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Research article

Influence of type 2 diabetes microangiopathy on bone mineral density and bone metabolism: A meta-analysis

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HIGHLIGHTS

- The effect of type 2 diabetes microangiopathy on bone mineral density and bone metabolism is still unclear.
- Type 2 diabetes microangiopathy can reduce the lumbar spine, femoral neck and Ward's triangle BMD.
- Type 2 diabetes microangiopathy has a higher risk of osteoporosis or osteoporosis fractures.

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ABSTRACT

Background: Diabetic microangiopathy is a type of vascular dysfunction. The effect of type 2 diabetes microangiopathy (DMA) on bone mineral density (BMD) and bone metabolism is still unclear.
Objective: A meta-analysis was performed to investigate the effects of microangiopathy on BMD and bone metabolism in type 2 diabetic patients.
Methods: We searched the PubMed, Embase, Cochrane Library and CNKI databases to identify observational studies investigating the effects of type 2 diabetes microangiopathy on BMD or bone metabolism. The time limit for the literature retrieval was from the establishment of the database to September 25, 2021. The Newcastle–Ottawa scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ) scale were used to evaluate the quality of the studies. RevMan 5.3 software was used for the data analysis. Stata 14.0 was used to quantitatively evaluate the publication bias of the outcome indicators.
Results: In total, 12 observational studies were included, including 7 cohort studies, 4 case–control studies and 1 cross-sectional study. In total, 2,500 patients with type 2 diabetes were included. Among them, 1,249 patients had microangiopathy (DMA group), and 1,251 patients did not have microangiopathy (control group). The results of the meta-analysis showed that the BMDs of the femoral neck (SMD = −1.34, 95% CI = −2.22 to −0.45, P = 0.003), lumbar spine (SMD = −0.69, 95% CI = −1.31 to −0.08, P = 0.03) and Ward's triangle (SMD = −2.84, 95% CI = −4.84 to −0.83, P = 0.006) in the DMA group were lower than those in the control group. In the comparison of the bone metabolism indexes, the contents of N-terminal propeptide of type I procollagen (P1NP) (SMD = 0.18, 95% CI = 0.03 to 0.32, P = 0.02), osteocalcin (SMD = 6.97, 95% CI = 3.46 to 10.48, P < 0. 0001), parathyroid hormone (PTH) (SMD = 0.38, 95% CI = 0.03 to 0.73, P = 0.03) and C-telopeptide of type 1 collagen (CTX) (SMD = 0.39, 95% CI = 0.03 to 0.75, P = 0.03) in serum from the DMA group were higher than those in serum from the control group. The serum content of 25-hydroxyvitamin D_3 ($25(OH)D_3$) (SMD = −0.63, 95% CI = −1.19 to −0.07, P = 0.03) in the DMA group was lower than that in the control group. There was no significant difference in serum alkaline phosphatase (ALP), calcium or phosphorus between the two groups (P > 0.05).

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Conclusions: Type 2 diabetes microangiopathy can reduce the lumbar spine, femoral neck and Ward's triangle BMD and has a higher risk of osteoporosis or osteoporosis fractures. The levels of P1NP, PTH, CTX and OC in the serum of patients with type 2 diabetes microangiopathy are higher, and the lower 25(OH)D_3 content may be a mechanism by which DMA destroys bone metabolism balance.

1. Introduction

Type 2 diabetes can be accompanied by multiple complications, including microangiopathy. With improvements in people's quality of life and the aging of the population, the incidence rate of type 2 diabetes is gradually increasing, and the complications of diabetic nephropathy (DN), diabetic retinopathy (DR) and diabetic peripheral neuropathy (DPN) are also increasing [1, 2]. Previous studies have shown that patients with type 2 diabetes mellitus (T2DM) complicated with microangiopathy have a significantly higher risk of fracture [3, 4]. Diabetic microangiopathy is a type of vascular dysfunction that can change the blood supply of microvessels in bone, affect bone metabolism, lead to changes in the bone mineral density (BMD) and reduce bone quality [5, 6]. Some studies suggest that T2DM microangiopathy is related to changes in BMD, and T2DM microangiopathy can reduce BMD [7, 8]. Diabetes may affect bone quality by affecting bone cells [9]. Bone turnover markers (BTMs) are enzymes and metabolites secreted by bone cells that reflect bone formation, bone resorption and, subsequently, the dynamics of bone remodeling [10]. With the occurrence and development of diabetic microangiopathy, the decrease in BMD due to the decrease in hydroxylase activity, disturbance of calcium and phosphorus metabolism, functional hypoparathyroidism and muscle strength weakening, the incidence of osteoporosis is higher in patients with diabetes [11, 12, 13, 14]. BTMs can be used as independent predictors of osteoporosis and osteoporotic fractures [15]. However, the process of bone turnover may be affected by diabetes and its complications. In recent years, an increasing number of researchers have focused on BMD and bone metabolism in diabetic microangiopathy, but no definite conclusions have been drawn. The aim of this study was to explore the relationship between T2DM complicated with microangiopathy and BMD and bone metabolism and discuss the role of BTMs in this relationship through a meta-analysis to provide scientific evidence for preventing osteoporosis and reducing fractures in patients with T2DM.

2. Materials and methods

This study follows the requirements of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [16].

