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Anti-Diabetic and Antiresorptive Pharmacotherapies for Prevention and Treatment of Type 2 Diabetes-Induced Bone Disease: Protocol for a Two-Part Systematic Review and Network Meta-Analysis

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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 T2DM patients are skeletal diseases caused by changes in the bone microenvironment. As a result, T2DM patients are at risk for higher prevalence of fragility fractures.

There are a variety of treatments available for counteracting this effect. Some anti-diabetic 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 randomized controlled trial (RCT) studies have also proposed antiresorptive 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 anti-diabetics (Part I) and antiresorptive (Part II) pharmacotherapies in terms of their ability to decrease fracture incidences, increase bone mineral density (BMD), improve indications of bone turnover markers (BTMs), and decrease pain in adult T2DM patients.

Methods and Analysis

We will search MEDLINE, EMBASE, PubMed, Web of Science, CINAHL, CENTRAL and Chinese literature sources (CNKI, CQVIP, Wanfang Data, Wanfang Med Online) for randomized controlled trials (RCTs) which fit our criteria. We will include adult T2DM patients who have taken anti-diabetics (Part I) or antiresorptive (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 (RoB) will be evaluated in duplicate for each study, and the quality of evidence will be examined using CINeMA in accordance to the GRADE framework. We will use R and gemtc to perform the NMA. We will report changes in BMD, BTM and pain scores in either weighted or standardized mean difference, and we will report fracture incidences as odds ratios. We will use the surface under the cumulative ranking curve (SUCRA) 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 anti-diabetic medications and antiresorptive pharmacotherapies for maintaining bone health in T2DM patients.

Systematic Review Registration

International Prospective Register for Systematic Reviews (PROSPERO) — CRD42019139320

ARTICLE SUMMARY

Strengths and limitations of this study:

- Literature search in Chinese databases will yield new RCT evidence regarding the efficacy of anti-diabetics in treating T2DM bone disease
- Using network meta-analytical techniques to analyze the relative efficacy of antiresorptive 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, GRADE 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 anti-diabetics with antiresorptive therapies or combinations of the two.

Introduction

Diabetes mellitus (DM) is an epidemic collection of metabolic diseases featuring substantial morbidity and mortality around the globe. Type 2 diabetes mellitus (T2DM), which constitutes 90-95% of all adult DM cases in the US, is the most common type of DM[1]. T2DM is characterized 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 T2DM patients 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 to those without T2DM[7]. Research shows that hyperglycemia 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 T2DM patients at a higher risk for skeletal conditions such as osteoporosis and Charcot's arthropathy[9,10].

There have been several large-scale observational studies investigating associations between bone mineral density (BMD) — an indicator for osteoporosis and a surrogate marker for fragility fractures — and T2DM. These studies all produced contradictory results with higher, lower, or similar values when compared to healthy controls. The inconsistencies were likely due to differences in their study methodologies, including differences in sites of BMD measurement and bone densitometry techniques, as well as the demographics of the study population[11–14]. However, previous studies have demonstrated that T2DM patients 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 T2DM patients 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 anti-diabetic medications, namely metformin and sulfonylureas, have a positive effect on bone health and may potentially lower fracture incidence in T2DM patients[20,21]. Hence, anti-diabetic 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 anti-diabetics. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, for example, can increase bone resorption and negatively affect bone health in T2DM patients[22]. Meanwhile, a series of large scale randomized controlled trials (RCTs) have presented alternative strategies to combating T2DM bone disease by using antiresorptive 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 anti-diabetic medications on fracture risks in T2DM patients; 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 antiresorptive therapy in T2DM patients; nonetheless the meta-analysis did not account for all available antiresorptive 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 anti-diabetic and antiresorptive pharmacotherapies on adult T2DM patients? We will also investigate the comparative effects of these drugs on BMD, BTMs, and bone pain as our secondary outcomes. We will compare anti-diabetic medications for Part I of our analysis, and antiresorptive 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 (PRISMA) incorporating NMA of health care interventions[28]. This study is prospectively registered on The International Prospective Register of Systematic Reviews (PROSPERO) — CRD42019139320. 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 antiresorptive therapies that can affect bone metabolism. However, because anti-diabetic medications are sometimes crucial for stopping the progression of T2DM, anti-diabetic 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 a RCT uses a crossover design, latest data from before the first crossover will be used.

