

## Systematic review

A list of fields that can be edited in an update can be found [here](#)

### 1. \* Review title.

Give the title of the review in English

Comparison of the effects of metformin and thiazolidinediones on bone metabolism: a systematic review and meta-analysis

### 2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

### 3. \* Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

29/04/2022

### 4. \* Anticipated completion date.

Give the date by which the review is expected to be completed.

01/09/2022

### 5. \* Stage of review at time of this submission.

**This field uses answers to initial screening questions. It cannot be edited until after registration.**

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No
Provide any other relevant information about the stage of the review here.		

#### 6. \* Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Congwen Yang

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Miss Yang

#### 7. \* Named contact email

Give the electronic email address of the named contact.

995089435@qq.com

#### 8. Named contact address

Give the full institutional/organisational postal address for the named contact.

#### 9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

13053848265

#### 10. \* Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Weifang Medical University

Organisation web address:

#### 11. \* Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Miss Congwen Yang. Weifang Medical College  
Dr Rudong Chen. Shandong First Medical University

## 12. \* Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding support

## Grant number(s)

State the funder, grant or award number and the date of award

## 13. \* Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

## 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

## 15. \* Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Comparison of the effects of metformin and thiazolidinediones on bone metabolism

## 16. \* Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We have searched in the following databases PubMed, Embase and Cochrane Library to search for English-language literature over a ten-year period. Search strings will be created as follows: (metformin) and (thiazolidinediones or pioglitazone or rosiglitazone ) and (bone metabolism or bone biomarkers or osteoporosis or bone density). All publications in English up to April 2022 will be searched without any country or article type restrictions.

Searches of the electronic database will be supplemented by manual searches of the reference lists of included articles.

## 17. URL to search strategy

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

[https://www.crd.york.ac.uk/PROSPEROFILES/326866\\_STRATEGY\\_20220601.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/326866_STRATEGY_20220601.pdf)

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

### 18. \* Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

People with diabetes have a higher risk of developing osteoporosis than people without diabetes.

Thiazolidinediones and metformin are commonly used in the treatment of diabetes. The purpose of this study was to compare the effects of two medications on bone metabolites.

### 19. \* Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of fractures, but the mechanism(s) responsible for the increased bone fragility remain unclear. Moreover, blood glucose-lowering therapy using thiazolidinediones (TZDs) has also been reported to cause bone loss and to further increase the risk of fractures.

### 20. \* Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Diabetic patients treated with metformin.

### 21. \* Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Patients with diabetes receiving thiazolidinedione therapy.

### 22. \* Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

(1) published high-quality randomized controlled trials. (2) The study population was adults aged ≥18 years  
(3) Clinical intervention trials comparing thiazolidinediones and metformin (4) Outcomes reported for bone mineral density, and bone turnover markers.

### 23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

### 24. \* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is

defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Femoral neck BMD and percentage change in bone turnover markers (procollagen type I N-terminal propeptide [PINP], osteocalcin,  $\beta$ -C-terminal telopeptide of type I collagen [CTX] and bone-specific alkaline phosphatase [BAP]).

### Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

### 25. \* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

osteocalcin, Calcium, 25-Hydroxyvitamin D, Intact PTH.

### Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

### 26. \* Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Only published clinical studies will be included, and the included studies will be required to contain at least one outcome. Only studies published in English will be included. Studies must have a follow-up rate of at least 80%, and at least two main patient-important outcome included. Two authors will assess eligible studies independently. Data extraction: We will use a standard data extraction form to retrieve the relevant data from eligible articles. The extracted data will include: authors, study location, sample size, study design, publishing date, gender, population, age, duration of follow-up, interventions, and outcomes. If necessary, we will contact the corresponding authors of the included RCTs to make sure the information was integrated and to get any missing data.

### 27. Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The modified seven-point Jadad scale will be used to evaluate the quality of the RCTs. If the score is greater than four points, the study is considered to be of high quality. For non-RCTs, study quality will be assessed by the nine-point Newcastle-Ottawa Scale (NOS). Studies achieving a score of greater than five points are considered to be of high quality. Grading of Recommendations Assessment Development and Evaluation (GRADE) system will be used to evaluate the quality of evidence grade strength of recommendations.

### 28. \* Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and

software package to be used.

RReview Manager Software for Windows (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) will be used to perform the meta-analyses. The mean difference (MD) or standard mean difference (SMD) will be recommended to assess continuous variable outcomes with a 95% confidence interval [CI]. For dichotomous outcomes, the results will be presented as relative risks (RR) or odds ratio (OR) with a 95%CI. The Q test will be used to evaluate the heterogeneity of studies based on the values of P and I<sup>2</sup>. When I<sup>2</sup><50% and P >0.1, the fixed-effect model will be used, otherwise, we will apply the random-effects model for meta-analysis.

### 29. \* Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach. To be determined based on the data retrieved.

### 30. \* Type and method of review.

Select the type of review, review method and health area from the lists below.

#### Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

No

Living systematic review

No

Meta-analysis

Yes

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)



No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

### Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health

No

Complementary therapies

No

COVID-19

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

Yes

Eye disorders

No

General interest  
No

Genetics  
No

Health inequalities/health equity  
No

Infections and infestations  
No

International development  
No

Mental health and behavioural conditions  
No

Musculoskeletal  
No

Neurological  
No

Nursing  
No

Obstetrics and gynaecology  
No

Oral health  
No

Palliative care  
No

Perioperative care  
No

Physiotherapy  
No

Pregnancy and childbirth  
No

Public health (including social determinants of health)  
No

Rehabilitation  
No

Respiratory disorders  
No

Service delivery  
No

Skin disorders  
No

Social care  
No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

### 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

### 32. \* Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

China

### 33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

### 34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

### 35. Dissemination plans.

Do you intend to publish the review on completion?

No

Give brief details of plans for communicating review findings.?

### 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

### 37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

### 38. \* Current review status.

Update review status when the review is completed and when it is published. New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review\_Ongoing

### 39. Any additional information.

Provide any other information relevant to the registration of this review.

### 40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.