


BMJ Open Antidiabetic and antiosteoporotic pharmacotherapies for prevention and treatment of type 2 diabetes-induced bone disease: protocol for two network meta-analyses

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ABSTRACT

Introduction Patients with type 2 diabetes mellitus (T2DM) are at risk for a variety of severe debilitating effects. One of the most serious complications experienced by patients with T2DM are skeletal diseases caused by changes in the bone microenvironment. As a result, patients with T2DM are at risk for higher prevalence of fragility fractures. There are a variety of treatments available for counteracting this effect. Some antidiabetic medications, such as metformin, have been shown to have a positive effect on bone health without the addition of additional drugs into patients' treatment plans. Chinese randomised controlled trial (RCT) studies have also proposed antiosteoporotic pharmacotherapies as a viable alternative treatment strategy. Previous network meta-analyses (NMAs) and meta-analyses regarding this topic did not include all available RCT trials, or only performed pairwise comparisons. We present a protocol for a two-part NMA that incorporates all available RCT data to provide the most comprehensive ranking of antidiabetics (part I) and antiosteoporotic (part II) pharmacotherapies in terms of their ability to decrease fracture incidences, increase bone mineral density (BMD) and improve indications of bone turnover markers (BTMs) in adult patients with T2DM.

Methods and analysis We will search Medical Literature Analysis and Retrieval System Online, Excerpta Medica Database, PubMed, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials and Chinese literature sources (China National Knowledge Infrastructure, Chongqing VIP Information, Wanfang Data, Wanfang Med Online) for RCTs, which fit our criteria. We will include adult patients with T2DM who have taken antidiabetics (part I) or antiosteoporotic (part II) therapies with relevant outcome measures in our study. We will perform title/abstract and full-text screening as well as data extraction in duplicate. Risk of bias will be evaluated in duplicate for each study, and the quality of evidence will be examined using Confidence in Network Meta-Analysis in accordance to the Grading of Recommendations Assessment, Development and Evaluation framework. We will use R and gemtc to perform the NMA. We will report changes in BMD and BTMs in either weighted or standardised mean difference,

Strengths and limitations of this study

- Literature search in Chinese databases will yield new randomised controlled trial (RCT) evidence regarding the efficacy of antidiabetics in treating type 2 diabetes mellitus bone disease.
- Using network meta-analytical techniques to analyse the relative efficacy of antiosteoporotic therapies will allow us to include new treatment arms, such as zoledronic acid and risedronate.
- Only RCTs will be included and the quality of trials and networks will be evaluated using Risk of Bias, Grading of Recommendations Assessment, Development and Evaluation and comparison-adjusted funnel plots.
- Chinese clinicians may not use the same procedures and practices as Western clinicians, therefore, the outcomes from Chinese RCTs may not apply to the Western healthcare systems.
- The study design does not allow the comparison of antidiabetics with antiosteoporotic therapies or combinations of the two.

and we will report fracture incidences as ORs. We will use the Surface Under the Cumulative Ranking Curve scores to provide numerical estimates of the rankings of interventions.

Ethics and dissemination The study will not require ethics approval. The findings of the two-part NMA will be disseminated in peer-reviewed journals and presented at conferences. We aim to produce the most comprehensive quantitative analysis regarding the management of T2DM bone disease. Our analysis should be able to provide physicians and patients with up-to-date recommendations for antidiabetic medications and antiosteoporotic pharmacotherapies for maintaining bone health in patients with T2DM.

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INTRODUCTION

Diabetes mellitus (DM) is an epidemic collection of metabolic diseases featuring substantial morbidity and mortality around the

globe. Type 2 DM (T2DM), which constitutes 90%–95% of all adult DM cases in the USA, is the most common type of DM.¹ T2DM is characterised by relative insulin deficiency, stemming from pancreatic β -cell dysfunction and insulin resistance in organs.² T2DM can be caused by a variety of factors, including excess body weight, physical inactivity, as well as sugar and fat consumption.³ Over the past decades, there has been a significant increase in the incidence of T2DM around the world, from 108 million in 1980 to 451 million in 2017.^{4 5} As a result of this trend, the number of people with T2DM globally is expected to increase to 693 million by 2045.⁵ With rising incidence, it is crucial for physicians to be informed of the most optimal clinical strategies to counteract T2DM's debilitating effects.