Types of Interventions

We will include any commonly used anti-diabetic medications for Part I of the analysis. This may include (but not limited to) sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidases inhibitor, dipeptidyl-peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonist, and sodium glucose cotransporter 2 (SGLT2) inhibitors. If data permits, 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 anti-diabetic therapies will be included as treatment arms as well.

We will include any antiresorptive pharmacotherapies used to manage bone loss for Part II of the analysis. This may include (but not limited to) bisphosphonates (e.g. alendronate, risedronate, zoledronic acid), calcitonin, calcium, vitamin D or D analogs (e.g. calcitriol or alfacalcidol). If data permits, placebo

and untreated (i.e. no antiresorptive treatment) will also be included as treatment arms. We will include combinations of multiple antiresorptive therapies.

We will differentiate treatment arms by daily dosages (e.g. alendronate 5 mg v. 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 permits, we will conduct separate analyses for vertebral and nonvertebral 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 analyze 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 Bone Turnover Markers

We will analyze the following BTMs in our NMA:

- Bone resorption biomarkers: Tartrate-Resistant Acid Phosphatase 5b (TRAP 5b), Carboxy-terminal Crosslinked Telopeptide of type 1 collagen (CTX-1), Amino-terminal Crosslinked Telopeptide of type 1 collagen (NTX-1).

- Bone formation biomarkers: Bone Alkaline Phosphatase (BAP), Osteocalcin (OC), Procollagen type 1 N-terminal Propeptide (P1NP).

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.

Change in Bone Pain Score

We will include absolute change in bone pain score from baseline using final values measured during the latest follow-up period. We will include pain score measured using any pain scale in the 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 **Supplementary Data**).

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 **Supplementary Data**).

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 (WHO-ICTRP) 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 QCRI[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 risk of bias in randomized 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 risk, the study will be assigned a high RoB. If more than half of the domains have unclear risk or if there is a balance of low and high risk domains, the study will be assigned an unclear RoB.

Special Considerations for Chinese Trials

Chinese RCTs are often reported with a poor description of blinding, randomization, 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 to 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 analyzed separately.

Data Items

Bibliometric Data
Authors, year of publication, trial registration number, digital object identifier (DOI), publication journal, funding sources and conflict of interest.

Methodology
# of participating centers, study setting, blinding methods, phase of study, enrollment duration, randomization and allocation methods, technique for BMD measurement, technique for fracture detection, BTM detection methods and assay types, bone pain scale.

Baseline Data
randomized, # analyzed, # lost to follow-up, mean age, sex, # postmenopausal, mean duration since diabetes diagnosis, fracture (vertebral and nonvertebral) prevalence at baseline, baseline BMD, BTMs, pain scale measurements.

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, absolute change in pain score from baseline.

Other Data
Adverse events, description of anti-diabetic and antiresorptive therapy (i.e. dosage, duration), mean follow-up.

Statistical Analysis

Network Meta-Analysis
We will conduct all statistical analyses using R 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 anti-diabetics 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 antiresorptive 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 anti-diabetic medications into account for this portion of the analysis.

For changes in BMD and pain scores, we will report the results of the analysis as weighted mean differences (WMDs) with 95% credible intervals (CrIs) if all included studies utilized the same scale (e.g. if BMD changes are only reported as percentage changes, or if pain outcomes are only reported as 10 point VAS scores). Otherwise, we will report these outcomes as standardized 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 standard deviation (SD) values. However, because SMDs are difficult to interpret for most clinicians, we will supplement our BMD results with weighted mean differences (WMD) as well, considering only percentage changes in BMD[41,42]. BTMs will be analyzed as WMD of percentage changes. Fracture incidences will be reported as odds ratios with corresponding 95% CrIs. We will run all network models for a minimum of 100,000 iterations to ensure convergence.

If there are outcomes for which we did not gather enough information to perform a NMA, we will provide a qualitative description of the available data and study outcomes.

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[43].

Missing Data

We will attempt to contact the authors of the original studies to obtain missing or unpublished data. Missing standard deviation values may be imputed using methods described in the Cochrane Handbook for Systematic Reviews of Interventions[44].

Heterogeneity Assessment

We will assess statistical heterogeneity within each outcome network using I^2 statistics and the Cochrane Q test[45]. 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[46]. 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[47]. We will use Egger's regression test to check for asymmetry within the funnel plot to identify possible publication bias[48].

Quality of Evidence

We will use the Confidence in Network Meta-Analysis (CINeMA) web application to evaluate confidence in the findings from our NMA[49]. CINeMA adheres to the 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[50,51].

