Effects of metformin on bone mineral density and bone turnover markers: a systematic review and meta-analysis

Jinhua Hu,1 Jingjie Han,1 Min Jin,1 Jing Jin,2 Jialei Zhu 2

ABSTRACT

Objectives Metformin is associated with osteoblastogenesis and osteoclastogenesis. This study aims to investigate the impacts of metformin therapy on bone mineral density (BMD) and bone turnover markers.

Design Systematic review and meta-analysis of randomised controlled trials.

Methods Searches were carried out in PubMed, EMBASE, Web of science, Cochrane library, ClinicalTrials.gov from database inception to 26 September 2022. Two review authors assessed trial eligibility in accordance with established inclusion criteria. The risk of bias was assessed using the Cochrane Risk of Bias tool (RoB V2.0). Data analysis was conducted with Stata Statistical Software V16.0 and Review Manager Software V5.3.

Results A total of 15 studies with 3394 participants were identified for the present meta-analysis. Our pooled results indicated that metformin had no statistically significant effects on BMD at lumbar spine (SMD=−0.05, 95% CI=−0.19 to 0.09, p=0.47, participants=810; studies=7), at femoral (MD=−0.01 g/cm², 95% CI=−0.04 to 0.01 g/cm², p=0.25, participants=601; studies=3) and at hip (MD=0.01 g/cm², 95% CI=−0.02 to 0.03 g/cm², p=0.56, participants=634; studies=4). Metformin did not lead to significant change in osteocalcin, osteoprotegerin and bone alkaline phosphatase. Metformin induced decreases in N-terminal propeptide of type I procollagen (MD=−6.09 µg/L, 95% CI=−9.38 to −2.81 µg/L, p=0.0003, participants=2316; studies=7) and C-terminal telopeptide of type I collagen (MD=−55.80 ng/L, 95% CI=−97.33 to −14.26 ng/L, p=0.008, participants=2325; studies=7).

Conclusion This meta-analysis indicated that metformin had no significant effect on BMD. Metformin decreased some bone turnover markers as N-terminal propeptide of type I procollagen and C-terminal telopeptide of type I collagen. But the outcomes should be interpreted with caution due to several limitations.

INTRODUCTION

Patients with diabetes mellitus suffer from a significantly higher risk of osteoporosis.1 Bone mineral density (BMD) was most often reported to be decreased in type 1 diabetes mellitus (T1DM) but not in type 2 diabetes mellitus (T2DM).2 The pathophysiology of bone changes associated with T1DM and T2DM may not be the same. Bone microarchitectural deterioration which is not depicted by BMD measurements may also contribute to fracture risk in diabetes mellitus.3 Fracture risk was higher with longer diabetes duration particularly in T2DM with insulin, sulfonylurea, and thiazolidinedione therapy.4 5 Metformin is the most commonly prescribed for the management of T2DM. Stimulation of AMP-activated protein kinase (AMPK), which makes mitochondrial respiratory chain blockage leading to oxidative phosphorylation separation and increased AMP/ATP ratio, is responsible for the glucose-lowering effect and adjustable insulin sensitivity of metformin.6 7 The mechanisms through which metformin protects against risk of fracture are not well understood at present. There are some neutral outcomes of metformin associated with bone8–10 However, growing evidence about metformin pointing to protective effects against bone fracture is exposed.11–15 Metformin appears to be positive in terms of fracture risk based on the current evidence, but no final conclusions can be drawn. Bone material quality is maintained by the process of bone remodelling, which relies on a balance between osteoclast-dependent bone resorption and osteoblast-dependent bone formation. It has been shown that metformin has direct influence on osteoblastic cell differentiation. According to correlational studies, metformin causes an osteogenic effect through the transactivation of Runx-related