One of the many complications that patients with T2DM suffer from are skeletal weakness and fragility fractures.⁶ Patients with T2DM experience accelerated bone resorption, impaired osteoblast-mediated bone formation and poorer bone quality compared with those without T2DM.⁷ Research shows that hyperglycaemia as a result of insulin resistance can lead to the production of advanced glycation end products (AGEs) in collagen, which stimulate apoptosis of osteoblasts and induce abnormal arrangement and alignment of collagen.⁸ The effect of AGEs on the bone microenvironment, along with abnormal cytokine production and impaired neuroskeletal functions, put patients with T2DM at a higher risk for skeletal conditions such as osteoporosis and Charcot's arthropathy.^{9 10}

Several observational studies investigating associations between bone mineral density (BMD)—an indicator for osteoporosis and a surrogate marker for fragility fractures—and T2DM had shown that patients with T2DM exhibit increased BMD values when compared with healthy controls or baseline.^{11–14} However, previous studies have demonstrated that patients with T2DM experience an increased risk of fractures independent of BMD.^{15–17} Bone turnover markers (BTMs), which is an indicator for the rate of bone formation and resorption, has been shown to deteriorate in patients with T2DM as well.¹⁸ These signs and symptoms, combined with high prevalence of vertebral bone pain in the T2DM population, suggest that managing T2DM-induced bone disease is crucial to improving the patients' quality of life and clinical outcomes.¹⁹

Recent studies have shown that some antidiabetic medications, namely metformin and sulfonylureas, have a positive effect on bone health and may potentially lower fracture incidence in patients with T2DM.^{20 21} Hence, antidiabetic medications can be used as a potential treatment strategy for T2DM bone disease without having to introduce new medications into patients' treatment plans. However, this effect is not observed in every class of antidiabetics. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, for example, can increase bone resorption and negatively affect bone health in patients with T2DM.²² Meanwhile, a series of large scale randomised controlled trials (RCTs) have presented alternative strategies to

combating T2DM bone disease by using antiosteoporotic therapies—such as bisphosphonates, calcitonin, vitamin D and calcium supplementations—with promising results.^{23 24}

We identified two previous network meta-analyses (NMAs) that evaluated the impact of antidiabetic medications on fracture risks in patients with T2DM; however, these studies focused only on SGLT2 inhibitors and thus did not incorporate all available RCT data.^{25 26} We identified a single meta-analysis from China regarding the use of alendronate as an antiosteoporotic therapy in patients with T2DM; nonetheless the meta-analysis did not account for all available antiosteoporotic treatment arms.²⁷

Therefore, we propose to conduct a two-part systematic review and NMA of RCTs to investigate the following research questions: What are the comparative effects (in terms of fracture incidences) of different antidiabetic and antiosteoporotic pharmacotherapies on adult patients with T2DM? We will also investigate the comparative effects of these drugs on BMD and BTMs as our secondary outcomes. We will compare antidiabetic medications for part I of our analysis, and antiosteoporotic pharmacotherapies for part II of our analysis.

METHODS AND ANALYSIS

We will conduct this two-part systematic review and NMA in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses incorporating NMA of healthcare interventions.²⁸ Any significant amendments to this protocol will be reported and published with the results of the review.

Eligibility criteria

Types of participants

We will include adult patients (18 years or older) who have been diagnosed with T2DM according to criteria recommended by the World Health Organization (WHO), the American Diabetes Association (ADA) or the International Diabetes Federation (IDF).^{29–31}

Our database search will likely produce studies with a broad range of publication dates; consequently, we may see different sets of criteria from WHO, ADA and IDF as these recommendations tend to be updated periodically. To include a sufficient amount of data for analysis, we will not place restrictions regarding the exact set of criteria used by the study.