CINeMA utilizes 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[52]. 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, post-menopausal status, and age[53]. Previous fractures at baseline are also associated with a higher risk of subsequent fractures[54,55]. 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 % female in the patient population, % postmenopausal in the patient population and the median age of the population for BMD, BTM, pain 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 hypothesize 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, greater pain 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 hypothesize that increased drug duration will increase BMD and bone formation BTM levels, while decreasing pain and fractures. Increased follow-up duration and time since diagnosis will have the opposite effects.

Since we will not consider the effect of concurrent anti-diabetic medications in Part II of our analysis, we will conduct a categorical meta-regression of concurrent anti-diabetic medications for Part II to examine the impact of anti-diabetics. 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 specialized 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 anti-diabetic 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 antiresorptive therapies in T2DM patients 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 upon 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 antiresorptive agents among T2DM patients using a NMA approach, and it will be the most comprehensive analysis evaluating the effect of anti-diabetics on bone health with multi-language 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[56]. Furthermore, we will use NMA techniques to analyze RCTs concerning antiresorptive 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-analytic study design[23,24,57]. Lastly, we will only include RCT data, and we will use tools such as The Cochrane Collaboration's tool for assessing risk of bias in randomized 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 healthcare system. Additionally, we cannot directly compare the efficacy of antiresorptive therapy to anti-diabetics, nor to combinations of antiresorptive therapies and anti-diabetics with our study design.

Despite these limitations, our two-part NMA will likely be the largest quantitative synthesis assessing anti-diabetic and antiresorptive therapies among T2DM patients to date. Our study should help physicians and patients with selecting anti-diabetic regimens that are the most beneficial for T2DM patients' bone health, as well as selecting the optimal antiresorptive 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

The study will not require ethics approval.

We do not wish to engage in the practice of publishing minimum publishable units (publons)[58]. 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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AUTHOR STATEMENT

JWD made significant contributions to conception and design of the work, drafted the work, and substantially reviewed it. UA and SD 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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CONFLICTS OF INTEREST

No potential conflicts of interest were reported by the authors.

Anti-Diabetic and Antiresorptive Pharmacotherapies for Prevention and Treatment of Type 2 Diabetes-Induced Bone Disease

Protocol for a Two-Part Systematic Review and Network Meta-Analysis

Supplementary Material: Sample Search Strategy

October 2, 2019

Supplementary 1: MEDLINE Search Strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Line	
1	exp Diabetes Mellitus, Type 2/
2	(diabet*).ti,ab,kw,kf.
3	(NIDDM).ti,ab,kw,kf.
4	insulin* secret* dysfunct*.mp.
5	hyperinsulin*.ti,ab,kw,kf.
6	insulin sensitiv*.ti,ab,kw,kf.
7	(glucose adj2 (toleran* or intoleran*)).ti,ab,kw,kf.
8	Glucose Intolerance/
9	insulin* resist*.ti,ab,kw,kf.
10	((non insulin or noninsulin) adj2 depend*).ti,ab,kw,kf.
11	metabolic syndrom*.ti,ab,kw,kf.
12	(T2DM or T2D).ti,ab,kw,kf.
13	exp Insulin Resistance/
14	or/1-13
15	exp Osteoporosis/
16	osteoporos?s.ti,ab,kw,kf.
17	exp Bone Diseases, Metabolic/
18	osteop?eni*.ti,ab,kw,kf.
19	Bone Diseases/
20	exp Bone Resorption/
21	(bone resorption or osteolys?s or malabsorption).ti,ab,kw,kf.
22	Bone Density/
23	BMD.ti,ab,kw,kf.
24	exp Fractures, Bone/

25	fracture*.ti,ab,kw,kf.
26	(bone* adj2 (loss* or disease* or resorption* or densit* or content* or fragil* or mass* or demineral* or decalcif* or calcif* or strength*)).ti,ab,kw,kf.
27	osteomalacia.ti,ab,kw,kf.
28	Bone turnover markers.ti,ab,kw,kf.
29	Bone pain.ti,ab,kw,kf.
30	or/15-29
31	14 and 30
32	exp randomized controlled trial/
33	exp Randomized Controlled Trials as Topic/
34	random*.mp.
35	Random Allocation/
36	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).mp.
37	double-blind method/ or single-blind method/
38	or/32-37
39	31 and 38

Supplementary 2: CNKI Search Strategy

+ is equivalent to **OR**	***** is equivalent to **AND**	**-** is equivalent to **NOT**
Search conducted at **https://kns.cnki.net/kns/brief/result.aspx** under **"专业检索"**		