2.1. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) The study was designed as an observational study and included cohort, case–control and cross-sectional studies; 2) the aim of the study was to investigate the effects of microangiopathy on BMD or bone metabolism in T2DM; 3) the experimental group had T2DM with microangiopathy (DMA group), while the control group had T2DM without microangiopathy; 4) clear diagnostic criteria for T2DM were used, and the types of microangiopathy were specifically described; and 5) the outcome indexes included BMD or bone metabolism-related indexes. There was no restriction on the language in which the study was published.

The exclusion criteria were as follows: 1) duplicate studies; 2) incomplete original data or failure to obtain original data upon request; and 3) unclear outcome indicators or nonquantitative indicators, such as images.

2.2. Literature retrieval strategy

We searched the PubMed, Embase, Cochrane Library and China National Knowledge Infrastructure (CNKI) databases to collect observational studies investigating the effects of T2DM microangiopathy on BMD or bone metabolism. The retrieval time was limited to September 25, 2021. In addition, we consulted and searched relevant references included in the literature to ensure the comprehensiveness and accuracy of the retrieved literature. Two researchers searched independently and obtained the same results. In case of any disagreement, the issue was discussed and resolved with the corresponding author. The search terms included diabetes mellitus, microangiopathy, vasculopathy, bone mineral density and bone metabolism. The retrieval strategy for each database is shown in supplementary material 1.

2.3. Literature screening and data extraction

Thee literature screening and data extraction were carried out independently by two researchers and cross-checked. Any differences were discussed and resolved or submitted to the corresponding author for adjudication. During the literature screening, first, the title was read, and then, the abstract and full text were read after excluding obviously irrelevant studies to ultimately determine whether to include a study. The data extraction included 1) basic information regarding the included study, including the title, author, year of publication, and type of study; 2) basic characteristics of the research subjects, including sex and age; 3) outcome indicators and measurement data; and 4) information related to the study quality evaluation.

2.4. Evaluation of study quality

The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the cohort studies and case–control studies [17]. The NOS scale includes the following three aspects: study population selection, intergroup comparability and result measurement, with a total of 8 items and 9 points. Studies with a score >6 were considered high quality; those with a score of 6 were considered medium quality; and those with a score less than 6 were considered low quality. The Agency for Healthcare Research and Quality (AHRQ) was used to evaluate the quality of the included cross-sectional studies [18]. There were 11 items. If the answer was "yes", 1 point was given; if the score was less than 4, the study quality was considered poor. The higher the score, the higher the quality of the study.

2.5. Statistical analysis

The extracted data were analyzed with RevMan 5.3 software. Since the indicators of bone metabolism and BMD are continuous variables and the measuring instruments are different, the combined effect quantities are expressed by the standardized mean difference (SMD) and 95% confidence interval (CI). The heterogeneity among the included studies was quantitatively evaluated with an I^2 test and chi-square test. If the statistical heterogeneity among the research results was small ($I^2 \leq 50\%$), a fixed effect model was used for the meta-analysis; if the statistical heterogeneity among the research results was large ($I^2 > 50\%$), a random effect model was used for the meta-analysis. If more than 3 studies included an outcome indicator, Stata 14.0 software was used to evaluate whether there was publication bias with Egger's test.

3. Results

3.1. Retrieval process and results

After a preliminary search, 408 relevant studies were obtained; 262 duplicate studies were eliminated, 199 studies were eliminated after

reading the titles and abstracts, 51 studies did not meet the inclusion criteria after reading the full text and were eliminated, and, in total, 12 high-quality studies were finally included [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. The process and results of the literature screening are shown in Figure 1.

3.2. Characteristics and quality of the included literature

In total, 12 articles were included in this study, including 2,500 patients; among them, there were 1,249 cases of T2DM complicated with microangiopathy and 1,251 cases of T2DM without microangiopathy. The types of microangiopathy included DN, DR and DPN. The basic characteristics of the included literature are shown in Table 1. The 12 observational studies included in this study included 7 cohort studies [19, 20, 21, 23, 24, 25, 27], 4 case–control studies [22, 28, 29, 30] and 1 cross-sectional study [26]. The AHRQ score of the 1 cross-sectional study was 9, and the study quality was high. According to the NOS scoring criteria, the scores of the 7 cohort studies and 4 case–control studies were 7–9 and 6–8, respectively. The NOS and AHRQ scores of the 12 included studies were greater than or equal to 6, suggesting that the study quality was very high. Specific information regarding the study quality scores is shown in supplementary material 2.

3.3. Meta-analysis results

3.3.1. BMD

3.3.1.1. Femoral neck BMD (g/cm^2). In total, 6 studies reported the results of femoral neck BMD [21, 22, 26, 28, 29, 30], and there was heterogeneity among the studies ($P < 0.00001$, $I^2 = 97\%$); thus, a random effect model was used to analyze the combined SMD. The results showed that the femoral neck BMD decreased more significantly in the DMA group than in the control group (SMD = −1.34, 95% CI = −2.22 to −0.45, P = 0.003; Figure 2), and the difference was statistically significant.

3.3.1.2. Lumbar spine BMD (g/cm^2). Four studies [21, 22, 29, 30] reported the research results of lumbar BMD. There was heterogeneity among the studies ($P < 0.00001$, $I^2 = 89\%$); thus, a random effect model was used to analyze the combined SMD. The meta-analysis results showed that the lumbar BMD in the DMA group was less than that in the control group (SMD = −0.69, 95% CI = −1.31 to −0.08, P = 0.03; Figure 3), and the difference was statistically significant.