Patients included in part I of the analysis should not receive any form of additional antiosteoporotic therapies that can affect bone metabolism. However, because antidiabetic medications are sometimes crucial for stopping the progression of T2DM, antidiabetic therapies will be allowed for part II of the analysis due to ethical concerns.

Patients labelled as 'pre-diabetic' as defined by the diagnostic criteria will not be included for this study.

Types of studies

We will include parallel-groups RCTs. If an RCT uses a cross-over design, latest data from before the first cross-over will be used.

Types of interventions

We will include any commonly used antidiabetic medications for part I of the analysis. This may include (but not limited to) sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidases inhibitor, dipeptidyl-peptidase-4 inhibitors, glucagon-like peptide-1 agonist and SGLT2 inhibitors. If data permit, placebo, insulin supplementation and/or lifestyle changes/no pharmacotherapy treatment will also be included. Because concurrent therapies are common in clinical settings, any combinations of antidiabetic therapies will be included as treatment arms as well.

We will include any antiosteoporotic pharmacotherapies used to manage bone loss for part II of the analysis. This may include (but not limited to) bisphosphonates (eg, alendronate, risedronate, zoledronic acid), calcitonin, calcium, vitamin D or D analogues (eg, calcitriol or alfacalcidol). If data permit, placebo and untreated (ie, no antiosteoporotic treatment) will also be included as treatment arms. We will include combinations of multiple antiosteoporotic therapies.

We will differentiate treatment arms by daily dosages (eg, alendronate 5 mg vs alendronate 10 mg); however, if there are RCTs that cannot be included into the network due to the inclusion of dosages, we will disregard dosages and combine treatment arms to facilitate network connections.

Primary outcomes

Fracture incidence

We will evaluate fracture incidences based on data collected at the latest follow-up. If data permit, we will conduct separate analyses for vertebral and non-vertebral fractures. Definitions of fractures will be defined as per individual study criteria.

Secondary outcomes

Change in BMD

We will evaluate change in BMD from baseline, in both percentage and absolute change. BMD change must be calculated based on BMD data collected at the latest follow-up.

We will analyse BMD readings taken at the lumbar spine, femoral neck, total hip, Ward's triangle and the greater trochanter. Absolute and percentage changes in T-score and Z-score will not be included in this analysis.

Change in BTMs

We will analyse the following BTMs in our NMA:

- ▶ Bone resorption biomarkers: tartrate-resistant acid phosphatase 5b, carboxy-terminal cross-linked telopeptide of type 1 collagen, amino-terminal cross-linked telopeptide of type 1 collagen.

- ▶ Bone formation biomarkers: bone alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide.

These BTMs are chosen for their common use in the investigation of bone diseases and the availability of extensive literature regarding their applications.^{32 33} While our preliminary database search has shown that there are several large scale RCTs that reported some of these BTMs, the availability of BTM data in our target literature sources was not a factor in our method design.³⁴

Change in BTM levels will be recorded as percentage changes from baseline. We will include only percentage changes calculated using the BTM level measured at the latest follow-up in our analysis.

Search methods for identification of studies

Electronic database search

We will conduct a librarian-assisted search of Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to October 2019. We will use relevant Medical Subject Headings (MeSH) terms to ensure broad and appropriate inclusions of titles and abstracts (see online supplementary data 1).

Major Chinese databases, including Wanfang Data, Wanfang Med Online, China National Knowledge Infrastructure (CNKI) and Chongqing VIP Information (CQVIP), will also be searched using a custom Chinese search strategy (see online supplementary data 2).

A single, comprehensive set of search strategies will be used to identify studies relevant to both parts of the analysis. We will not perform separate database searches for both parts of the analysis.