——————————— Start of Search Phrase ———————————

('糖尿病'+'diabetes')*('二型'+'2型'+'成人发病型'+'type 2'+'adult onset'+'胰岛素抵抗'+'insulin resist')*('骨质疏松'+'骨折'+'骨密度'+'骨转换标志物'+'骨痛'+'BGP'+'TRAP'+'CTX'+'NTX'+'BAP'+'P1NP'+'骨疾病'+'osteoporosis'+'fracture'+'bone pain'+'bone mineral density'+'bone turnover marker'+'bone disease')*('随机'+'双盲'+'单盲'+'randomize'+'double blind'+'single blind')-('鼠'+'兔'+'狗'+'羊'+'动物'+'中医'+'中药'+'中西医'+'中西药'-'mouse'-'mice'-'rabbit'-'dog'-'sheep'-'animal'-'herbal')

——————————— End of Search Phrase ———————————

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
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	5
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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	5
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	6
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	Suppl
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - 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)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	7

		obtaining and confirming data from investigators	
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	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#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 I2, Kendall's τ)	9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Anti-Diabetic and Anti-Osteoporotic Pharmacotherapies for Prevention and Treatment of Type 2 Diabetes-Induced Bone Disease: Protocol for Two Network Meta-Analyses

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Keywords:	Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, Fractures, DIABETES & ENDOCRINOLOGY, network meta-analysis, anti-diabetics

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Anti-Diabetic and Anti-osteoporotic Pharmacotherapies for Prevention and Treatment of Type 2 Diabetes-Induced Bone Disease: Protocol for Two Network Meta-Analyses

Jiawen Deng, Umaima Abbas, Oswin Chang, Thanansayan Dhivagaran, Stephanie Sanger, Anthony Bozzo

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diabetes, bone disease, fractures, network meta-analysis, anti-osteoporotic agent, anti-diabetics

Word Count: 3,740

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 T2DM patients are skeletal diseases caused by changes in the bone microenvironment. As a result, T2DM patients are at risk for higher prevalence of fragility fractures.

There are a variety of treatments available for counteracting this effect. Some anti-diabetic 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 randomized controlled trial (RCT) studies have also proposed anti-osteoporotic 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 anti-diabetics (Part I) and anti-osteoporotic (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 T2DM patients.

Methods and Analysis

We will search MEDLINE, EMBASE, PubMed, Web of Science, CINAHL, CENTRAL and Chinese literature sources (CNKI, CQVIP, Wanfang Data, Wanfang Med Online) for randomized controlled trials (RCTs) which fit our criteria. We will include adult T2DM patients who have taken anti-diabetics (Part I) or anti-osteoporotic (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 (RoB) will be evaluated in duplicate for each study, and the quality of evidence will be examined using CINeMA in accordance to the GRADE framework. We will use R and gemtc to perform the NMA. We will report changes in BMD and BTMs in either weighted or standardized mean difference, and we will report fracture incidences as odds ratios. We will use the surface under the cumulative ranking curve (SUCRA) 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 anti-diabetic medications and anti-osteoporotic pharmacotherapies for maintaining bone health in T2DM patients.

Systematic Review Registration

International Prospective Register for Systematic Reviews (PROSPERO) — CRD42019139320

ARTICLE SUMMARY

Strengths and limitations of this study:

- Literature search in Chinese databases will yield new RCT evidence regarding the efficacy of anti-diabetics in treating T2DM bone disease
- Using network meta-analytical techniques to analyze the relative efficacy of anti-osteoporotic 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, GRADE 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 anti-diabetics with anti-osteoporotic therapies or combinations of the two.

Introduction

Diabetes mellitus (DM) is an epidemic collection of metabolic diseases featuring substantial morbidity and mortality around the globe. Type 2 diabetes mellitus (T2DM), which constitutes 90-95% of all adult DM cases in the US, is the most common type of DM[1]. T2DM is characterized 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 T2DM patients 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 to those without T2DM[7]. Research shows that hyperglycemia 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 T2DM patients 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 T2DM patients exhibit increased BMD values when compared to healthy controls or baseline[11-14]. However, previous studies have demonstrated that T2DM patients 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 T2DM patients 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 anti-diabetic medications, namely metformin and sulfonylureas, have a positive effect on bone health and may potentially lower fracture incidence in T2DM patients[20,21]. Hence, anti-diabetic 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 anti-diabetics. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, for example, can increase bone resorption and negatively affect bone health in T2DM patients[22]. Meanwhile, a series of large scale randomized controlled trials (RCTs) have presented alternative strategies to combating T2DM bone disease by using anti-osteoporotic 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 anti-diabetic medications on fracture risks in T2DM patients; 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 anti-osteoporotic therapy in T2DM patients; nonetheless the meta-analysis did not account for all available anti-osteoporotic 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 anti-diabetic and anti-osteoporotic pharmacotherapies on adult T2DM patients? We will also

