglycemic agents, with good hypoglycemic effect and low risk of hypoglycemia. If metformin is used alone and glucose control does not reach the target, combination medication should be performed^[4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors^[4] are usually used as add-on treatment in T2DM uncontrolled on metformin monotherapy. It plays a role by preventing the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP). DPP4 inhibitors are a relatively new class of anti-diabetic agent. Sitagliptin, saxagliptin, vildagliptin, lindagliptin and alogliptin are short-acting agents, requiring daily or twice-daily dosing. Omarigliptin and trelagliptin are long-acting agents, dosing frequency could reduce to once-weekly. So far, there has been a large amount of literatures^[5-9] to prove the efficacy and safety of DPP-4 inhibitors, compared with traditional hypoglycemic drugs including α -glucosidase inhibitors, sulphonylureas, non-sulphonylureas and thiazolidinediones. Currently, there are few researches^[10] about head to head comparison between different kinds DPP-4 inhibitors. Variations in the structure and PK/PD profiles^[11] may contribute to potential differences in the clinical profiles of different kinds of DPP-4 inhibitors.

Network meta-analysis (NMA) is a new tool that could integrate the evidence from direct and indirect comparisons. Besides, NMA allows the simultaneous comparison of multiple interventions while maintaining the internal randomization of individual trials^[12]. Previous researches have shown that DPP-4 inhibitors can improve glycaemic control with a low risk of hypoglycaemia in patients with T2DM. But it's not clear whether there are differences in efficacy, safety and tolerability between different kinds of DPP-4 inhibitors. The aim of the present research is to systematically compare and rank different DPP-4 inhibitors (including sitagliptin, saxagliptin, vildagliptin, lindagliptin, alogliptin, omarigliptin and trelagliptin) on the efficacy, safety and tolerability in the treatment of T2DM.

Methods/design

The proposed systematic review was registered in the PROSPER database (CRD42021253822).

Eligibility criteria

Randomized controlled trials fulfilling the following requirements will be eligible in our network analysis:

Patients

Patients aged over 18 and with T2DM will be included, regardless of gender, or ethnic origins. The diagnosis of T2DM should have been established using standard criteria. Pregnant or breastfeeding female patients and patients with T2DM on Maintenance Hemodialysis will be excluded.

Interventions

DPP-4 inhibitors, including sitagliptin, saxagliptin, vildagliptin, lindagliptin, alogliptin, omarigliptin and trelagliptin.

Comparisons

DPP-4 inhibitors compared with each other, traditional antidiabetic agents includes α -glucosidase inhibitors, sulphonylureas, non-sulphonylureas and thiazolidinediones, or placebo

Outcomes

Studies with clinically relevant outcomes will be included. Interested outcomes include changes in HbA1c concentration, weight and FPG from baseline to the end of treatment and proportions of patients in achieving HbA1c < 7.0%, patients with treatment-emergent adverse events leading to treatment discontinuation and patients with hypoglycaemia.

Study design

Parallel-group randomized controlled trials (RCTs) will be included, regardless of the blinding design. To investigate long-term efficacy and safety of different kinds of DPP-4 inhibitors, RCTs with duration of trial $\geq$ 24 weeks will be excluded.

Search strategy

English language studies will be searched in the electronic databases(PubMed, the Cochrane Library and EMBASE), without time restriction. In addition, complementary sources will be used, including reference lists from relevant studies assessed for eligibility and researches registered in ClinicalTrials.gov.

The search strategy will be defined by (i) patient's condition (i.e. T2DM), (ii) studied drugs (i.e. sitagliptin, saxagliptin, vildagliptin, lindagliptin, alogliptin, omarigliptin and trelagliptin) and (iii) study design. For the latter, the specific search strategy of RCTs defined in the Cochrane Handbook will be used^[13]. Literature reviews will be excluded. Each parameter will be defined by several MeSH terms and/or free terms in titles and abstracts.

