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Type 2 diabetes and bone mineral density
A meta-analysis and systematic review

Minghan Li, MD[a,b,c,d], Hanqiao Sun, MD[b,c], Honggu Chen, MD[e], Weiwei Ma, MD[a,b,c,d], Ying Li, MD[a,d,*]

Abstract

Background: Type 2 diabetes (T2D), a widespread chronic metabolic disorder, presents frequently in clinical settings. The relationship between T2D and bone mineral density (BMD) has been subject to ongoing investigation, yielding inconclusive results.

Methods: A systematic literature search was conducted across several databases, including CNKI, VIP, CBM, Wanfang, PubMed, Cochrane Library, and Embase, targeting observational studies that explored the impact of microangiopathy associated with T2D on BMD or bone metabolism. The search spanned from the inception of each database to July 1, 2023. The Newcastle–Ottawa Scale was employed for quality assessment, and RevMan 5.3 software was utilized for data analysis. Stata 14.0 was used for the quantitative evaluation of publication bias regarding outcome measures.

Results: The inclusion criteria were met by 30 observational studies, comprising 6470 participants—3121 with diabetes and 3349 without. The meta-analysis revealed no significant difference in overall BMD between the nondiabetic and T2D groups (mean difference [MD] = –0.07, 95% confidence interval [CI] [–0.17, 0.03], $Z = 1.45$, $P = .15$). However, BMD at the lumbar vertebrae was significantly higher in nondiabetic individuals compared with those with T2D (MD = –0.14, 95% CI [–0.22, –0.06], $Z = 3.32$, $P = 0.0009$), as was the case with femoral neck BMD (MD = –0.11, 95% CI [–0.18, –0.04], $Z = 3.08$, $P = .002$). A difference in femoral neck BMD between nondiabetics and individuals with T2D approached but did not reach statistical significance (MD = –0.14, 95% CI [–0.27, 0.00], $Z = 1.94$, $P = .05$). An inverted funnel plot analysis suggested possible publication bias, as evidenced by an asymmetrical distribution of studies around the axis of symmetry, with overlap observed in several cases.

Conclusion: The findings indicate a significant association between T2D and reduced BMD at critical sites such as the lumbar vertebrae and femoral neck, highlighting an increased risk of osteoporosis or osteoporotic fractures in these regions.

Abbreviations: BMD = bone mineral density, CI = confidence interval, MD = mean difference, NOS = Newcastle-Ottawa Scale, OP = osteoporosis, RE = random-effects, T2D = type 2 diabetes.

Keywords: bone mineral density, meta-analysis, osteoporosis, systematic review, type 2 diabetes

1. Introduction

Type 2 diabetes (T2D) is a widespread endocrine and metabolic disorder encountered frequently in clinical settings. A 2019 study highlighted that an estimated 135.6 million individuals over the age of 65 were living with diabetes globally, a figure projected to rise to 195.2 million by 2030, primarily due to the expanding elderly population.[1] Concurrently, osteoporosis (OP), a systemic skeletal disorder characterized by diminished bone mass and deteriorating bone tissue microarchitecture – resulting from an imbalance between osteoblast and osteoclast activity – presents significant health concerns.[2] Clinical evidence increasingly suggests that T2D patients are at an increased risk of developing OP or sustaining osteoporotic fractures, positing OP as a potential complication of T2D. This association may be attributed to various factors, including insulin resistance, alterations in calcium and phosphorus metabolism, and hormonal changes,[3] laying a critical groundwork for examining the interplay between T2D and OP.

Despite the prevalence of both conditions in the middle-aged and elderly demographics, and their tendency to follow protracted courses, the causal relationship between T2D and OP

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The datasets generated during and/or analyzed during the current study are publicly available.

Because patient privacy is not involved, this manuscript does not require ethical approval, and the review will be disseminated in peer-reviewed journals.

[a] *Hubei University of Chinese Medicine, Wuhan, China,* [b] *Affiliated Hospital of Hubei University of Chinese Medicine, Wuhan, China,* [c] *Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, China,* [d] *School of Acupuncture-Moxibustion and Orthopedics, Hubei University of Chinese Medicine, Wuhan, China,* [e] *The Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China.*

** Correspondence: Ying Li, Hubei University of Chinese Medicine, Wuhan, 430061, China (e-mail: li_yingzhao@126.com).*

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– whether T2D precipitates OP or vice versa – remains elusive. Recent years have seen clinical studies and literature reviews investigating the link between T2D and bone mineral density (BMD), yet there remains a scarcity of systematic, standardized evidence-based research in this domain. Indeed, certain studies have even suggested that T2D might not confer a protective effect on BMD.[4] This research thus seeks to undertake a meticulous evaluation and meta-analysis of randomized controlled trials focusing on the nexus between T2D and BMD. Our objective is to bolster the corpus of systematic evidence in evidence-based medicine, elucidating the relationship between T2D and BMD, thereby informing clinical management strategies.