Other data sources

We will hand search the reference list of previous meta-analyses and NMAs for included articles. We will also review ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for registered published or unpublished studies.

Data collection and analysis

Study selection

We will perform title and abstract screening independently and in duplicate using Rayyan.³⁵ Studies will only be selected for full-text screening if both reviewers deem the study relevant, to either part I or part II of the analysis.

Full-text screening will also be conducted in duplicate. We will resolve any conflicts via discussion and consensus or by recruiting a third author for arbitration. We will identify articles specific to part I and II and separate them at this stage of article screening. Due to our inclusion criteria, we do not expect any article to be included in both part I and II.

Data collection

We will carry out data collection independently and in duplicate using data extraction sheets developed a priori. We will resolve discrepancies by recruiting a third author to review the data. The extraction sheets are similar for both parts of the analysis, as described in the Data items section.

Risk of bias

We will assess risk of bias (RoB) independently and in duplicate using The Cochrane Collaboration's tool for assessing RoB in randomised trials.³⁶ Two reviewers will assess biases within each article in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.

If a majority of domains are considered to be low risk, the study will be assigned a low RoB. Similarly, if a majority of domains are considered to be high or unclear risk, the study will be assigned a high or unclear RoB, respectively. If a study has equal numbers of low and high, low and unclear, or high and unclear domains (eg, three high-risk domains, three low-risk domains and one unclear domain), the study will be assigned an unclear overall RoB.

Special considerations for Chinese trials

Chinese RCTs are often reported with a poor description of blinding, randomisation and allocation concealment techniques. This is partially due to Chinese clinicians' inadequate understanding of RCT designs; we also speculate that limitations in the format of Chinese journal articles, which are often restricted to shorter lengths (1–2 pages) compared with Western studies, forced Chinese authors to condense descriptions of their methodology.³⁷

Because of these factors, we will report RoB results separately for Western and Chinese articles. If we observe significant differences in RoB between the two sets of articles, we will include additional analyses in the supplementary material of the final publication(s) with Chinese and English RCTs being analysed separately.

Data items

Bibliometric data

Authors, year of publication, trial registration number, digital object identifier, publication journal, funding sources and conflict of interest.

Methodology

of participating centres, study setting, blinding methods, phase of study, enrolment duration, randomisation and allocation methods, technique for BMD measurement, technique for fracture detection, BTM detection methods and assay types.

Baseline data

randomised, # analysed, # lost to follow-up, mean age, sex, # postmenopausal, mean duration since diabetes

diagnosis, fracture (vertebral and non-vertebral) prevalence at baseline, baseline BMD, BTMs.

Outcomes

Final BMD measurements or percentage/absolute change in BMD from baseline, # vertebral fracture incidences at latest follow-up, # non-vertebral fracture incidences at latest follow-up. Percentage change in BTMs from baseline.

Other data

Adverse events, description of antidiabetic and antiosteoporotic therapy (ie, dosage, duration), mean follow-up.

Statistical analysis

Network meta-analysis

We will conduct all statistical analyses using R V.3.5.1.³⁸ We will perform NMAs using the gemtc 0.8–3 library which is based on the Bayesian probability framework.³⁹ Because we expect significant heterogeneity among studies due to differences in methodology, we will use a random effects model.⁴⁰

For part I of the analysis, we will use patients receiving no active antidiabetic medication, such as patients managing T2DM using lifestyle choices, as a reference for comparison. If this treatment arm does not exist, placebo or insulin-only patients will be used instead.

For part II of the analysis, patients receiving no antioestrogenic interventions will be used as a reference for comparison. If this treatment arm does not exist, placebo patients will be used instead. To simplify our analysis, we will not take concurrent antidiabetic medications into account for this portion of the analysis.