3.3.1.3. Ward's triangle BMD (g/cm^2). According to the heterogeneity test results ($P < 0.00001$, $I^2 = 97\%$), we used a random effect model to analyze the combined SMD of Ward's triangle BMD. The results showed that compared with the control group, Ward's triangle BMD in the DMA group was significantly lower (SMD = −2.84, 95% CI = −4.84 to −0.83, P = 0.006; Figure 4), and the difference was statistically significant.

3.3.2. Bone metabolism

3.3.2.1. Bone formation markers

3.3.2.1.1. N-terminal propeptide of type I procollagen (P1NP) (ng/ml). In total, 6 studies [19, 21, 23, 24, 25, 28] reported P1NP data. There

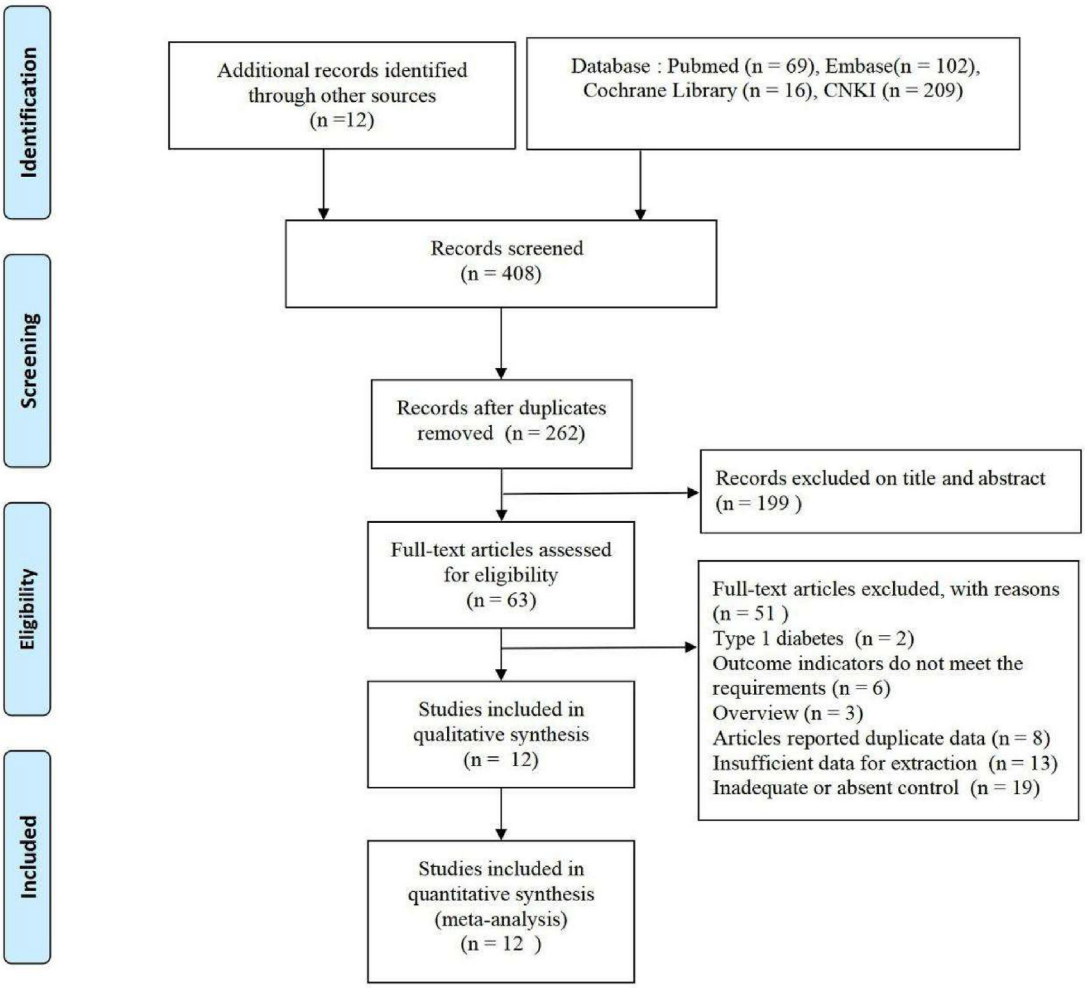

Figure 1. Flowchart showing the process of the literature search.

Table 1. Characteristics of the included studies.