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis about the effect of metformin on bone mineral density and bone turnover markers was the most comprehensive evidence synthesis to date.
⇒ The publication bias is not tested because of small sample-sized studies.
⇒ There was heterogeneity in the measurement of bone turnover markers among the included studies.
⇒ Majority of the research participants were patients with diabetes, and these are prone to selection bias.
transcription factor 2 (Runx2) via AMPK.\textsuperscript{14,15} Metformin can also increase alkaline phosphatase (ALP) and osteocalcin, and enhance bone morphogenetic protein-2 (BMP-2) expression.\textsuperscript{16} Metformin has other effects on osteoblasts by preventing adipogenic differentiation factor peroxisome proliferator-activated receptor gamma (PPAR\textgamma) and increase Runx2/PPAR\textgamma.\textsuperscript{17,18} Hyperglycaemia alters the microenvironment of bone cells, disturbing bone microstructure and decreasing bone formation.\textsuperscript{19} Deleterious effects of high glucose on osteoblasts, such as advanced glycation endproducts and reactive oxygen species, can also be blocked by metformin.\textsuperscript{20–22} Metformin also accordingly downregulates the crucial cytokines involved in osteoclastogenesis, such as nuclear factor-κB receptor activator ligand (RANKL), macrophage colony stimulating factor.\textsuperscript{23–24} Metformin may inhibit osteoclast activation through AMPK/NF-κB/ERK signalling pathway.\textsuperscript{25} Metformin, at least in part, downregulates autophagy and regulates immunity during osteoclastogenesis.\textsuperscript{26–28} In conclusion, metformin not only induces osteoblastogenesis, but also inhibits osteoclastogenesis in a direct or indirect way.\textsuperscript{29}

Despite the abovementioned evidence, randomised clinical trials (RCTs) of metformin on bone are exploratory and fewer. Therefore, we aim to systematically review metformin on bone density and bone turnover markers in RCTs. This systematic review will provide more evidence to prove the therapeutic potential of metformin in bone tissues and clarify the limitations of existing studies.

METHODS
This study conformed to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.

Patient and public involvement
No patient involved.

Inclusion criteria
Population: we included RCTs of participants. Samples from the same population were excluded. Interventions: metformin alone or metformin combined therapy without bone damage drugs such as thiazolidinedione. We excluded studies in control group with metformin combined therapy. Outcomes: a study had to use defined clinical outcomes. The primary outcome was BMD at any site measured by dual-energy X-ray absorptiometry scans or conventional CT image scans. The secondary outcomes were bone turnover markers and bone turnover markers including serum level of osteocalcin (OC), osteoprotegerin (OPG), bone alkaline phosphatase (BAP), N-terminal propeptide of type I procollagen (PINP), C-terminal telopeptide of type I collagen (CTX). Publications without original data, such as reviews, editorials, research design protocol and conference abstracts were ineligible for inclusion. We included studies without language or date restrictions.

Search strategy
PubMed, EMBASE, Web of science, Cochrane library, ClinicalTrials.gov were searched for potentially relevant papers from inception to 25 January 2022, and updated on 26 September 2022. Literature search strategies were developed using terms which were related to metformin, osteoporosis, bone density, bone turnover and randomised controlled trial. Online supplemental table 1 provides full details of the search strategy. Two reviewers (JHan and MJ) independently reviewed the first 682 records and screened duplications, titles and abstracts for full-text articles for inclusion. The disagreements were resolved by a third researcher (JHu).

Data extraction
Two authors (JHan and MJ) independently extracted data from eligible researches to reduce reviewer errors. Data extracted from the eligible studies were first author, year of publication, study location, study population, study duration, sample size, characteristics of participants as gender, age and body mass index, control and intervention, bone site measures, BMD outcomes and bone turnovers of interest. When the intermediary results were reported, we only extracted the final data at the end of the intervention period.

Risk of bias assessment
Two authors (MJ and JJ) independently evaluated risk of bias using the Cochrane Risk of Bias tool (RoB V.2.0).\textsuperscript{30} The bias was based on randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Based on the recommendations of the Cochrane Handbook, risk of bias was judged to be ‘low risk of bias’, ‘some concerns’ and ‘high risk of bias’,
were quantified using the I² statistic (I² using the Q statistic. The intervention effects across studies was assessed by funnel plots in this study as it was not recommended when fewer than 10 studies included. Potential publication bias was not assessed by funnel plots in this study as it was not recommended when fewer than 10 studies included.