Study selection

All identified studies will be imported into the Endnote reference manager for study selection. Firstly, Automatic and manual de-duplication will be carried out. Secondly, titles and abstracts of identified references are screened by two reviewers independently. Thirdly, The eligible references will be reviewed on full texts.Conflicts will beresolved by discussion among the team. A PRISMA flowchart will be drawn to document the screening process.

Data extraction and Risk of bias assessment

Two investigators will extract data using pre-specified forms with epidata software and independently assess the accuracy of abstractions and resolve any discrepancies by consensus after discussion with the third investigator. The following characteristics will be extracted for included studies: first author, year of publication, study design, number of participants enrolled, study design, total study duration, sequence generation, allocation sequence concealment, participant characteristics (age, gender, BMI, total number, ethnicity), interventions and outcomes (change in HbA1c, weight and FPG from baseline to the end of treatment, proportions of patients in achieving HbA1c < 7.0%, treatment-emergent adverse events leading to treatment discontinuation and with hypoglycaemia).

Risk of bias assessment was conducted by two reviewers independently, according to the Cochrane Collaboration risk of bias tool across 5 domains (sequence generation, allocation concealment, blinding, detection bias, and attrition bias).

Data synthesis and statistical analysis

The main objective of this data synthesis is to compare the effectiveness and tolerability of different kinds of DPP-4 inhibitors. NMA is useful in synthesizing all available data, including direct and indirect comparison. Statistical heterogeneity was assessed by I^2 statistic. If the source of heterogeneity can't be located, single literature exclusion method is used to find out the literature that has great influence on the study of heterogeneity. When direct evidence is available from at least two studies, we will perform pairwise meta-analysis in a random-effects model by STATA 13.0 software for each outcome. A Bayesian network meta-analysis was conducted for indirect and mixed comparisons using WinBUGS 1.4.3 software. And effect estimates (RR, MD) for the outcome measures will be calculated.

Assessment of transitivity and inconsistency

To evaluate the assumption of transitivity, we will compare the similarity of the included populations and study settings in terms of age, gender, BMI and Basic hypoglycemic agents.

A design-by-treatment interaction model will be applied to assess potential design inconsistency and loop inconsistency.

Subgroup analyses

Exploratory subgroup analyses will be performed, if a sufficient number of studies are identified. Analyses will focus on the difference in efficacy, safety and tolerability among different ethnic groups and between once-weekly and once-daily preparation.

Discussion

T2DM is a major public health problem and the leading cause of kidney failure and non-traumatic lower-limb amputations in the worldwide. Studies indicated the hypoglycemic effect of DPP-4 inhibitors, compared with α -glucosidase inhibitors, sulphonylureas and other traditional antidiabetic agents.

however, there is a dearth of research directly comparing the efficiency and tolerance of different kinds of DPP-4 inhibitors, which has made it difficult to assess which drug yields the best outcome for T2DM patients.

Network meta-analysis could summarize all available data from RCTs to integrate direct and indirect evidences. Our NMA will be the first to systematically summarize, compare and rank the efficacy, safety and tolerability of different kinds of DPP-4 inhibitors in T2DM. We are confident that our research project will significantly contribute to optimizing hypoglycemic therapy.

One limitation of our research is that we just included English language studies, which could lead to bias. Besides, there are potential drawbacks of NMA that may require consideration, such as the observational feature of indirect evidences.

Abbreviations

T2DM: Type 2 diabetes mellitus; HbA1c: Hemoglobin A1c; UKPDS: UK Prospective Diabetes Study; DPP-4: Dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulintropic peptide; PK/PD: pharmacokinetics/pharmacodynamics; NMA: network meta-analysis; RCTs: randomized controlled trials; RR: relative risk; MD: mean difference

Declarations

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Authors contributions

JLC and GQC designed and wrote the systematic review protocol. YLH, XXH and JQC revised the manuscript. All authors read the systematic review protocol and agreed with its submission.

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Competing interests

The authors declare that they have no competing interests

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