investigate the comparative effects of these drugs on BMD and BTMs as our secondary outcomes. We will compare anti-diabetic medications for Part I of our analysis, and anti-osteoporotic 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 (PRISMA) incorporating NMA of health care interventions[28]. This study is prospectively registered on The International Prospective Register of Systematic Reviews (PROSPERO) — CRD42019139320. 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 anti-osteoporotic therapies that can affect bone metabolism. However, because anti-diabetic medications are sometimes crucial for stopping the progression of T2DM, anti-diabetic 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 a RCT uses a crossover design, latest data from before the first crossover will be used.

Types of Interventions

We will include any commonly used anti-diabetic medications for Part I of the analysis. This may include (but not limited to) sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidases inhibitor, dipeptidyl-peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonist, and sodium glucose cotransporter 2 (SGLT2) inhibitors. If data permits, 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 anti-diabetic therapies will be included as treatment arms as well.

We will include any anti-osteoporotic pharmacotherapies used to manage bone loss for Part II of the analysis. This may include (but not limited to) bisphosphonates (e.g. alendronate, risedronate, zoledronic acid), calcitonin, calcium, vitamin D or D analogs (e.g. calcitriol or alfacalcidol). If data permits, placebo and untreated (i.e. no anti-osteoporotic treatment) will also be included as treatment arms. We will include combinations of multiple anti-osteoporotic therapies.

We will differentiate treatment arms by daily dosages (e.g. alendronate 5 mg v. 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 permits, we will conduct separate analyses for vertebral and nonvertebral 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 analyze 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 Bone Turnover Markers

We will analyze the following BTMs in our NMA:

- Bone resorption biomarkers: Tartrate-Resistant Acid Phosphatase 5b (TRAP 5b), Carboxy-terminal Crosslinked Telopeptide of type 1 collagen (CTX-1), Amino-terminal Crosslinked Telopeptide of type 1 collagen (NTX-1).

- Bone formation biomarkers: Bone Alkaline Phosphatase (BAP), Osteocalcin (OC), Procollagen type 1 N-terminal Propeptide (P1NP).

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 **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 **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 (WHO-ICTRP) 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 QCRI[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 risk of bias in randomized 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 (e.g. 3 high risk domains, 3 low risk domains and 1 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, randomization, 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 to 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 analyzed separately.

Data Items

Bibliometric Data
Authors, year of publication, trial registration number, digital object identifier (DOI), publication journal, funding sources and conflict of interest.

Methodology
# of participating centers, study setting, blinding methods, phase of study, enrollment duration, randomization and allocation methods, technique for BMD measurement, technique for fracture detection, BTM detection methods and assay types.

Baseline Data
randomized, # analyzed, # lost to follow-up, mean age, sex, # postmenopausal, mean duration since diabetes diagnosis, fracture (vertebral and nonvertebral) 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 anti-diabetic and anti-osteoporotic therapy (i.e. dosage, duration), mean follow-up.

Statistical Analysis

Network Meta-Analysis
We will conduct all statistical analyses using R 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 anti-diabetics 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 anti-osteoporotic 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 anti-diabetic 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 utilized the same scale (e.g. if BMD changes are only reported as percentage changes). Otherwise, we will report these outcomes as standardized 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 standard deviation (SD) values. However, because SMDs are difficult to interpret for most clinicians, we will supplement our BMD results with weighted mean differences (WMD) as well, considering only percentage changes in BMD[41,42]. BTMs will be analyzed as WMD of percentage changes. Fracture incidences will be reported as odds ratios 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 a NMA (e.g. 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 standard deviation 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 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 utilizes 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, post-menopausal 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 % female in the patient population, % 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 hypothesize 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 hypothesize 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 anti-diabetic medications in Part II of our analysis, we will conduct a categorical meta-regression of concurrent anti-diabetic medications for Part II to examine the impact of anti-diabetics. 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 specialized 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 anti-diabetic 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 anti-osteoporotic therapies in T2DM patients 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 upon 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 anti-osteoporotic agents among T2DM patients using a NMA approach, and it will be the most comprehensive analysis evaluating the effect of anti-diabetics on bone health with multi-language 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 analyze RCTs concerning anti-osteoporotic 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-analytic 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 risk of bias in randomized 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 healthcare system. Additionally, we cannot directly compare the efficacy of anti-osteoporotic therapy to anti-diabetics, nor to combinations of anti-osteoporotic therapies and anti-diabetics with our study design.