2. Information and methods

2.1. Approach

This meta-analysis was rigorously conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure methodological integrity and transparency.

2.2. Literature search

A comprehensive digital search was carried out across multiple databases, including Chinese Journal Full-text Database, VIP, China biology medicine, Wanfang, PubMed, Cochrane Library, and Embase, focusing exclusively on clinical studies that explored the relationship between BMD and T2D, in comparison with nondiabetic individuals. This search spanned all records from the inception of each database until July 2023. Search terms were carefully selected to encompass "type 2 diabetes" or "T2DM," "non-type 2 diabetes" or "healthy individuals," and "bone mineral density" or "BMD," among others. Searches were not limited by language and focused on retrieving full-text articles.

2.3. Inclusion criteria

Studies were selected based on the following criteria: (1) inclusion of both T2DM patients and nondiabetic individuals who underwent simultaneous physical examinations; (2) employment of a case-control or cross-sectional study design; (3) utilization of valid methods for bone density assessment; (4) availability of complete data on bone density metrics. Excluded were animal studies, incomplete reports, reviews, case studies, surveys, conference abstracts, and literature not pertinent to the study objective.

2.4. Literature screening and data extraction

Two independent reviewers meticulously screened titles, abstracts, and full texts to determine study eligibility according to the predefined criteria. Selected articles underwent data extraction, capturing details such as authorship, publication year, sample size, participant age range, study design, bone density measurement techniques, and specific measurement sites. Data were succinctly organized in a table for clarity and ease of reference.

2.5. Assessment of literature quality

The Newcastle-Ottawa Scale (NOS) was utilized by the reviewers to assess study quality, adhering to the Cochrane Handbook's recommendations. The NOS evaluates 3 key dimensions – Selection, Comparability, and Outcome – on a scale up to 9 points. Scores were interpreted as follows: 0 to 3 for low quality, 4 to 6 for moderate quality, and 7 to 9 for high-quality studies.

2.6. Statistical analysis

The meta-analysis was conducted using RevMan 5.3 software (London, UK), following specified procedures: (1) Effect Size Selection: Binary outcomes were analyzed using relative risk or odds ratio, while continuous outcomes employed mean difference (MD) with 95% confidence intervals (CI). (2) Heterogeneity Assessment: A fixed-effect model was applied if $P > .1$ and $I^2 \leq 50\%$, indicating low heterogeneity. Conversely, high heterogeneity ($P \leq .1$ or $I^2 > 50\%$) necessitated a random-effects (RE) model. Sensitivity analyses were conducted to explore the sources of heterogeneity among the studies included.

3. Results

3.1. Literature search results

The initial search process retrieved a total of 9528 documents. After the elimination of duplicate entries, the pool was narrowed down to 3285 documents. These documents underwent a rigorous screening process, including the examination of titles, abstracts, and full texts, strictly in accordance with the established inclusion and exclusion criteria. This thorough review culminated in the selection of 30 studies as suitable for inclusion in this meta-analysis, as depicted in Figure 1.

3.2. Characteristics of included studies

The meta-analysis incorporated 30 studies, totaling 6470 participants divided between 3121 individuals with diabetes and 3349 without. These studies were published between the years 2004 and 2022, covering a wide age range of participants, from approximately 34 to 83 years. The methodologies employed were predominantly case-control and cross-sectional designs. For the assessment of BMD, dual-energy X-ray absorptiometry was the most commonly used technique. Measurements were primarily focused on various anatomical sites including the whole body, lumbar vertebra, neck of femur, greater trochanter, hip, and femoral shaft. A comprehensive breakdown of these details is provided in Table 1.

3.3. Evaluation of literature quality

The evaluation of the 30 included studies, based on the NOS criteria focusing on Selection, Comparability, and Outcome, confirmed that the overall quality of the literature was high. This assessment underscores the reliability of the findings derived from these studies. The details of this evaluation are systematically presented in Table 2.