Study	Study Design	Sample Size (M/F)		Mean Age,years		Body mass index, kg/m^2		Types of microangiopathy in diabetic patients	NOS or AHRQ score
		DMA Group	DM Group	DMA Group	DM Group	DMA Group	DM Group		
He et al. 2018 [19]	CS	138 (88/50)	163 (101/62)	47.19 ± 4.84	46.94 ± 6.53	24.69 ± 3.56	24.72 ± 3.63	DR	7*
Zhao et al. 2013 [20]	CS	26 (16/10)	62 (24/38)	60.96 ± 9.15	61.39 ± 10.0	25.92 ± 3.02	24.62 ± 3.45	DR, DN	7*
Liu et al. 2019 [21]	CS	50 (21/29)	88 (40/48)	59.38 ± 9.07	55.92 ± 9.3	25.93 ± 3.4	27.06 ± 3.6	DR, DN	8*
Wang et al. 2016 [22]	CC	43 (21/22)	49 (25/25)	66. 8 ± 7. 9	64. 9 ± 6. 2	22. 8 ± 3. 6	22. 9 ± 4. 2	DR, DN	8*
Lou et al. 2018 [23]	CS	57 (–/–)	72 (–/–)	61. 6 ± 8. 2	61. 2 ± 8. 7	25. 80 ± 3. 59	25. 13 ± 4. 015	DR	8*
Xiao et al. 2017 [24]	CS	187 (90/97)	163 (73/90)	55.3 ± 0.18	48.17 ± 0.45	25. 01 ± 0.03	24. 37 ± 0.15	DN, DR, DPN	8*
Shanbhogue et al. 2016 [25]	CSS	25 (12/13)	26 (9/17)	65.3 ± 7.1	51.4 ± 11.1	31.7 ± 5.0	30.6 ± 6.6	DN, DR, DPN	9†
Zhang et al. 2017 [26]	CS	229 (82/147)	179 (62/117)	61.4 ± 4.0	61.2 ± 4.1	27.3 ± 3.8	27.6 ± 5.5	DR	9*
Wu et al. 2020 [27]	CS	86 (54/32)	190 (132/58)	59.35 ± 12.81	54.28 ± 11.31	21.97 ± 4.01	21.76 ± 4.87	DR	8*
Tan et al. 2021 [28]	CC	297 (149/148)	160 (103/57)	63. 42 ± 8. 71	61. 19 ± 8. 66	24. 10 ± 3. 23	24. 33 ± 3. 07	DN, DR, DPN	7*
Kong et al. 2003 [29]	CC	33 (15/18)	27 (11/16)	61.79 ± 7.91	58.12 ± 8.4	23.90 ± 3.25	24.9 ± 2.8	DN, DR, DPN	6*
Luo et al. 2018 [30]	CC	78 (39/39)	72 (36/36)	52. 4 ± 7. 3	53. 1 ± 6. 9	22. 47 ± 3. 38	21. 06 ± 2. 89	DN, DR, DPN	7*

M, male; F, female; DMA, diabetes microangiopathy; DM, diabetes mellitus; CS, cohort study; CC, case-control study; CSS, cross-sectional study; DR, diabetic retinopathy; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; *NOS = Newcastle-Ottawa Scale; †AHRQ = American Agency for Healthcare Research and Quality.

was heterogeneity among the studies (P = 0.06, I^2 = 52%); thus, a random effect model was used for the data analysis. The results showed that the serum P1NP content in the DMA group was higher than that in the control group (SMD = 0.18, 95% CI = 0.03 to 0.32, P = 0.02; Figure 5), and the difference was statistically significant.

3.3.2.1.2. Osteocalcin (ng/ml). In total, 4 studies [24, 27, 29, 30] reported osteocalcin data. There was heterogeneity among the studies (P < 0.0001, I^2 = 100%); thus, a random effect model was used for the data analysis. The results showed that the content of calcitonin in the serum in the DMA group was higher than that in the control group (SMD = 6.97, 95% CI = 3.46 to 10.48, P < 0.0001; Figure 6), and the difference was statistically significant.

3.3.2.2. Parameters affecting the bone metabolism index

3.3.2.2.1. Parathyroid hormone (PTH) (pg/ml). According to the results of the heterogeneity test (P < 0.000001, I^2 = 89%), we used a random effect model to analyze the combined SMD of PTH. The results showed that compared with the control group, the PTH content in the DMA group was lower (SMD = 0.38, 95% CI = 0.03 to 0.73, P = 0.03; Figure 7), and the difference was statistically significant.

3.3.2.2.2. 25-Hydroxyvitamin D_3 (25(OH)D_3) (ng/ml). According to the results of the heterogeneity test (P < 0.000001, I^2 = 97%), we used a random effect model to analyze the combined SMD of 25(OH)D_3. The results showed that the content of serum 25(OH)D3 in the DMA group was lower than that in the control group (SMD = −0.63, 95% CI = −1.19 to −0.07, P = 0.03; Figure 8), and the difference was statistically significant.

3.3.2.3. Blood biochemical indexes

3.3.2.3.1. Alkaline phosphatase (ALP) (μg/l). Three studies [21, 28, 30] reported ALP data. The heterogeneity among the studies was low (P = 0.35, I^2 = 5%); thus, a fixed effect model was used for the data analysis. The results showed that there was no significant difference in the serum content of ALP between the DMA group and the control group (SMD = −0.06, 95% CI = −0.21 to 0.09, P = 0. 44; Figure 9).

3.3.2.3.2. Serum calcium (mmol/l). In total, 8 studies [19, 20, 21, 23, 27, 28, 29, 30] reported data concerning the serum calcium content. There was heterogeneity among the studies (P < 0.000001, I^2 = 98%); thus, a random effect model was used for the data analysis. The results showed that compared with the control group, the serum calcium content in the DMA group was lower, but the difference was not statistically significant (SMD = −0.08, 95% CI = −0.97 to 0.82, P = 0.87; Figure 10).

3.3.2.3.3. Serum phosphorus (mmol/l). In total, 5 studies [20, 21, 23, 27, 28] reported data concerning the serum phosphorus content. The heterogeneity among the studies was low (P = 0.09, I^2 = 49%); thus, a fixed effect model was used for the data analysis. The results showed that there was no significant difference in the serum phosphorus content between the DMA group and the control group (SMD = 0.04, 95% CI = −0.09 to 0.16, P = 0.55; Figure 11).

3.3.2.4. Bone resorption marker

3.3.2.4.1. C-telopeptide of type 1 collagen (CTX) (ng/ml). In total, 5 studies [19, 23, 24, 25, 28] reported data concerning the serum CTX content. There was heterogeneity among the studies (P < 0.000001, I^2 = 92%); thus, a random effect model was used for the data analysis. The results showed that the CTX content in the serum of the patients in the DMA group was higher than that in the patients in the control group, and the difference was statistically significant (SMD = 0.39, 95% CI = 0.03 to 0.75, P = 0.03; Figure 12).