Despite these limitations, our two-part NMA will likely be the largest quantitative synthesis assessing anti-diabetic and anti-osteoporotic therapies among T2DM patients to date. Our study should help physicians and patients with selecting anti-diabetic regimens that are the most beneficial for T2DM patients' bone health, as well as selecting the optimal anti-osteoporotic 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

The study will not require ethics approval.

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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AUTHOR STATEMENT

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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CONFLICTS OF INTEREST

No potential conflicts of interest were reported by the authors.

Anti-Diabetic and Antiresorptive Pharmacotherapies for Prevention and Treatment of Type 2 Diabetes-Induced Bone Disease

Protocol for a Two-Part Systematic Review and Network Meta-Analysis

Supplementary Material: Sample Search Strategy

October 2, 2019

Supplementary 1: MEDLINE Search Strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Line	
1	exp Diabetes Mellitus, Type 2/
2	(diabet*).ti,ab,kw,kf.
3	(NIDDM).ti,ab,kw,kf.
4	insulin* secret* dysfunct*.mp.
5	hyperinsulin*.ti,ab,kw,kf.
6	insulin sensitiv*.ti,ab,kw,kf.
7	(glucose adj2 (toleran* or intoleran*)).ti,ab,kw,kf.
8	Glucose Intolerance/
9	insulin* resist*.ti,ab,kw,kf.
10	((non insulin or noninsulin) adj2 depend*).ti,ab,kw,kf.
11	metabolic syndrom*.ti,ab,kw,kf.
12	(T2DM or T2D).ti,ab,kw,kf.
13	exp Insulin Resistance/
14	or/1-13
15	exp Osteoporosis/
16	osteoporos?s.ti,ab,kw,kf.
17	exp Bone Diseases, Metabolic/
18	osteop?eni*.ti,ab,kw,kf.
19	Bone Diseases/
20	exp Bone Resorption/
21	(bone resorption or osteolys?s or malabsorption).ti,ab,kw,kf.
22	Bone Density/
23	BMD.ti,ab,kw,kf.
24	exp Fractures, Bone/

25	fracture*.ti,ab,kw,kf.
26	(bone* adj2 (loss* or disease* or resorption* or densit* or content* or fragil* or mass* or demineral* or decalcif* or calcif* or strength*)).ti,ab,kw,kf.
27	osteomalacia.ti,ab,kw,kf.
28	Bone turnover markers.ti,ab,kw,kf.
29	Bone pain.ti,ab,kw,kf.
30	or/15-29
31	14 and 30
32	exp randomized controlled trial/
33	exp Randomized Controlled Trials as Topic/
34	random*.mp.
35	Random Allocation/
36	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).mp.
37	double-blind method/ or single-blind method/
38	or/32-37
39	31 and 38

Supplementary 2: CNKI Search Strategy

+ is equivalent to **OR**	***** is equivalent to **AND**	**-** is equivalent to **NOT**
Search conducted at **https://kns.cnki.net/kns/brief/result.aspx** under **"专业检索"**		

——————————— Start of Search Phrase ———————————

('糖尿病'+'diabetes')*('二型'+'2型'+'成人发病型'+'type 2'+'adult onset'+'胰岛素抵抗'+'insulin resist')*('骨质疏松'+'骨折'+'骨密度'+'骨转换标志物'+'骨痛'+'BGP'+'TRAP'+'CTX'+'NTX'+'BAP'+'P1NP'+'骨疾病'+'osteoporosis'+'fracture'+'bone pain'+'bone mineral density'+'bone turnover marker'+'bone disease')*('随机'+'双盲'+'单盲'+'randomize'+'double blind'+'single blind')-('鼠'+'兔'+'狗'+'羊'+'动物'+'中医'+'中药'+'中西医'+'中西药'-'mouse'-'mice'-'rabbit'-'dog'-'sheep'-'animal'-'herbal')

——————————— End of Search Phrase ———————————

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
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	5
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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	5
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	6
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	Suppl
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - 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)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	7

		obtaining and confirming data from investigators	
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	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#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 I2, Kendall's τ)	9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9