RESULTS
Study selection
A total of 682 records were identified in our initial and updated search. Four hundred and forty one records were screening of titles and abstracts after the removal of duplicates. We retrieved 26 full texts, and 1531–47 studies were finally included according to inclusion and exclusion criteria. Eleven articles were excluded for the following reasons: duplication population (n=5),48–52 exclusion criteria. Eleven articles were excluded for the following reasons: duplication population (n=5),48–52

respectively. The discrepancies were resolved by a third researcher (JHu).

Data synthesis and analysis
Extracted data for meta-analysis were analysed with Stata Statistical Software V.16.0 and Review Manager Software V.5.3. The heterogeneity between studies was examined using the Q statistic. The intervention effects across studies were quantified using the I² statistic (I² ≤50% was considered low to moderate heterogeneity, 50%–75% substantial heterogeneity and 75%–100% high heterogeneity). We used fixed-effect models if low to moderate heterogeneity was detected; otherwise, random effect models were used to pool the weighted mean difference (WMD) or standardised mean difference (SMD) with 95% CIs. WMD was pooled in meta-analysis when the measurement method and unit were uniform across studies, otherwise SMD was used. The p value <0.05 was defined as the significant level for all tests. Sensitivity analysis was performed by removing studies one by one to assess the robustness of the summary estimates. Potential publication bias was not assessed by funnel plots in this study as it was not recommended when fewer than 10 studies included.