3.3.2.4.2. Quantitative evaluation of publication bias. Stata 14.0 software was used to carry out Egger's test of the outcome indicators that were reported in more than three studies. Egger's test was performed for ALP, and the results showed that P = 0.028, suggesting that there may be publication bias in the research results of ALP. No publication bias was found in the other outcome indicators (P > 0.05). The results of the

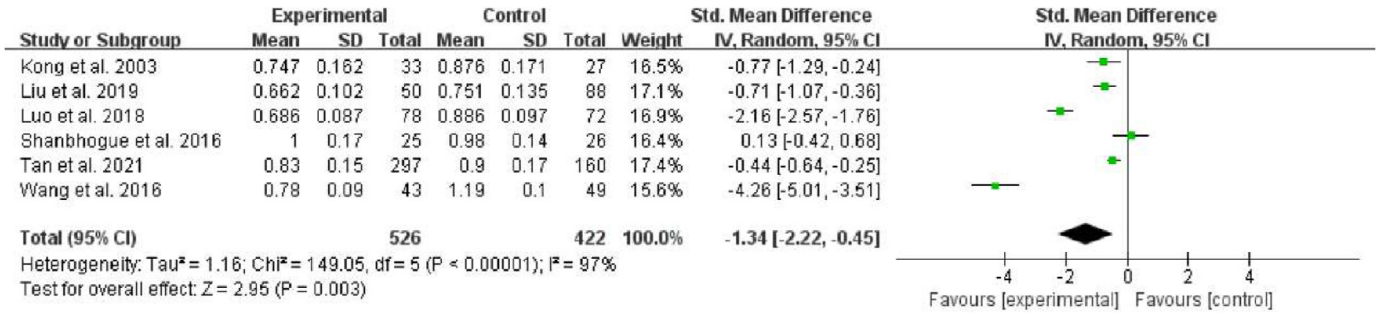

Figure 2. Forest plot for comparison of femoral neck BMD between two groups.

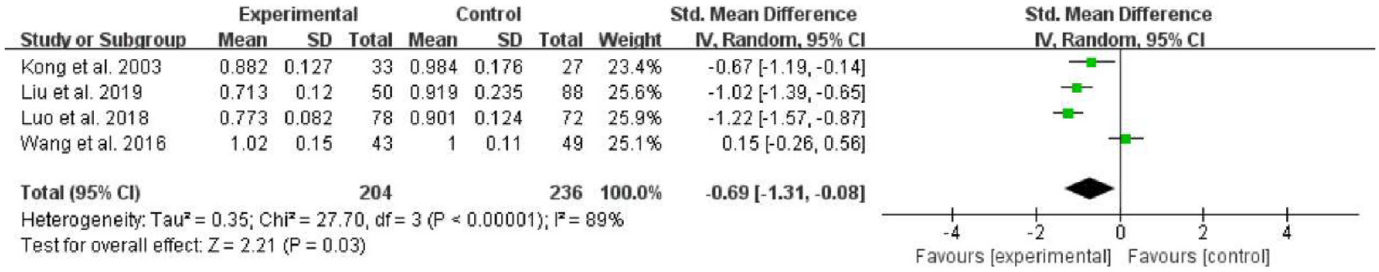

Figure 3. Forest plot for comparison of Lumbar Spine BMD between two groups.

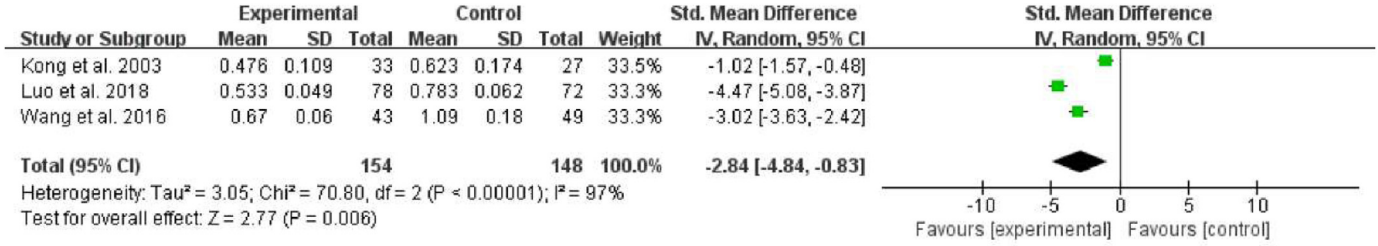

Figure 4. Forest plot for comparison of Ward's Triangle BMD between two groups.

quantitative analysis of publication bias are shown in supplementary material 3.

4. Discussion

With the aging of the population, the incidence of osteoporosis is increasing. Factors, such as diabetes, aging and lack of physical activity, may cause bone loss [31, 32]. Diabetes and its complications, especially diabetic microangiopathy, not only coexist with osteopenia and osteoporosis but also influence the development of other diseases. Studies have shown that with the occurrence and progression of diabetic microangiopathy, the degree of osteoporosis becomes more serious [6, 33, 34]. Oikawa's study found that [35] diabetic microangiopathy can lead to blood supply distribution and neurotrophic disorders, trabecular ischemia and hypoxia in bone tissue. In this study, a meta-analysis of 12 observational studies revealed that the BMDs of the femoral neck, lumbar spine and Ward's triangle of patients with T2DM microangiopathy were significantly lower than those of patients without microangiopathy. Regarding the bone metabolism-related indexes, the contents of P1NP, osteocalcin, PTH and CTX in the serum from DMA patients increased, while the content of 25(OH)D_3 decreased.