3.4. Meta-analysis results

3.4.1. Whole body bone mineral density. The meta-analysis included 6 studies[8,10,14,15,20,34] that examined whole-body BMD among a total of 826 participants. Using a RE model, the analysis found no statistically significant difference in BMD between nondiabetic individuals and those with T2D [MD = −0.07, 95% CI (−0.17, 0.03), $Z = 1.45$, $P = .15$]. These findings are visually represented in Figure 2.

3.4.2. Lumbar vertebra bone density. In this meta-analysis, 23 studies[5,9–11,13,15,17–28,30–32,34] focusing on the lumbar vertebra BMD included a cumulative total of 4768 participants. The analysis, employing a RE model, demonstrated that BMD at the lumbar vertebra was significantly lower in nondiabetic individuals compared to those with T2D (MD = −0.14, 95% CI [−0.22, −0.06], $Z = 3.32$, $P = .0009$). These results are depicted in Figure 3.

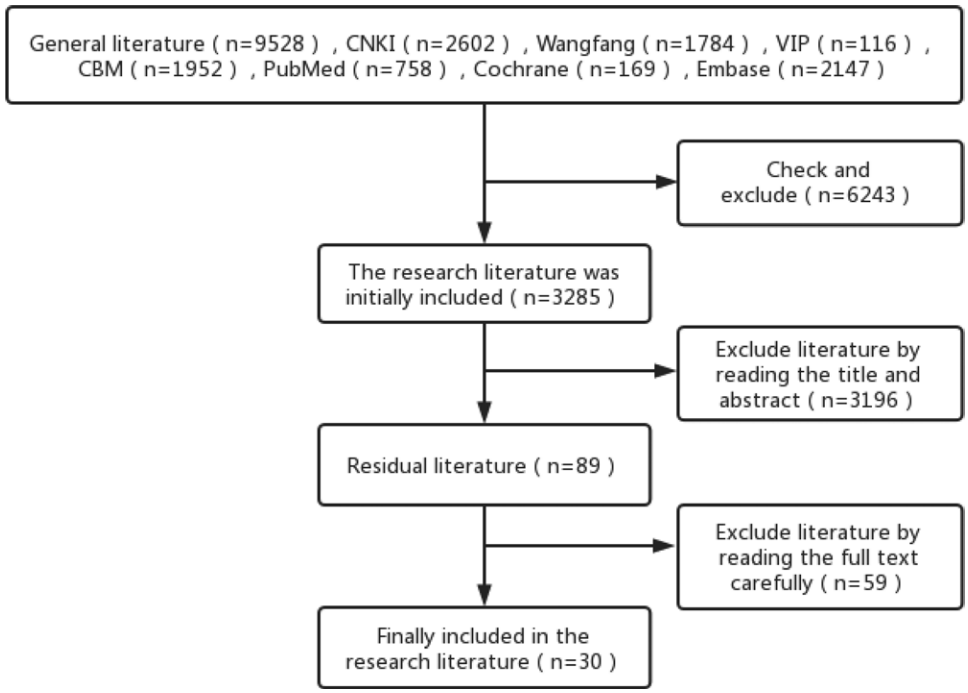

Figure 1. Flowchart of literature screening.

3.4.3. Neck of femur bone density. The meta-analysis reviewed 27 studies[5–13,15,16,18–20,22–34] assessing BMD at the neck of the femur, covering a total of 5404 participants. Utilizing a RE model for the analysis, it was found that nondiabetic individuals had significantly higher BMD at the neck of the femur compared to those with T2D (MD = −0.11, 95% CI [−0.18, −0.04], $Z = 3.08$, $P = .002$). These findings are illustrated in Figure 4.

3.4.4. Femoral BMD. In this section of the meta-analysis, 7 studies[16,22,24,25,28,30,33] were analyzed, focusing on the BMD at the greater trochanter, involving a cohort of 1374 participants. The analysis, conducted using a RE model, showed that there was no statistically significant difference in BMD between nondiabetic individuals and those with T2D (MD = −0.14, 95% CI [−0.27, 0.00], $Z = 1.94$, $P = .05$). These results are presented in Figure 5.

3.5. Analysis of bias

For the purpose of assessing potential bias, the BMD at the neck of femur, which was the focus of the greatest number of included studies, was selected for bias analysis. The examination of an inverted funnel plot revealed a nonuniform distribution of data points on either side of the symmetry axis. Notably, there was an overlap of data points skewed towards the outer margins of the funnel. This pattern suggests the presence of a potential publication bias within the body of literature included in this analysis (Fig. 6).

