Bone Mineral Density in Patients With Primary Ovarian Insufficiency: A Systematic Review and Meta-Analysis

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Abstract

Backgrounds: A large number of studies have investigated the effect of early menopause on osteoporosis outcomes and the relationship between the content of bone mineral density (BMD) and primary ovarian insufficiency (POI). Methods: To provide a systematic literature review and meta-analysis on BMD content among women with POI. Search strategy: We performed a systematic literature search in the databases PubMed, Embase, Cochrane Library and Web of Science databases from inception through 1 April 2022 . Selection criteria: Studies including women with POI and controls were eligible. Data collection and analysis: Two reviewers independently evaluated study eligibility. We used DerSimonian-Laird random effects model for meta-analysis. Main results: A total of 10 studies featuring 578 women with POI and 480 controls were selected. The meta-analysis showed that the BMD content of femur neck(SMD:-0.76; 95% CI: -1.20 to -0.31; P=0.0008), the BMD content of nondominating forearm (SMD:-0.67; 95% CI: -1.15 to -0.18; P=0.007) were significantly decreased in women with POI. There was no significant change in the BMD content of lumbar spine (SMD: -0.32; 95% CI: -0.74 to 0.10; P=0.14), the total hip (SMD: -0.08; 95% CI: -0.79 to 0.63; P=0.82), as well as the hip neck (SMD: -0.15; 95% CI: -0.85 to 0.56; P=0.68). Conclusions: Scientific evidence suggests that the BMD content altered in patients with primary ovarian insufficiency compared with healthy controls. Therefore, we recommend that early medical intervention (e.g., hormone replacement therapy) to minimize the risk of fracture morbidity and mortality associated with osteopenia in patients with POI.

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Conclusions: Scientific evidence suggests that the BMD content altered in patients with primary ovarian insufficiency compared with healthy controls. Therefore, we recommend that early medical intervention (e.g., hormone replacement therapy) to minimize the risk of fracture morbidity and mortality associated with osteopenia in patients with POI.

Keywords : primary ovarian insufficiency, bone mineral density, osteoporosis, hormone replacement therapy, meta-analysis

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INTRODUCTION

Osteoporosis in postmenopausal women usually occurs 5˜10 years after menopause and affects millions of postmenopausal women worldwide (Cosman et al., 2015). Osteoporosis is defined as progressive systemic skeletal disease, which is characterized by low bone mass, deterioration of bone micro structure, reduction of bone mineral density (BMD) and bone strength that increase the risk of fracture (Christiansen, 1987). The occurrence of osteoporosis is a multifactorial process, and BMD is considered as one of the important indicators for clinical assessment of the severity of osteoporosis (Billington et al., 2020). A 10% increase in peak bone mass delays the onset of osteoporosis by 13 years, while postmenopausal women are at increased the risk of osteoporosis and fracture because of the deficiency of estradiol, which leads to the enhancement of osteoclast activity and the rapid loss of bone minerals (Mirkin et al., 2019).

Young women with hypogonadism are also at increased risk of reduced BMD, and a number of studies have investigated the effect of earlier age at menopause on osteoporosis outcomes (Alici-Davutoglu et al., 2013b; Freitas et al., 2021; Podfigurna et al., 2020b). Women with early menopause have 1.5˜3.0 times higher risk of fracture than women with menopause at the age of 49˜55years (Hadji et al., 2019). Primary ovarian insufficiency (POI), which is a typical disease characterized by early menopause(before age 40years) in women, is defined asamenorrhea for four months and an elevated follicle stimulating hormone (FSH) level>25IU/L (measured twice at least four weeks apart) in women under 40 years old (Webber et al., 2016). Hence, POI, by virtue of early menopause and chronic estradiol deficiency, is a risk factor for osteoporosis. Meanwhile, young women with POI have significantly reduced BMD compared with women with regular menstruation (B et al., 1998).

Knowledge of the potential associations of BMD with POI has public health significance for reducing the risk of osteoporosis and fracture in women. POI may provide important information to disentangle the effects of menopause and age on bone loss. Thus, this systematic review and meta-analysis aimed to evaluate the content of BMD in women with POI and healthy controls.