Table 1 Characteristics of included researches

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Sample size</th>
<th>Gender (% woman)</th>
<th>Age (year)</th>
<th>BMI (kg/m²)</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilezikian et al (2013)</td>
<td>PDW</td>
<td>226</td>
<td>100.0</td>
<td>63.8 (6.5)</td>
<td>31.4 (5.8)</td>
<td>MET 2000 mg/day</td>
<td>ROSI 8 mg/day</td>
<td>BMD, PINP, CTX, BAP</td>
</tr>
<tr>
<td>Esteghamati et al (2015)</td>
<td>T2DM</td>
<td>82</td>
<td>56.1</td>
<td>50.6 (2.6)</td>
<td>29.6 (0.9)</td>
<td>MET 1000 mg/day</td>
<td>PIO 30 mg/day</td>
<td>OPG</td>
</tr>
<tr>
<td>Hegazy (2014)</td>
<td>PDW</td>
<td>40</td>
<td>100.0</td>
<td>62.0 (4.0)</td>
<td>26.9 (11.4)</td>
<td>MET 1000 mg/day</td>
<td>SIG 100 mg/day</td>
<td>BMD, OC, BAP</td>
</tr>
<tr>
<td>Ibáñez et al (2008)</td>
<td>LBWPP</td>
<td>38</td>
<td>100.0</td>
<td>7.9 (0.6)</td>
<td>18.4 (1.9)</td>
<td>MET 425–850 mg/day</td>
<td>Not treated</td>
<td>BMD</td>
</tr>
<tr>
<td>Kanazawa et al (2010)</td>
<td>T2DM</td>
<td>45</td>
<td>40.0</td>
<td>66.0 (10.0)</td>
<td>23.5 (3.4)</td>
<td>MET 500–750 mg/day</td>
<td>PIO 15–30 mg/day</td>
<td>BMD, OC</td>
</tr>
<tr>
<td>Koshihizaka et al (2021)</td>
<td>T2DM</td>
<td>103</td>
<td>39.8</td>
<td>56.1 (12.0)</td>
<td>28.2 (4.8)</td>
<td>MET 1000–1500 mg/day</td>
<td>IPR 50 mg/day</td>
<td>BMD, BAP</td>
</tr>
<tr>
<td>Ladson et al (2011)</td>
<td>PCOS</td>
<td>114</td>
<td>100.0</td>
<td>28.9 (4.5)</td>
<td>38.2 (7.9)</td>
<td>MET 2000 mg/day</td>
<td>Placebo</td>
<td>BMD</td>
</tr>
<tr>
<td>Lingialah et al (2019)</td>
<td>PCOS</td>
<td>118</td>
<td>100.0</td>
<td>27.6 (4.0)</td>
<td>26.5 (6.0)</td>
<td>MET 500–2000 mg/day</td>
<td>Placebo</td>
<td>PINP, CTX</td>
</tr>
<tr>
<td>Mori et al (2017)</td>
<td>T2DM</td>
<td>58</td>
<td>58.6</td>
<td>64.6 (8.1)</td>
<td>25.0 (3.9)</td>
<td>MET 750 mg/day</td>
<td>PIO 15–30 mg/day</td>
<td>CTX, BAP</td>
</tr>
<tr>
<td>Nordklint et al (2018)</td>
<td>T2DM</td>
<td>407</td>
<td>31.9</td>
<td>60.1 (9.0)</td>
<td>32.1 (4.2)</td>
<td>MET 2000 mg/day</td>
<td>Placebo</td>
<td>BMD</td>
</tr>
<tr>
<td>Pernicova et al (2020)</td>
<td>IDCP</td>
<td>53</td>
<td>54.7</td>
<td>46.0 (14.9)</td>
<td>27.9 (8.8)</td>
<td>MET 2550 mg/day</td>
<td>Placebo</td>
<td>BMD, OC, PINP, CTX</td>
</tr>
<tr>
<td>Soifer et al (2015)</td>
<td>NAFLD</td>
<td>63</td>
<td>50.8</td>
<td>53.5 (12.5)</td>
<td>32.1 (5.7)</td>
<td>MET 850–1700 mg/day</td>
<td>Placebo</td>
<td>PINP, OPG</td>
</tr>
<tr>
<td>Stage et al (2016)</td>
<td>T2DM</td>
<td>371</td>
<td>38.3</td>
<td>56.2 (8.4)</td>
<td>33.9 (5.7)</td>
<td>MET 2000 mg/day</td>
<td>Placebo</td>
<td>PINP, CTX, OPG</td>
</tr>
<tr>
<td>van Lierop et al (2012)</td>
<td>T2DM</td>
<td>71</td>
<td>0.0</td>
<td>56.5 (5.6)</td>
<td>28.8 (3.5)</td>
<td>MET 2000 mg/day</td>
<td>PIO 30 mg/day</td>
<td>PINP, CTX</td>
</tr>
<tr>
<td>Zimnan et al (2010)</td>
<td>T2DM</td>
<td>1605</td>
<td>42.9</td>
<td>56.7 (9.8)</td>
<td>32.5 (6.4)</td>
<td>MET 2000 mg/day</td>
<td>ROSI 8 mg/day, GLY 15 mg/day</td>
<td>PINP, CTX, BAP</td>
</tr>
</tbody>
</table>

Data were expressed as mean (SD).

BAP, bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CTX, C-terminal telopeptide of type I collagen; IDCP, inflammatory disease treated with continuous prednisolone; IPR, irapagliplizin; LBWPP, low birth weight girls with precocious pubarche; NAFLD, Nonalcoholic fatty liver disease; OC, osteocalcin; OPG, osteoprotegerin; PCOS, polycystic ovarian syndrome; PDW, postmenopausal diabetic women; PINP, N-terminal propeptide of type I procollagen; PIO, pioglitazone; ROSI, rosiglitazone; SIG, sitagliptin; T2DM, type 2 diabetes mellitus.
insufficient data (n=2),\textsuperscript{53,54} research protocol (n=2),\textsuperscript{55,56} ineligible control group (n=1)\textsuperscript{57} and no baseline data (n=1).\textsuperscript{58} A literature flowchart of our search strategy is shown in figure 1.