3.6. Sensitivity analysis

The meta-analysis revealed notable heterogeneity in the comparisons of bone density across various anatomical sites – such as the whole body, lumbar vertebra, neck of femur, greater trochanter, and hip – between type 2 diabetic individuals and nondiabetic populations. To address this, a sensitivity analysis was conducted employing a RE model for the metrics in question. Moreover, a stepwise exclusion of specific studies was undertaken to reassess the combined effect sizes.

In the case of whole-body bone density, the analysis identified that one study[15] was a significant source of heterogeneity. Excluding this study led to a substantial reduction in heterogeneity ($P = .23$, $I^2 = 30\%$). Post-exclusion, the RE model displayed a shift in the findings (MD = −0.03, 95% CI [−0.07, −0.00], $Z = 2.06$, $P = .04$), indicating that whole-body BMD in individuals with T2D was marginally lower than in the nondiabetic group.

For the meta-analysis focusing on the greater trochanter (referred to as rough rump) bone density, one study[26] was pinpointed as a major contributor to heterogeneity. Its removal eradicated heterogeneity ($P = .90$, $I^2 = 0\%$), but the adjusted results (MD = −0.03, 95% CI [−0.07, −0.01], $Z = 1.57$, $P = .12$) suggested no significant difference in bone density at this site between diabetic and nondiabetic subjects, diverging from initial findings.

No significant changes in outcomes were observed upon the exclusion of studies related to bone density at the lumbar vertebra, neck of femur, greater trochanter, and hip. This lack of variation in results post-exclusion serves to underscore the overall robustness and reliability of the meta-analysis findings within this study.

4. Discussion

Previous research has established a link between T2D and BMD. A case-control study in China found that T2D patients had a 35.77% higher clinical risk of OP compared to the general population.[35] Similarly, a meta-analysis showed that T2D patients had lower BMD at the lumbar spine and femoral neck, increasing their risk for OP and related fractures.[36] Additionally, a 5-year cohort study in Italy identified T2D as a significant risk factor for OP onset, attributed to decreased hydroxylase activity, altered calcium and phosphorus metabolism, functional hypoparathyroidism, and reduced muscle strength compared to normoglycemic individuals.[37,38]

Recent studies have highlighted high glucose levels as an OP risk factor in diabetic patients, potentially due to high glucose's ability to promote osteoclast differentiation by down-regulating SIRT1 and OPG expression while up-regulating RANK and RANKL cytokines. This effect may also be related to increased reactive oxygen species production in a high-glucose

Table 1

Characteristics of included studies.