METHODS

Reporting Guidelines

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009), and was prospectively registered on PROSPERO (registration number:CRD42020149341). This study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Chatenoud and Vecchia, 2000).

Search Strategy

The PICO (population/intervention/comparison/outcome) components were as follows: P (women before the age of 40), I (women with primary ovarian insufficiency), C (healthy women), O (the content of BMD).To identify eligible studies, an exhaustive literature search was performed in the PubMed, Embase, Cochrane Library and Web of Science databases (with language was restricted to English; without restricting by location and journal) through April 2022 to identify published studies using the following keywords: "primary ovarian insufficiency" OR "premature ovarian insufficiency" OR "premature ovarian failure" OR "premature menopause" OR "POI" OR "POF" OR "menopause premature" OR "early menopause" AND "bone density" OR "bone mineral density" OR "BMD" OR "bone" OR "bone mass" OR "bone status" OR "bone structure" OR "bone turnover" OR "bone metabolism" OR "bone mineral content" OR "skeleton" OR "osteoporoses" OR "osteoporosis" OR "osteopenia".

Inclusion and Exclusion Criteria

The inclusion criteria for eligible studies were as follows:(1) original human observational studies; (2) all subjects involved in studies had no gynecological surgery or undergone therapy that could induce menopause;(3) studies focusing on the association between the content of BMD and POI; and (4) studies included data on the content of BMD for patients with POI and healthy individuals.

The exclusion criteria were as follows: (1) laboratory or animals studies; (2) reviews or case reports; (3) repeated publications; (4) studies without healthy control groups; (5) studies not providing exact data on the content of BMD; (6) studies involved subjects were older than 40 years; and (7) studies with sample size $<$10.

Study Selection and Data Extraction

Literature screening and data extraction were independently done by two researchers (MJ and YG). Differences between two reviewers were addressed in consultation with a third reviewer (LH). Firstly, references were imported into EndNote, and duplicates were identified. Secondly, literature titles and abstracts were screened, and those did not meet the inclusion criteria were excluded. Finally, the full text of the references were read, and the studies were further excluded according to the inclusion and exclusion criteria. Each corresponding author was contacted and asked for the raw data when continuous variables were absent in reports. PRISMA flowchart explaining the selection process was shown in Figure 1. The data including the content of BMD [mean$\pm$standard deviation (SD)] were extracted from the references, and all data were rechecked by HW.

Quality Assessment

The quality assessment of eligible studies was performed according to the Newcastle-Ottawa Scale (NOS) star system (Stang, 2010), and all included studies were rated above 7.

Statistical Analysis

The extracted data from the included studies were analyzed with a meta-analysis. Since the existing references were not consistent with regard to units, the pooled standardized mean difference (SMD) and 95% confidence intervals (CI) were used to determine the associations between BMD and POI. Heterogeneity in the studies was tested using Cochran's Q two-sided test of homogeneity (Hardy and Thompson, 1998). If I-square (I^2) <50%, a Mantel-Haenszel fixed-effect model was used, otherwise, a DerSimonian-Laird random-effects model was used (DerSimonian and Laird, 1986; Huang et al., 2020). Subgroup analysis was performed to identify associations between the content of BMD and the characteristics of studies to examine if this could explain heterogeneity.Sensitivity analysis was performed to test the robustness of the pooled SMD by excluding each study. Funnel plot method (in cases where the number of included references were [?]10) was used to test publication bias. All analyses were performed using RevMan software, and P <0.05 was considered to be statistically significant.

RESULTS

Literature Search

From the initial 1951 articles, 1834 were excluded after reading titles and abstracts because they did not meet the inclusion criteria. 117 articles were included for full-text assessment, from which 107 were excluded: sixteen without healthy controls; twenty-six involved subjects were older than 40 years; three involved data cannot be extracted; one repeated publication; sixty-one research topic inappropriate. A total of 10 eligible papers were included (Figure 1), all of the studies featured as observational design and included individual data from 578 cases and 480 healthy controls (Alici-Davutoglu et al., 2013a; Conway et al., 1996; Hartmann et al., 1997; Kurabayashi et al., 1993; Leite-Silva et al., 2009; Mann et al., 2008; Metka et al., 1992; Park and Song, 1995; Podfigurna et al., 2020a; Uygur et al., 2005). The baseline characteristics, such as author, year, region, study design, number of case/control subjects, age, duration of amenorrhea, body mass index (BMI), drug usage, measuring method of BMD and primary conclusion included in the studies were shown in Table 1.