In this study, by comparing the BMD of the femoral neck, lumbar spine and Ward's triangle, we were able to draw a clear conclusion that in patients with type 2 diabetes mellitus, the risk of bone loss and osteoporosis is significantly higher in patients with microangiopathy. However, in osteoporosis, changes in BMD can directly reflect the bone

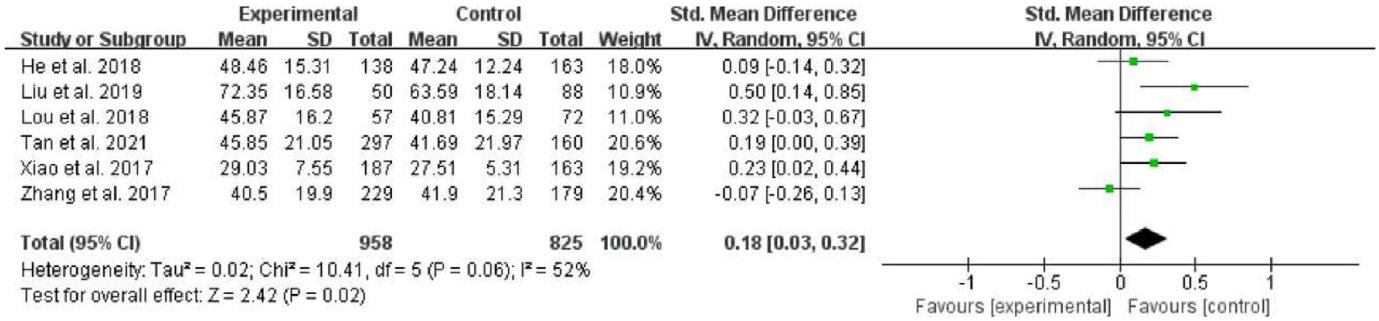

Figure 5. Forest plot for comparison of P1NP between two groups.

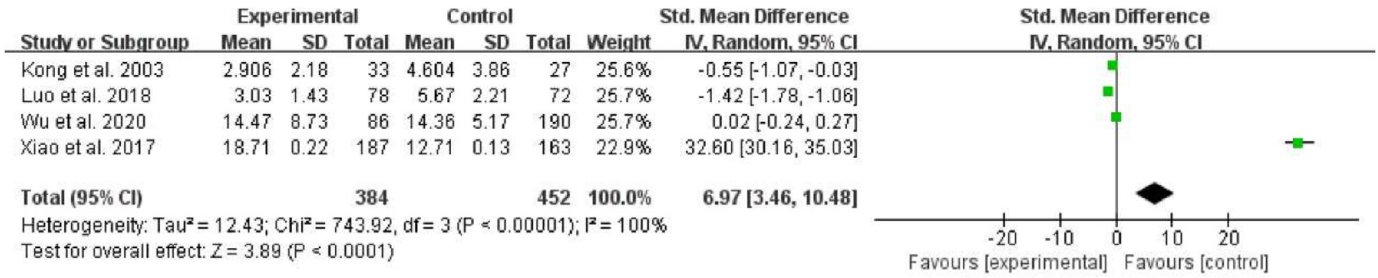

Figure 6. Forest plot for comparison of osteocalcin between two groups.

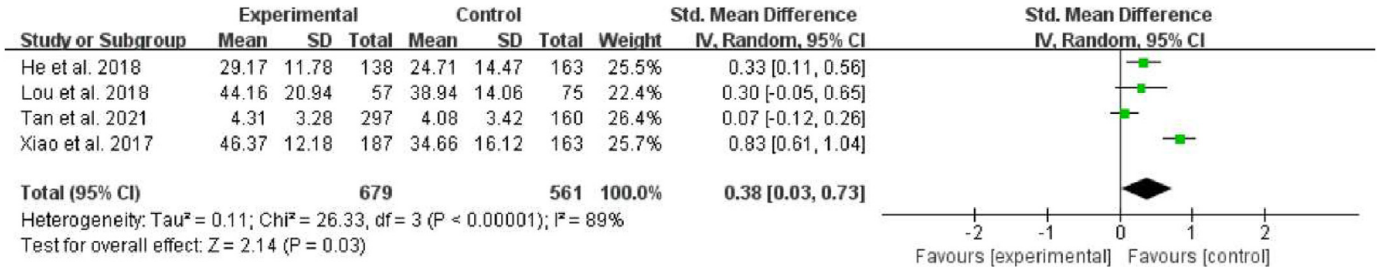

Figure 7. Forest plot for comparison of PTH between two groups.