	Sample size		Age		Study type	Bone mineral density detection	Detection sites
	T2DM	Non-T2DM	T2DM	Non-T2DM			
Harjit P Bhattoa 2013[5]	68	68	61.4 (51–78)	61.4 (51–78)	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L1–4), neck of femur
Yu Haiyan2015[6]	278	504	–	–	Cross-sectional study	Dual-energy X-ray absorptiometry	Neck of femur
Wu Aiqin 2011[7]	72	80	55.9 ± 3.3	55.6 ± 3.9	Cross-sectional study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L1–4)
Zhou Xiangjuan2009[8]	106	106	59.89 ± 9.6	61.1 ± 9.32	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density, lumbar vertebra (L2–4), neck of femur
Sun Shenghua2009[9]	65	68	65.25 ± 5.42	58.43 ± 10.12	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Sun Wenwen2009[10]	104	46	59 ± 12	55 ± 10	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density, lumbar vertebra (L2–4), neck of femur
Ji Faquan2018[11]	487	138	53.79 ± 15.78	51.28 ± 14.80	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur, hip joint
Chang Shuang2022[12]	68	48	66.22 ± 4.96	65.98 ± 4.76	Case-control study	X-ray bone densitometer	Neck of femur
Liao Chaoping2015[13]	129	130	67.7 ± 3.8	68.5 ± 2.3	Case-control study	Bone mineral density detector	Lumbar vertebra (L2–4), neck of femur
Zhang Jie2009[14]	105	93	60.47 ± 11.85	62.16 ± 10.87	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density
Zhang Xiaole2017[15]	60	60	65.78 ± 11.41	66.14 ± 11.54	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density, lumbar vertebra (L1–4), neck of femur
Zhang Chenxi2015[16]	118	124	51.6 ± 12.5	51.6 ± 12.5	Case-control study	Dual-energy X-ray absorptiometry	Neck of femur, femoral great trochanter
Zhang Song2008[17]	50	36	41 ± 1	41 ± 1	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4)
Zhang Yan2014[18]	68	68	51.7–3.1	51.5 ± 3.2	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Xu Dingbo2010[19]	80	80	62.6 ± 7.7	63.9 ± 6.4	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Li Dianbo2015[20]	30	30	58 ± 5.47	58 ± 7.16	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density, lumbar vertebra (L2–4), neck of femur
Li Cuiping2013[21]	82	700	56.04 ± 12.90	61.3 ± 8.9	Case-control study	Lunar Prodigy DEXA	Lumbar vertebra (L1–4)
Li Ying2014[22]	200	200	50–80	50–80	Case-control study	DEXA (Hologic-DXA)	Lumbar vertebra (L1–4), neck of femur, femoral great trochanter
Du Xuemei2006[23]	65	80	65.4 ± 10.0	65.9 ± 8.2	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Lin Bing2005[24]	54	54	71 ± 5	71 ± 6	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Mao Guizhi2015[25]	66	53	44.14 ± 9.37	45.49 ± 9.41	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L1–4), neck of femur
Wang Liang2010[26]	22	25	59.44 ± 8.79	64.06 ± 6.57	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L1–4), neck of femur
Wang Yongjian2004[27]	182	120	56.2 ± 7.8	56.7 ± 8.2	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Wang Ping2017[28]	128	50	67.9 ± 4.4	68.7 ± 4.6	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L1–4), neck of femur, femoral great trochanter
Cheng Xinqin2014[29]	72	60	67.05 ± 4.72	66.85 ± 4.37	Case-control study	Dual-energy X-ray absorptiometry	Neck of femur
Miao Qilei2014[30]	120	135	70.26 ± 10.21	68.91 ± 6.81	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur, femoral great trochanter
Jiang E2013[31]	60	60	70–83	70–79	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur
Xu Huixian2021[32]	74	75	67.16 ± 3.51	67.53 ± 3.72	Case-control study	Dual-energy X-ray absorptiometry	Lumbar vertebra (L2–4), neck of femur, hip joint
Ajiguri Abdul Reyimu2013[33]	40	40	69.21 ± 4.56	69.58 ± 3.88	Case-control study	Dual-energy X-ray absorptiometry	Neck of femur, femoral great trochanter
Ma Yuanfang 2011[34]	68	18	57.99 ± 7.54	55.39 ± 8.67	Case-control study	Dual-energy X-ray absorptiometry	Total body bone mineral density, lumbar vertebra (L2–4), neck of femur

T2DM = type 2 diabetes mellitus

Table 2

Literature quality evaluation table.

Eligible studies	Selection	Comparability	Outcome	NOS score
Harjit P Bhattoa 2013[5]	3	1	2	6
Yu Haiyan2015[6]	3	2	3	8
Wu Aiqin 2011[7]	3	1	2	6
Zhou Xiangjuan2009[8]	3	1	2	6
Sun Shenghua2009[9]	3	2	2	7
Sun Wenwen2009[10]	3	1	2	6
Ji Faquan2018[11]	3	2	3	8
Chang Shuang2022[12]	3	1	2	6
Liao Chaoping2015[13]	3	2	1	6
Zhang Jie2009[14]	3	2	2	7
Zhang Xiaole2017[15]	3	1	2	6
Zhang Chenxi2015[16]	3	1	2	6
Zhang Song2008[17]	3	1	2	6
Zhang Yan2014[18]	3	1	2	6
Xu Dingbo2010[19]	3	2	3	8
Li Dianbo2015[20]	3	1	2	6
Li Cuiping2013[21]	3	2	2	7
Li Ying2014[22]	3	2	2	7
Du Xuemei2006[23]	3	2	2	7
Lin Bing2005[24]	4	2	3	9
Mao Guizhi2015[25]	3	2	3	8
Wang Liang2010[26]	3	2	2	7
Wang Yongjian2004[27]	3	2	2	7
Wang Ping2017[28]	3	2	2	7
Cheng Xinqin2014[29]	3	2	2	7
Miao Qilei2014[30]	3	2	1	6
Jiang E2013[31]	3	2	1	6
Xu Huixian2021[32]	3	2	3	8
Ajiguri Abdul Reyimu2013[33]	3	2	2	7
Ma Yuanfang 2011[34]	4	2	3	9

NOS = Newcastle-Ottawa Scale.