**Study characteristics**

Details of study design and baseline characteristics are presented in table 1. Overall, 15 RCTs were included with 3394 participants, of whom 50.0\% were women and the mean age was 54.91 (14.81) years. Eight studies were conducted on patients with T2DM,\textsuperscript{31,32,34,35,38,41–43} two on women with postmenopausal diabetes,\textsuperscript{36,37} two on polycystic ovarian syndrome population,\textsuperscript{33,44} one on patients with non-alcoholic fatty liver disease,\textsuperscript{39} one on low birthweight girls with precocious pubarche\textsuperscript{47} and one on patients with inflammatory disease treated with continuous prednisolone.\textsuperscript{45}

Eight of 15 studies reported BMD.\textsuperscript{31,33,36,37,42,45–47} Eleven of 15 studies measured bone turnover associated with PINP,\textsuperscript{31,32,34,36–41,43–46} CTX,\textsuperscript{31,32,34,36–41,43–46} OC,\textsuperscript{31,32,34,36–41,43–46} OPG\textsuperscript{39} and BAP.\textsuperscript{31,32,34,36–41,43–46}

**Risk of bias**

The detailed risk of bias for each domain is presented in figure 2. About 13\% of the studies showed a high risk of bias, 67\% showed some concerns and 20\% showed a low risk of bias. Two studies were rated high risk of bias due to baseline imbalance in randomisation process.\textsuperscript{31,38}

**Effect of metformin in BMD**

Eight studies (n=1026) were included. As shown in figure 3, metformin did not have statistically significant effect in BMD compared with control at lumbar spine (SMD=−0.05, 95\% CI=−0.19 to 0.09, p=0.47), at femoral (MD=−0.01 g/cm\(^2\), 95\% CI=−0.04 to 0.01 g/cm\(^2\), p=0.25) and at hip (MD=0.01 g/cm\(^2\), 95\% CI=−0.02 to 0.03 g/cm\(^2\), p=0.56). There was no significant statistical heterogeneity between the above studies. The sensitivity analysis did not show any study that significantly affected the results (online supplemental figure 1).

**Effect of metformin in bone turnover markers**

The pooled effect estimates of differences between metformin and the control group were statistically significant at PINP (MD=−6.09 µg/L, 95\% CI=−9.38 to −2.81 µg/L, p=0.0003) and CTX (MD=−55.80 ng/L, 95\% CI=−97.33 to −14.26 ng/L, p=0.008), as shown in figure 4A,B. There were no significant differences between metformin and the control group at bone turnover markers including OC (MD=−0.74 µg/L, 95\% CI=−2.57 to 1.10 µg/L, p=0.43), OPG (SMD=−0.39, 95\% CI=−1.10 to 0.31, p=0.28) and BAP (SMD=−0.10, 95\% CI=−0.51 to 0.30, p=0.62), as shown in figure 4C–E. High heterogeneity was observed at bone turnover markers, except for OC. The sensitivity analysis suggested no study significantly affected the results (online supplemental figure 2).

**DISCUSSION**

In this meta-analysis, we evaluated the metformin on BMD and bone turnover markers. Treatment with metformin for 3 months–48 months did not significantly increase BMD at lumbar spine, femoral and total hip. In addition, the analysis did not reveal any effects of metformin therapy on OC, OPG and BAP. Nevertheless, PINP (MD=−6.09 µg/L, 95\% CI=−9.38 to −2.81 µg/L, p=0.0003) and CTX (MD=−55.80 ng/L, 95\% CI=−97.33 to −14.26 ng/L, p=0.008) were decreased by metformin. PINP and CTX decreased by 14.54\% and 7.48\% from baseline after metformin therapy. According to a study, BMD increased significantly at the total hip (6.02\%), lumbar spine (6.71\%) and femoral neck (5.09\%).
(5.06%), following PINP and CTX decreased by 42% and 41% when postmenopausal women received a single infusion of intravenous zoledronic acid at 12 months. Postmenopausal women received three oral bisphosphate therapies which also showed reductions on PINP (~72% to ~54%) and CTX (~80% to ~63%). Our results suggested that the effects of metformin on PINP and CTX were statistically significant. But the treatment differences were far inferior to bisphosphonate.