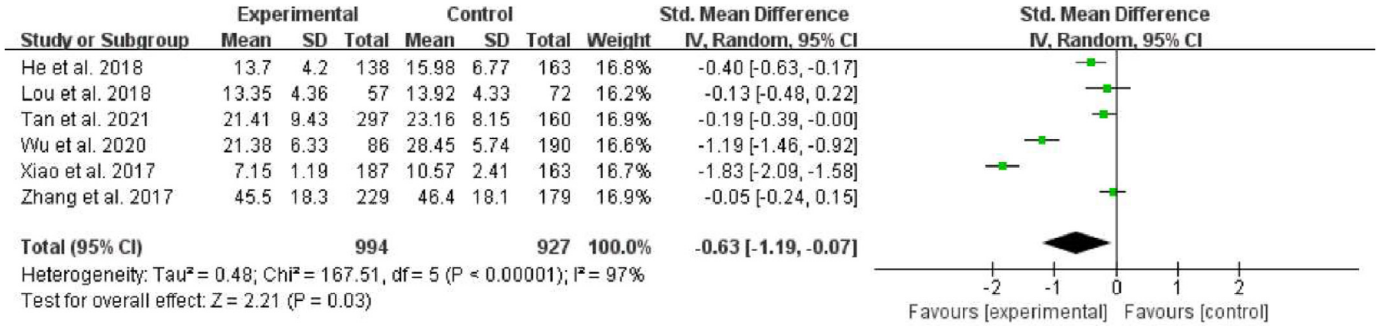

Figure 8. Forest plot for comparison of 25(OH)D_3 between two groups.

condition, but changes in BMD lag behind the biochemical indexes of bone metabolism. Therefore, bone metabolic indexes can reflect the current situation of bone metabolism, predict the risk of fractures, influence the decision to adopt preventive anti-osteoporosis treatment and evaluate the efficacy of anti-osteoporosis drugs [36, 37]. Therefore, this study also analyzed the association between T2DM complicated with microangiopathy and bone metabolism-related indicators. P1NP and CTX are bone metabolism markers recommended by the International Osteoporosis Foundation that reflect the synthesis of bone collagen and the activity of osteoclasts, respectively [38]. When bone mass decreases, bone metabolism accelerates, and P1NP and CTX increase. Consistent with the research results reported by Zhong et al. [39], when T2DM is combined with microangiopathy, bone metabolism is in a state of hyperactivity, and markers of bone formation and bone resorption are increased at a high level of bone turnover. PTH may be high in T2DM patients with microangiopathy, resulting in secondary parathyroid hyperthyroidism, osteoclast activity that is greater than osteoblast activity, and bone resorption that is stronger than bone formation. Therefore, when T2DM patients have microangiopathy, the bone mass decreases, the bone mineral density decreases, and the risk of OP increases [40]. The estrogen level of menopausal women is decreased, bone resorption is greater than bone formation, and the level of BTMs changes, leading to bone mass reduction and BMD reduction. Therefore, the relationship between changes in the BTM levels and BMD in women with DMA still needs further study. 25(OH)D_3 is the main form of vitamin D in vivo and can promote osteoblast synthesis

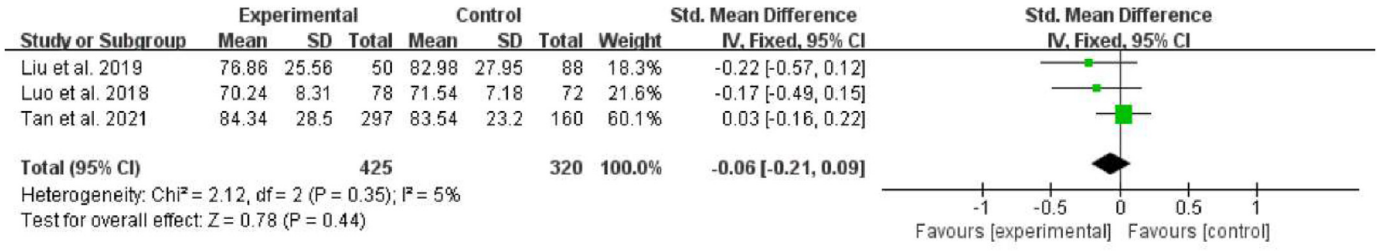

Figure 9. Forest plot for comparison of ALP between two groups.

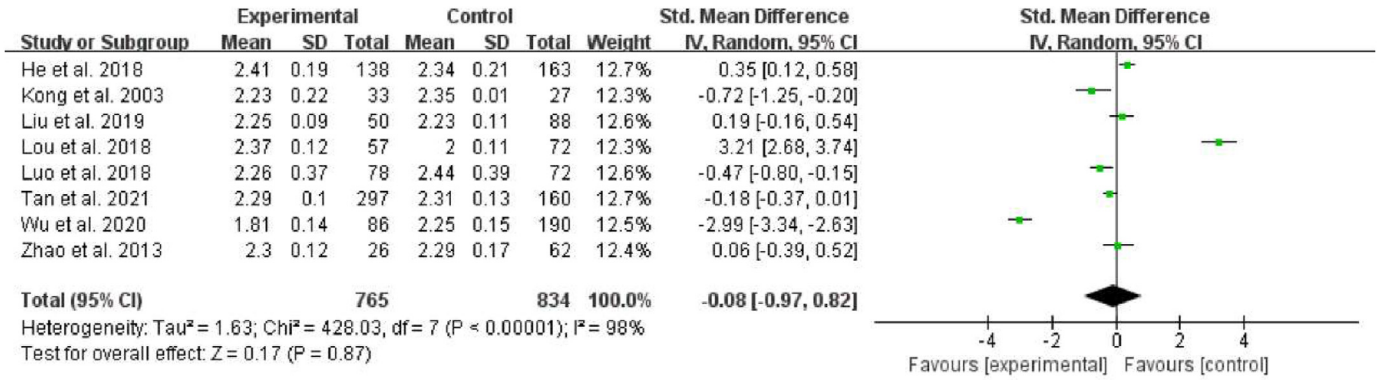

Figure 10. Forest plot for comparison of serum calcium between two groups.