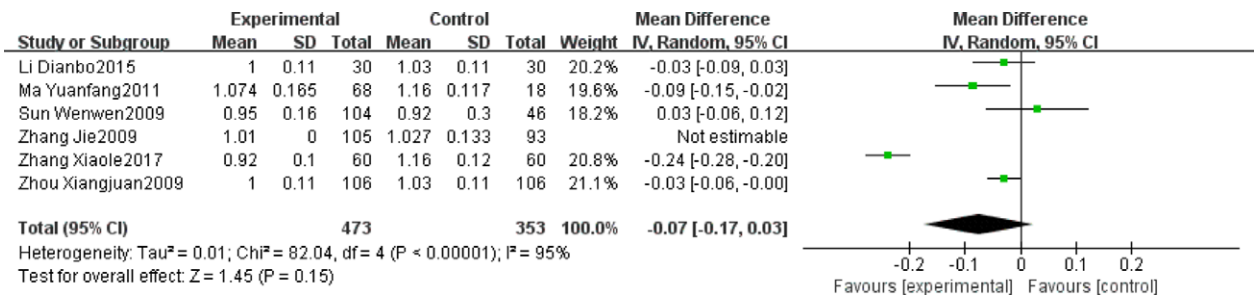

Figure 2. Forest plot of whole-body bone density.

environment, accelerating osteoclast apoptosis.[39–41]Inflammatory factors such as TNF-α and IL-6 are elevated in T2D patients, promoting apoptosis-related expression, reducing MG63 cell viability, and accelerating apoptosis. These factors also increase RANKL expression, stimulating osteoclast proliferation and disrupting bone metabolism balance.[42,43] Advanced diabetes mellitus stages lead to increased urine osmolality and nutrient ion excretion through osmotic diuresis, while inhibiting renal tubular reabsorption of essential ions, leading to hyperparathyroidism and OP.[44–46]Insulin resistance, a key T2D mechanism, significantly impacts OP onset. Bone, as an insulin target organ, experiences disrupted stem cell differentiation into osteoblasts and increased bone resorption in insulin resistance, leading to reduced bone density and OP. Insulin resistance also decreases renal 1-α hydroxylase levels, affecting active vitamin D synthesis, osteocalcin deposition, and bone formation, thus promoting OP.[47,48] Furthermore, insulin-resistant patients show elevated inflammatory factor expression, contributing to OP progression.[49]

This study faces several limitations, including issues with study design, such as inadequate randomization, lack of blinding, and the absence of allocation concealment information. These factors may introduce bias in the outcomes. Furthermore, the original studies' lack of adjustments for confounding variables in some multifactorial analyses impacts the robustness of the results, potentially leading to selection bias. The limited number of studies also constrained the analysis of relevant factors, further affecting the reliability of the findings. In addition, high heterogeneity was observed in the forest plots, likely influenced by factors such as the diversity of study populations, differences in methodologies, and variations in sample sizes. This heterogeneity may compromise the stability of effect sizes, necessitating a cautious interpretation of the results. To address these limitations, future research should focus on conducting more prospective cohort studies that comprehensively evaluate all relevant factors affecting OP incidence in T2D patients. This approach will help provide a clearer understanding and more robust evidence for this association.