For changes in BMD, we will report the results of the analysis as weighted mean differences (WMDs) with 95% credible intervals (CrIs) if all included studies used the same scale (eg, if BMD changes are only reported as percentage changes). Otherwise, we will report these outcomes as standardised mean differences (SMDs) to include all available RCT data. For BMD outcomes, we will use SMD even if BMD changes can be converted between absolute and percentage changes in order to avoid estimation of the SD values. However, because SMDs are difficult to interpret for most clinicians, we will supplement our BMD results with WMDs as well, considering only percentage changes in BMD.^{41 42} BTMs will be analysed as WMD of percentage changes. Fracture incidences will be reported as OR with corresponding 95% CrIs, and a continuity correction factor of 0.5 will be applied to studies with no fracture events in their treatment arms.⁴³ We will run all network models for a minimum of 100 000 iterations to ensure convergence.

Because we expect the number of fracture events to be moderate, if there are insufficient fracture data for performing an NMA (eg, no available network connections or no fracture events in any study), we will narratively describe the findings from our included studies regarding fracture incidences.

Treatment ranking

We will use the Surface Under the Cumulative Ranking Curve (SUCRA) scores to provide an estimate as to the ranking of treatments. SUCRA scores range from 0 to 1, with higher SUCRA scores indicating more efficacious treatment arms.⁴⁴

Missing data

We will attempt to contact the authors of the original studies to obtain missing or unpublished data. Missing SD values may be imputed using methods described in the Cochrane Handbook for Systematic Reviews of Interventions.⁴⁵

Heterogeneity assessment

We will assess statistical heterogeneity within each outcome network using I^2 statistics and the Cochrane Q test.⁴⁶ We will consider an I^2 index $\geq 50\%$ as an indication for serious heterogeneity, and I^2 index $>75\%$ as an indication for very serious heterogeneity. We will explore potential sources of heterogeneity using meta-regression analyses.

Inconsistency

We will assess inconsistency using the node-splitting method.⁴⁷ We will explore any indications of significant inconsistency using meta-regression analyses.

Publication bias

To assess small-study effects within the networks, we will use a comparison-adjusted funnel plot.⁴⁸ We will use Egger's regression test to check for asymmetry within the funnel plot to identify possible publication bias.⁴⁹

Quality of evidence

We will use the Confidence in Network Meta-Analysis (CINeMA) web application to evaluate confidence in the findings from our NMA.⁵⁰ CINeMA adheres to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluating the quality of evidence by assessing network quality based on six criteria: within-study bias, across-study bias, indirectness, imprecision, heterogeneity and incoherence.^{51 52}

CINeMA uses a frequentist approach to NMAs, which is different from the Bayesian approach used by gemtc. However, previous study has shown that there are no significant differences between frequentist and Bayesian network estimates, therefore, the results of the CINeMA analysis should be applicable to our Bayesian networks.⁵³ We will report the results of our GRADE analysis using a summary of findings table.

Meta-regression

There are several potential factors for increased bone resorption and increased fracture incidences apart from T2DM, such as gender, postmenopausal status and age.⁵⁴ Previous fractures at baseline are also associated with a higher risk of subsequent fractures.^{55 56} Variations in these characteristics between studies can result in significant

heterogeneity and inconsistency. Therefore, we will conduct meta-regression analyses to check for covariate effects associated with these characteristics.

We will conduct meta-regressions on percentage of female in the patient population, percentage of postmenopausal in the patient population and the median age of the population for BMD, BTM and fracture outcomes. We will also conduct meta-regression on common clinical parameters such as time since diagnosis, duration of drug administration and duration of follow-up for all outcomes. For fracture incidences, we will run a meta-regression on fracture prevalence at baseline. We hypothesise that an increase in mean age, as well as the percentage of females and postmenopausal patients in the population will result in less positive BMD changes, decreased bone formation BTM levels and increased fracture incidence. Longer time since diagnosis will also cause these effects. Similarly, an increase in the number of prevalent fractures at baseline will result in increased fracture incidence. We hypothesise that increased drug duration will increase BMD and bone formation BTM levels, while decreasing fractures. Increased follow-up duration and time since diagnosis will have the opposite effects.