Meta-Analysis Results

Meta-analysis of BMD of lumbar spine

Nine studies (n =987 participants) were included in the meta-analysis of BMD content of lumbar spine(Figure 2A), and there was significant heterogeneity among the studies (I^2 =87%;P <0.00001).There was no significant association between primary ovarian insufficiency and BMD content of lumbar spine (SMD: -0.32; 95% CI: -0.74 to 0.10; P= 0.14).

Meta-analysis of BMD of femur neck

Four studies (n =521 participants) compared the BMD content of femur neck between primary ovarian insufficiency women and healthy controls (Figure 2B), and there was significant heterogeneity among the studies (I^2 =80%; P =0.002). Primary ovarian insufficiency was significantly associated with a decreased BMD content of femur neck (SMD:-0.76; 95% CI: -1.20 to -0.31;P =0.0008).

Meta-analysis of BMD ofWard's triangle

Two studies (n =354 participants) compared the BMD content of Ward's triangle between primary ovarian insufficiency women and healthy controls. Park's study (Park and Song, 1995) reported that the BMD content of Ward's triangle in POI group was lower than that in the control group (SMD:-1.14; 95% CI: -1.41 to -0.86; P <0.00001). While Leite-Silva's study (Leite-Silva et al., 2009) showed that the BMD content of Ward's triangle in POI group was higher than that in the control group (SMD:1.10; 95% CI: 0.68 to 1.52; P <0.00001).

Meta-analysis of BMD oftrochanter

Two studies (n =354 participants)reported the data related to the effects of POI on BMD content of trochanter.Park's study (Park and Song, 1995) revealed that the BMD content of trochanter in POI group

was lower than that in the control group (SMD:-0.70; 95% CI: -0.96 to -0.43;P <0.00001). While Leite-Silva's (Leite-Silva et al., 2009)study showed that the BMD content of trochanter in POI group was higher than that in the control group (SMD:1.23; 95% CI: 0.80 to 1.66;P <0.00001).

Meta-analysis of BMD of nondominating forearm

Metka's study (Metka et al., 1992) disclosed that the BMD content of nondominating forearm in POI group was lower than that in the control group (SMD:-0.67; 95% CI: -1.15 to -0.18; P =0.007).

Meta-analysis of BMD of hip

Mann's study (Mann et al., 2008) revealed that there was no significant association between primary ovarian insufficiency and the BMD content of total hip (SMD: -0.08; 95% CI: -0.79 to 0.63; P= 0.82), as well as the BMD content of hip neck (SMD: -0.15; 95% CI: -0.85 to 0.56;P= 0.68).

Results of Subgroup Analysis

To search for the sources of heterogeneity and more accurately assess the differences between primary ovarian insufficiency women and healthy controls, subgroup analyses were conducted by geographical location, number of cases, mean BMI value of cases, mean age of cases, duration of amenorrhea of POI and drug usage.

As for geographical location (Table 2), a lower BMD content of lumbar spine was found in European (p =0.002) and Central Asian (p =0.04) women with POI than in healthy controls, but not in Asian (p =0.12). While a higher BMD content of lumbar spine was found in South American(p <0.00001), and the heterogeneity of Europe (I^2 =16%) and Central Asia (I^2 =28%) subgroup decreased. A lower BMD content of femur neck was found in Asian (p <0.00001) and South American (p <0.00001) women with POI than in healthy controls, but not in Central Asian cases (p =0.12), and the heterogeneity of Central Asia subgroup decreased(I^2 =46%).

As for number of cases (Table 3), in the subgroup with cases<50 (p =0.04), the BMD content of lumbar spine in women with POI was lower than that in healthy controls, but not in the subgroup with cases[?]50 (p =0.81).And the heterogeneity was reduced in the subgroup with the number of cases<50 (I^2 =67%). Women with POI had a lower BMD content of femur neck than the healthy controls with cases[?]50 (p <0.00001), but not in the subgroup with cases<50(p =0.12), the heterogeneity was reduced in this subgroup (I^2 =46%), and there was no heterogeneity in the subgroup with the number of cases[?]50 (I^2 =0%).