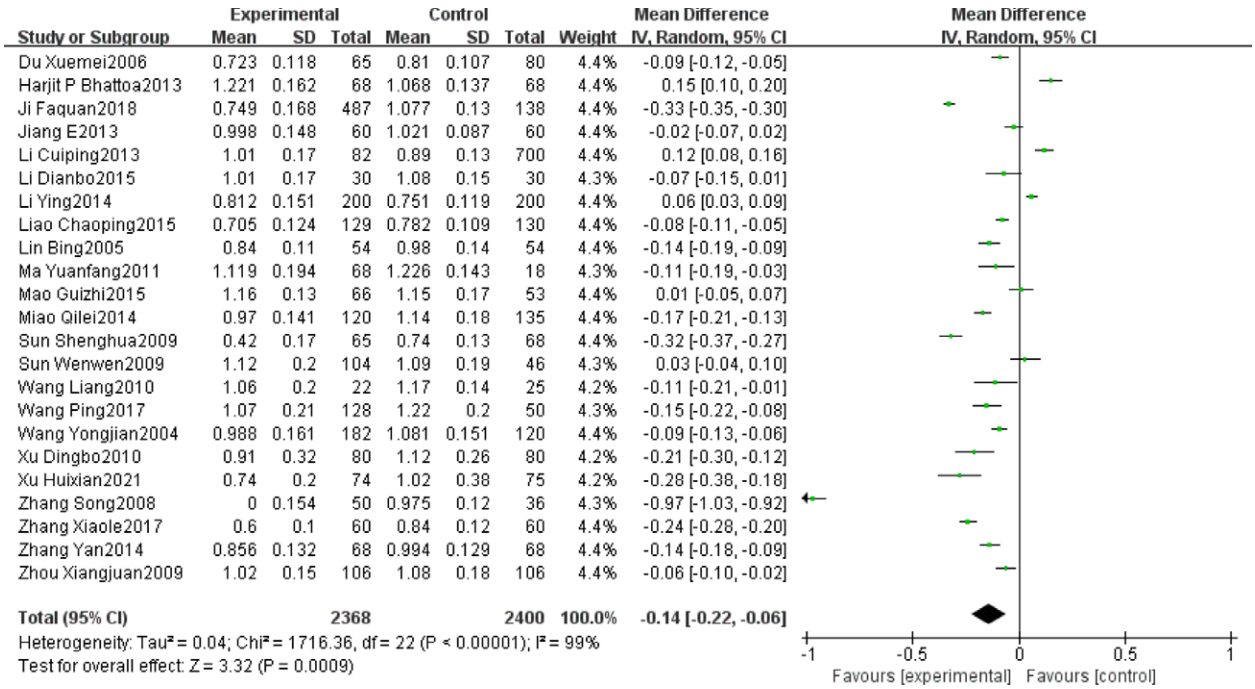

Figure 3. Lumbar vertebra bone density forest plot.

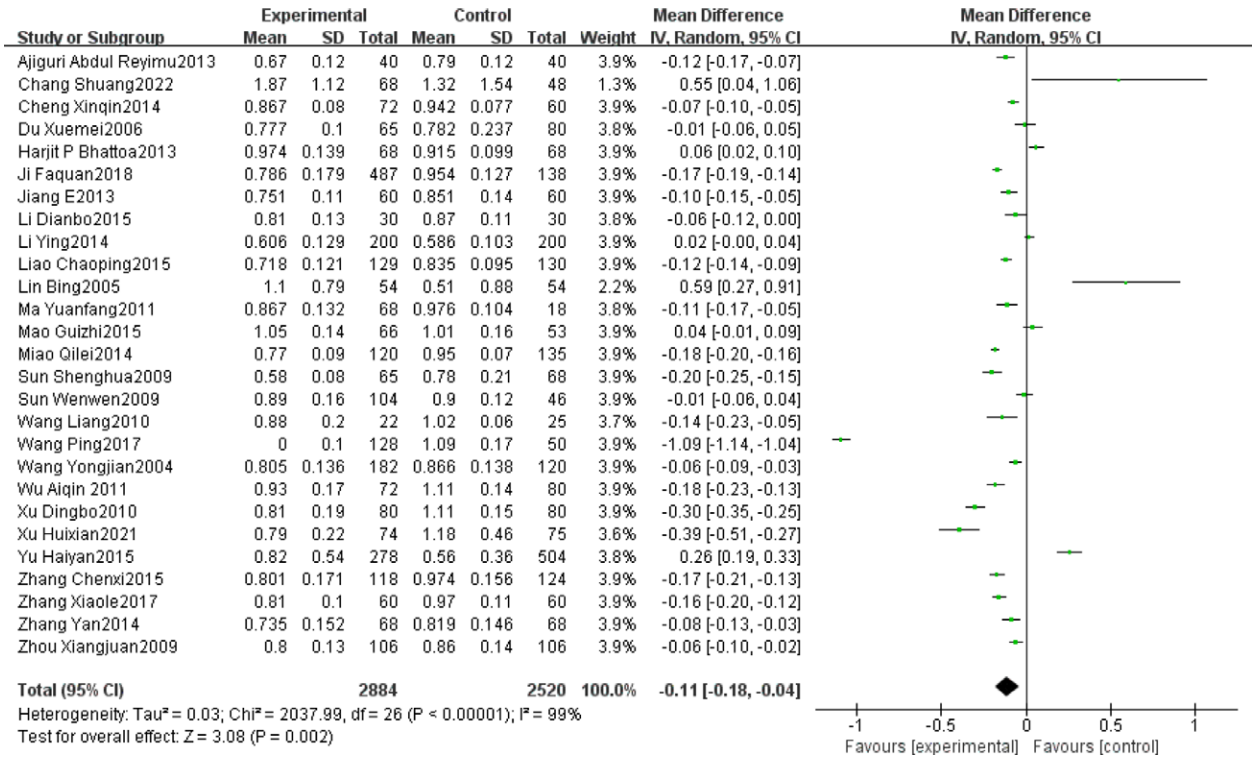

Figure 4. Forest plot of neck of femur bone density.