Since we will not consider the effect of concurrent antidiabetic medications in part II of our analysis, we will conduct a categorical meta-regression of concurrent antidiabetic medications for part II to examine the impact of antidiabetics. We will also conduct a categorical meta-regression on the location of the studies for both parts of the analysis to examine the impact of differences in the Chinese and Western healthcare environments.

Patient and public involvement

We invited select physicians who are specialised in diabetes and endocrinology or orthopaedics to help us refine our research question as well as primary and secondary outcomes. However, they were not involved in designing any other aspects of this study, nor were they involved in the drafting of this protocol. Due to the nature of our proposed study design, it was not appropriate for us to involve patients in our protocol or study.

DISCUSSION

Previous NMAs regarding antidiabetic medications and fracture risks focused on SGLT2 inhibitors and the literature searches were limited to Western databases.^{25 26} The Chinese meta-analysis concerning the use of antiosteoporotic therapies in patients with T2DM was limited to alendronate, and only performed searches on Chinese databases.²⁷ As a result, these latest analyses did not include all available RCT data.

This two-part study aims to significantly expand on all of the previous analyses by incorporating the entirety of global RCT evidence available. To our knowledge, our proposed study will be the first review to evaluate the relative effects of multiple antiosteoporotic agents among patients with T2DM using an NMA approach, and

it will be the most comprehensive analysis evaluating the effect of antidiabetics on bone health with multilanguage search strategies.

Our review will have several strengths. First, we will extend our database search to Chinese databases for part I of our analysis. Because of China's immense patient population and regulations that promote pharmaceutical research, the inclusion of Chinese RCTs will help strengthen the power and precision of our analyses.⁵⁷ Furthermore, we will use NMA techniques to analyse RCTs concerning antiosteoporotic pharmacotherapies. This strategy will allow us to include all available treatment arms, including risedronate, zoledronic acid and calcitonin. We have identified trials examining these treatments, however, they were not included in the latest analysis due to limitations with the pairwise meta-analytical study design.^{23 24 58} Lastly, we will only include RCT data, and we will use tools such as The Cochrane Collaboration's tool for assessing RoB in randomised trials, CINeMA and comparison-adjusted funnel plots to evaluate the quality of our included studies and networks.

Our review will also have limitations. Chinese clinicians may not adopt the same procedures and practices as Western clinicians (such as higher drug dosages and different drug formulations); as a result, outcomes from Chinese RCTs may not be applicable to the Western health-care system. Additionally, we cannot directly compare the efficacy of antiosteoporotic therapy to antidiabetics, nor to combinations of antiosteoporotic therapies and antidiabetics with our study design.

Despite these limitations, our two-part NMA will likely be the largest quantitative synthesis assessing antidiabetic and antiosteoporotic therapies among patients with T2DM to date. Our study should help physicians and patients with selecting antidiabetic regimens that are the most beneficial for patients with T2DM' bone health, as well as selecting the optimal antiosteoporotic regimen as a concurrent, supplemental therapy. Our study may also highlight promising treatment strategies that were not discussed in the previous analyses, providing physicians and researchers with future research directions.

ETHICS AND DISSEMINATION

We do not wish to engage in the practice of publishing minimum publishable units (publons).⁵⁹ Therefore, we will attempt to combine the proposed two-part study into a single publication for dissemination, as both parts are highly relevant to the topic of T2DM-induced bone disease. However, should the combined publication exceed the word and figure limits imposed by publishers, we will publish the proposed study as two separate publications. The findings of the proposed review will be disseminated in peer-reviewed journals and presented at conferences.

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Contributors JD made significant contributions to conception and design of the work, drafted the work and substantially reviewed it. UA and TD drafted the work and substantially reviewed it. OC and SS made significant contributions to the methodology of the work. AB made contributions to the conception of the work, substantially reviewed it and made revisions to the final work.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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