As for the mean BMI value of cases (Table 3), patients with the mean BMI not available had a lower BMD content of lumbar spine than the healthy controls(p <0.0001), but not in the subgroup with the mean BMI<24 kg/m^2(p =0.42) and the mean BMI[?]24 kg/m^2(p =0.30), and no heterogeneity was found in the subgroup with the mean BMI not available and the mean BMI[?]24 kg/m^2(I^2 =0%). The results showed that patients with the mean BMI<24 kg/m^2 (p <0.00001) and the mean BMI not available (p =0.03)had a lower BMD content of femur neck than healthy controls, but not in the subgroup with the mean BMI[?]24 kg/m^2 (p =0.36), and no heterogeneity was found in the subgroup with the mean BMI<24 kg/m^2(I^2 =0%).

As for the mean age of cases (Table 4), women over the age of 30 with POI had a lower BMD content of lumbar spine than healthy controls (p =0.02), but in the subgroup with the mean age of cases<30, BMD content of lumbar spine was not associated with POI (p =0.83),and the heterogeneity was reduced in the subgroup with the mean age of cases[?]30(I^2 =65%). Women under the age of 30 with POI had a lower BMD content of femur neck than healthy controls (p< 0.0001), but not in the subgroup with the mean age of cases[?]30 (p =0.14),and the heterogeneity was reduced in the subgroup with the mean age of cases<30(I^2 =44%).

As for duration of amenorrhea of POI (Table 4), in the subgroup with the duration<3, there was no correlation of BMD content of lumbar spine in women with POI and healthy controls(p =0.29),and the same conclusion was found in the subgroup with the duration[?]3 (p =0.70), while patients with the duration

not available had a lower BMD content of lumbar spine than the healthy controls(p =0.003), the heterogeneity of this subgroup decreased (I^2 =61%). Patients with the duration[?]3had a lower BMD content of femur neck than the healthy controls(p <0.00001), but not in the subgroup with the duration not available (p =0.12).Meanwhile, no heterogeneity was found in the subgroup with the duration[?]3 (I^2 =0%), the heterogeneity of the subgroup with the duration not available decreased (I^2 =46%).

As for hormone replacement therapy (HRT) usage (Table 5), in the subgroup with HRT not used, the BMD content of lumbar spinein women with POI was lower than that in healthy controls (p =0.02), but not in the subgroup with HRT used(p =0.82), and the heterogeneity was reduced in the subgroup with HRT not used (I^2 =64%). In the subgroup with HRT not used(p< 0.0001)and HRT used (p =0.04), the BMD content of femur neck in the cases was lower than in healthy controls,

As for bone metabolism agents usage (Table 5), in the subgroup with bone metabolism agents used (p =0.18), not used (p =0.29), and not available (p =0.08), the BMD content of lumbar spine was not associated with POI. There was no heterogeneity in the subgroup with bone metabolism agents used not available (I^2 =0%). Patients with bone metabolism agents not used had a lower BMD content of femur neck than the healthy controls(p <0.00001), but not in the subgroup with the bone metabolism agents used (p =0.36), and no heterogeneity was found in the subgroup with the bone metabolism agents not used(I^2 =0%).

Sensitivity Analysis

The studies were removed one by one to check the stability and reliability of the meta-analysis results.As for BMD content of lumbar spine, the results of this meta-analysis were weakly stable and sensitive to Leite-Silva's study (Leite-Silva et al., 2009). After removing this study, the heterogeneity decreased (I^2 =48%;p =0.06), and the BMD content of lumbar spine in women with POI changed to been lower than that in healthy controls (SMD: -0.47; 95% CI: -0.70 to -0.24;P <0.0001).As for BMD content of femur neck, the results of this meta-analysis were weakly stable and sensitive to Uygur's study (Uygur et al., 2005). After removing this study, the heterogeneity decreased (I^2 =0%; p =0.41), and the BMD content of femur neck in women with POI was still lower than that in healthy controls (SMD: -0.99; 95% CI: -1.20 to -0.78;P <0.00001).