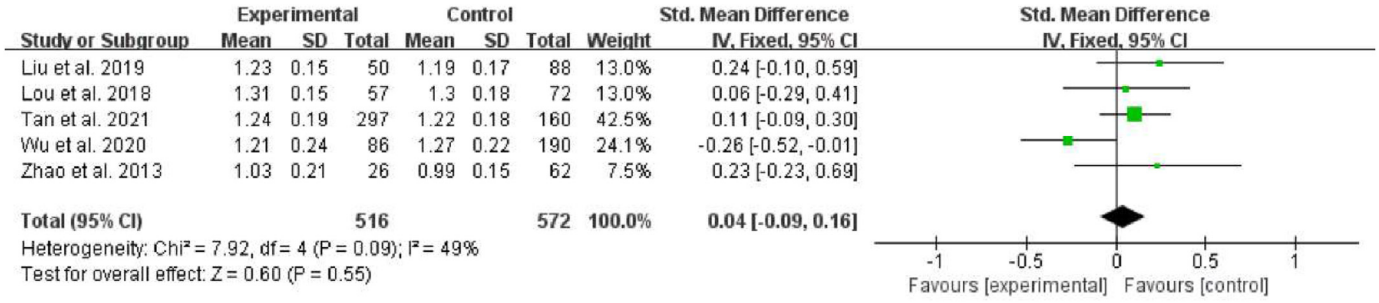

Figure 11. Forest plot for comparison of serum phosphorus between two groups.

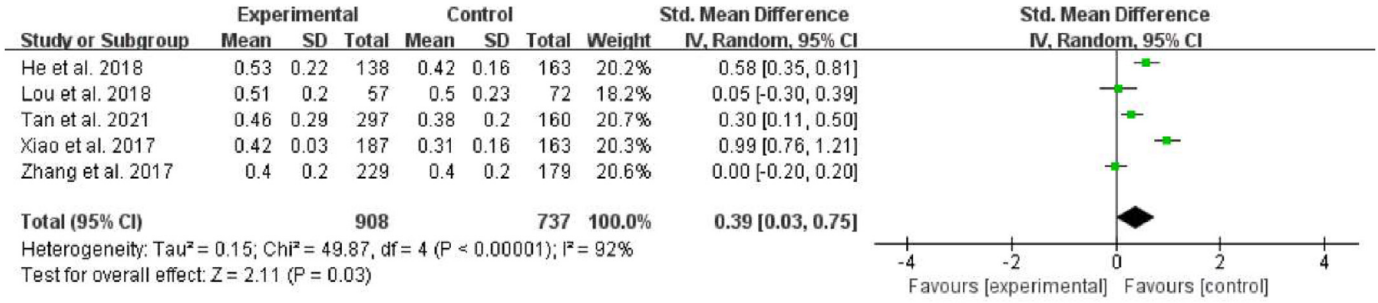

Figure 12. Forest plot for comparison of CTX between two groups.

and the secretion of osteocalcin [41]. 25(OH)D_3 plays a key role in regulating calcium and phosphorus metabolism and vascular protection, inhibiting islet cell apoptosis, and reducing insulin resistance and immune regulation [42]. Vitamin D regulates calcium and phosphorus metabolism, maintains the stability of serum calcium and phosphorus concentrations, and promotes intestinal calcium and phosphorus absorption and bone calcification [42]. Long-term deficiency of vitamin D leads to disordered calcium and phosphorus metabolism, and calcium and phosphorus deficiency leads to insufficient raw materials for bone synthesis, thus affecting bone. In addition, vitamin D can interact with PTH, and long-term vitamin D deficiency can upregulate the PTH levels to mobilize bone calcium into the blood, accelerate osteoclast activity, decalcify bone and lead to osteoporosis [43]. This meta-analysis further clarifies that T2DM complicated with microangiopathy can cause bone loss, which may lead to osteoporosis, and a possible mechanism is that the levels of P1NP, PTH, CTX and osteocalcin in serum are increased while the serum 25(OH)D_3 content is reduced, thereby destroying the bone mass balance.

Undeniably, there are some limitations in this meta-analysis. First, the literature included in this study comprised observational studies, which inevitably have certain selection bias due to the research design and are weaker than randomized controlled trials in terms of precision and accuracy. Second, three types of diabetic microangiopathy, DN, DR and DPN, were included in this study, which is not conducive to understanding the effects of specific microangiopathy types on BMD and bone metabolism. Third, this paper is a secondary literature study, and there is a lack of data concerning bone metabolism indicators corresponding to age and sex stratification, which affected our ability to further explore changes in bone mineral density in T2DM patients with microangiopathy.

5. Conclusion

This study shows that in patients with T2DM, the lumbar spine, femoral neck and Ward's triangle BMD of patients with microangiopathy are lower, and the risk of osteoporosis or osteoporotic fractures is higher. A possible pathological mechanism of this condition is that the higher serum P1NP, PTH, CTX, and osteocalcin content and lower 25(OH)D_3 content in patients with T2DM complicated with microangiopathy destroy the bone metabolism balance and lead to bone loss or osteoporosis. The effect of specific T2DM microangiopathies on BMD or bone metabolism still requires further study.

Declarations

Author contribution statement

Jinlong Zhao: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Guihong Liang and Miaohui Luo: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Weiyi Yang and Nanjun Xu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Minghui Luo and Jianke Pan: Analyzed and interpreted the data; Wrote the paper.

Jun Liu and Lingfeng Zeng: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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