Despite few supporting studies that did not show significant differences in cortical and trabecular bone architecture in metformin-treated rodents, our results are inconsistent with most previous animal studies that demonstrate metformin increases BMD or ameliorates bone microarchitecture parameters in vivo. Some retrospective studies indicate metformin is related to a higher BMD and a low risk of fracture. These controversial results may arise from the differences in response to metformin among rodent species. The difference crossing species barrier between human and animal studies is unpredictable. First, effects of metformin on BMD from animal experiment are verified in various studies is unpredictable. First, effects of metformin on PINP and CTX were statistically significant. But the treatment differences were far inferior to bisphosphonate.

PINP is recommended as the reference bone formation marker and CTX as bone resorption markers. PINP is cleaved from type I procollagen by osteoblast. PINP shows weak circadian variation and increases during bone formation-stimulating therapy. CTX is a telopeptide generated by collagen degradation, and is the most sensitive biomarker on antiresorptive therapy. The drop amplitude of CTX is applied as a target of antiresorptive treatment. PINP decreases in antiresorption therapy due to coupling factors to reflect curative effect indirectly. The antiresorptive agents such as bisphosphonates, raloxifene and denosumab, induce rapid reduction of CTX, pronounced than PINP. Our results show significant decreases in PINP and CTX following metformin therapy that suggests a link between metformin and antibone absorption. It seems like metformin has greater impact on osteoclasts rather than osteoblasts. Although more evidence pointing to osteoblasts, current researches have shown that metformin can reduce osteoclast number, inhibit the differentiation of osteoclasts. However, more than half of the included data involving PINP and CTX are from population with T2DM in our study. PINP and CTX are both decreased in patient with T2DM. It should be acknowledged that risk of bias as to population selection is insufficient in our results.

The results of this meta-analysis should be interpreted with caution due to several limitations. First, there are some deficiencies in the methodological quality-induced high risk of bias of some RCTs. Two of the included studies have imbalance baseline in randomisation process; one study has a higher lost follow-up rate; one study is a subset selective reporting; and 12 studies have unclear risk of bias of allocation concealment. Trials with inadequate or unclear concealment were reported to yield larger estimates of treatment effects. Empirical evidence suggests that all the deficiencies above possibly lower the statistical power to estimate the effects of metformin on the endpoints. Second, there are limited eligible studies in this meta-analysis, which do not allow us to carry out detailed subgroup analysis. Worse still, the small number of studies make it difficult to explore the source of heterogeneity. For instance, we cannot examine the effect of age, underlying disease, drug dose and course on the outcomes. Third, there is a high heterogeneity in the disease models, such as ovariectomy-induced osteoporosis, glucocorticoid-induced osteoporosis, insulin-deficient diabetes and fructose-induced metabolic syndrome. Drug efficacy in disease model is affected by various complicated factors in vivo. Second, the dose of metformin on bone in clinical studies is not adequately confirmed. The daily dosage of metformin used in our analysis range from 425 mg to 2550 mg. However, the daily dosage in animal experiment is higher from 100 mg/kg to 900 mg/kg. The current researches seem to show that a lower dose of metformin may have no obvious effect on BMD. The unclear effective dosage may cause a variation in efficacy evaluation of metformin on bone. It will be interesting to investigate if a safely booster dose of metformin can further improve BMD in human in future.
pooled-effect estimate of bone turnover markers. The heterogeneity is unaccountable and we perform the random effect analysis. Fourth, the publication bias is not tested because of small sample size. The publication bias of small number analysis. Fourth, the publication bias is not tested because gestivity is unaccountable and we perform the random effect future experiments.

CONCLUSION
In summary, there is no negative effect on BMD for patients treated with metformin, although no protective effect is discovered. PINP and CTX are decreased by metformin in our analysis, but the mechanisms through which metformin affects PINP and CTX are uncovered. BMD and bone turnover markers are not the primary outcome measures in the clinical studies we included. There is still a long way to go before the effects of metformin in bone tissues can be fully revealed. Further high-quality RCTs with accurate dose and enough follow-up time are required to accurately evaluate the effects of metformin on BMD and other bone turnover markers in healthy or particular population. The results of this systematic review provide certain reference for future experiments.

Contributors All authors meet all of the ICMJE criteria for authorship. All authors gave final approval to the submitted paper JL 2 acts as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. The data for the meta-analyses conducted are included in the manuscript.

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