Publication Bias

The publication bias for BMD content was not assessed, as the Cochrane Handbook for Systematic Reviews of Interventions (www.cochranehandbook.org) stated that the test for publication bias yields unreliable results when <10 studies were included.

DISCUSSION

Primary ovarian insufficiency, due to the long-term complications such as cardiovascular disease and osteoporosis, has been claimed a "serious chronic disease with far reaching effects on physical and emotional health" (Podfigurna-Stopa et al., 2016). The measurement of bone metabolism indicators combined with BMD can effectively reflect the process of bone turnover and predict the risk of fracture in patients with osteoporosis. 25-hydroxyvitamin D3 (25[OH]VD3) can stimulate the activity of osteoblasts, promote bone calcium deposition and bone formation, improve the activity of osteoclasts, enhance the effect of osteocalcin on bone, accelerate the reabsorption of calcium and phosphorus in renal tubules, and reduce the excretion of calcium and phosphorus in urine (Wang et al., 2018). Osteocalcin which is a non-collagenous bone matrix protein synthesized and secreted by osteoblasts reflect the activity of osteoblasts and bone metabolic level, and play an important role in bone development (Capozzi et al., 2020). Research shows that bone mineral density and 25(OH)VD3 contents in patients with POI are lower than those in healthy women, while the level of osteocalcin is higher than that in healthy controls (Dua et al., 2013), which are consistent with the results of this meta-analysis. Therefore, early menopause has adverse long-term effects on bone health.

The beneficial effects of intact ovarian function on bone healthy are generally ascribed to estradiol.Estradiol has a positive regulatory effect on promoting bone growth (Hayashi et al., 2019). It has also proven that endogenous estradiol inhibits the effect of osteoblasts which produces inflammatory factors such as interleukin and tumor necrosis factor, increases the content of osteoprotegerin, calcitonin, vitamin D and transforming

growth factor, promotes proliferation and differentiation of osteoblasts (Xiong et al., 2015). Estradiol can inhibit the binding of receptor activator of NF-KappaB and osteoclasts precursors, lead to apoptosis of osteoclasts and inhibit osteoclasts activity, and shorten the survival time of osteoclasts (Tella and Gallagher, 2014). Meanwhile, due to the activation of the ER/AKT signaling pathway, estradiol deficiency leads to an increase in bone fragility, which seriously affects the quality of life of patients (Słupski et al., 2021). Estradiol deficiency increases the decomposition of phosphate and bone trabecular matrix components, reduces the reabsorption of calcium ions, phosphorus factors, etc., and promotes bone loss (Ma et al., 2008). Decreased estradiol reduces bone sensitivity to mechanical stimulation, leads to pathological changes similar to disuse bone loss (Chow et al., 2016). In addition, estradiol deficiency increases the level of oxidative stress, which leads to inhibition of osteogenesis and activation of osteoclast (Kimball et al., 2021; Zhou et al., 2016). Furthermore, BMD in patients with premature ovarian failure gradually decreases with the prolongation of estradiol deficiency, and osteoporosis occurs earlier (Szeliga et al., 2018). Thus, women with POI have a higher rate of fracture morbidity and mortality later in life due to estradiol deficiency for longer than women with natural menopause.

Hormone replacement therapy (HRT) has been recommended by international guidelines for women with POI for many years (Webber et al., 2016). HRT is an exogenous supplement, which relieves clinical symptoms, prevents the occurrence and development of diseases, reduces the long-term complications with high disability rate and fatality rate (e.g., osteoporosis and cardiovascular disease), and improves living standards of women with POI (Webber et al., 2016). It has been reported that HRT can increase the BMD content (Di et al., 2005). Study has shown that the structure of the trabecular bone is more complete after 2 years of HRT (Benito et al., 2005). In 2016, the International Society of Menopause noted that HRT should be seen as a first-line treatment for fracture prevention (Baber et al., 2016). In 2017, the North American Menopause Society noted that 6 fractures of the body were reduced per 10,000 person-years due to the use of HRT (Society., 2017). Compared with postmenopausal women who have never used HRT, women who have used HRT for more than 7 years have a reduced risk of distal forearm and proximal humerus fracture (Keegan et al., 2003). Moreover, HRT protects the spine by maintaining the size of the individual disc and the total disc space, as well as the length of the spine, however, bisphosphonates do not have this effect (Studd, 2009). From the perspective of health economics, meanwhile, HRT is more cost-effective than drugs such as bisphosphate and calcitonin, and has systemic benefits other than anti-osteoporosis effects (Fisher et al., 2009). Unfortunately, the acceptance rate of HRT in women with POI is extremely low (Webber et al., 2017).