Author contributions

Conceptualization: Minghan Li.
Data curation: Hanqiao Sun.
Formal analysis: Hanqiao Sun.
Funding acquisition: Ying Li.
Investigation: Honggu Chen.
Methodology: Minghan Li.
Supervision: Ying Li.
Validation: Weiwei Ma.
Visualization: Hanqiao Sun.
Writing – original draft: Minghan Li.
Writing – review & editing: Minghan Li, Ying Li.

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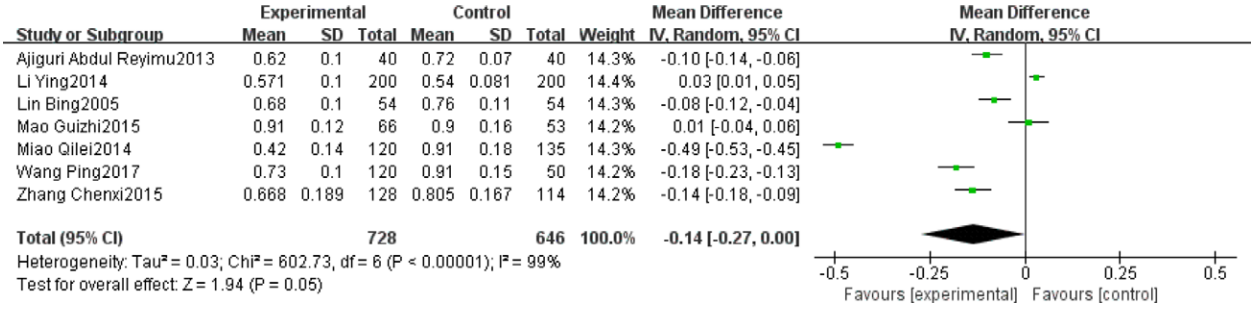

Figure 5. Forest plot of bone density in the greater trochanter.

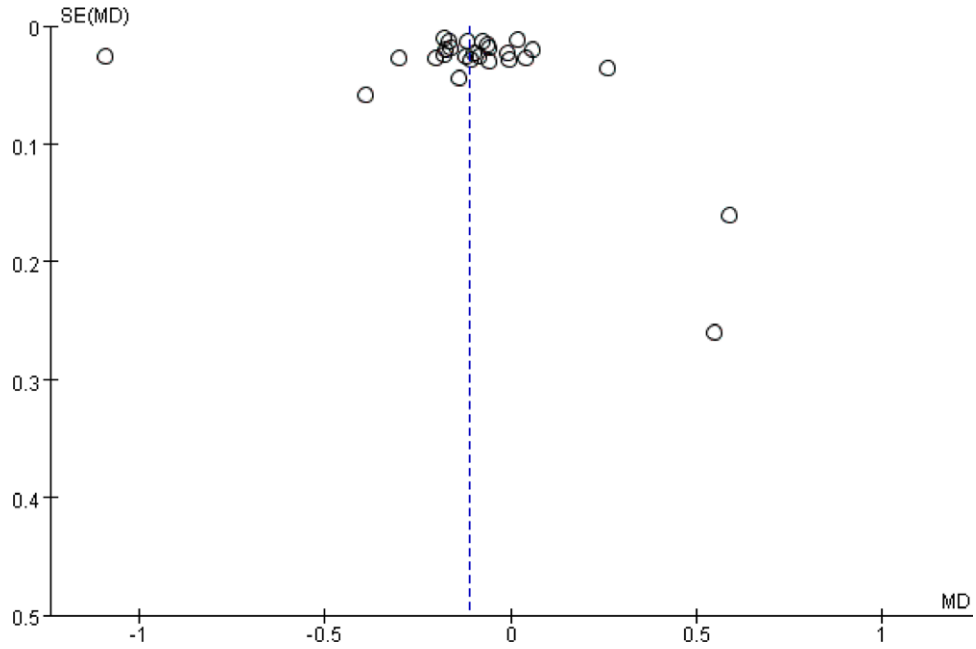

Figure 6. Neck of femur bone density inverted funnel plot.

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