Subgroup analysis was conducted to further explore the source of heterogeneity and more accurately evaluate the correlation between BMD content and POI. Heterogeneity in this meta-analysis of the correlation between BMD content of lumbar spine,femur neck and POI might come from region, number of cases, mean BMI value of cases, mean age of cases, duration of amenorrhea of POI, HRT use, as well as bone metabolism agents use. Meanwhile, due to the use of HRT, the conclusion on the BMD content of Ward's triangle and trochanter in Leite-Silva's study was contrary to Park's study. (1)People in different regions have different dietary habits, lifestyles and economic levels, which have different effects on BMD content; (2) most of the references included in this meta-analysis were designed as case-control studies. In case-control study, if the number of cases is enormous, the research results will be affected by more confounders; (3) Elevated BMI has a protective effect on the prevention of osteoporosis (Lespessailles et al., 2019). Therefore, BMI value might be one of the sources of heterogeneity; (4) ovarian reserve function is related to physiological age, when age is over 35 years, ovarian function significantly declines (LaPolt and P., 1998). Studies have shown that BMD increases with age before30 years, while after peak bone mass,the prevalence of osteoporosis shows an increasing trend with physiological age (Zhang et al., 2010). Thus physiological age was regarded as one of the sources of heterogeneity; (5) the longer menopause lasts, thus the longer estrogen deficiency lasts. Therefore, duration of amenorrhea of POI might be one of the sources of heterogeneity; and (6) both HRT and bone metabolism agents (e.g., calcium supplementation) can improve BMD. Hence HRT use or bone metabolism agents use might be one of the sources of heterogeneity.

Part of the sources of heterogeneity was found by subgroup analysis, however, the heterogeneity was still

obvious, hence, sensitivity analysis was conducted. In this meta-analysis,the combined results of the BMD content of lumbar spine and POI were sensitive to Leite-Silva's study (Leite-Silva et al., 2009). After excluding the reference, the heterogeneity decreased (I^2 decreased from 87% to 48%), and P value of the combined result was less than 0.05 (P value changed from 0.14 to <0.0001). Therefore, Leite-Silva's study (Leite-Silva et al., 2009) had significant impact on the heterogeneity of the combined results. After careful reading of the reference, we found thirty-five of the patients were HRT users with a mean duration of 28 months of use in this reference. Hence, HRT use might be the main source of heterogeneity in this reference. In the meantime, the combined results of the BMD content of femur neck and POI were sensitive to Uygur's study (Uygur et al., 2005), and the$P$ values of the combined results were all less than 0.05 before and after the exclusion of the reference.However, after excluding the reference, the heterogeneity decreased (I^2decreased from 80% to 0%), therefore, Uygur's study (Uygur et al., 2005) had significant impact on the heterogeneity of the combined results. After careful reading of the reference, we found intermittent use of HRT in women with POI, and thirty-six of the patients received calcium supplementation in this reference. Therefore, HRT and bone metabolism agents use might be the main sources of heterogeneity in this reference.

Nevertheless, a number of limitations in this meta-analysis should be acknowledged. Firstly, obvious heterogeneity existed among the original studies due to differences in sample size, background of subjects, diagnostic criteria of POI, and measuring method used to detect the content of bone mineral density. Secondly, there was no association between POI and the BMD content of lumbar spine, Ward's triangle, trochanter, as well as hip due to the effect of HRT and bone metabolism agents. In addition, insufficient number of references was also one of the reasons. Therefore, more references are needed to verify this result. Thirdly, the main confounders (e.g., dietorphysical activity) influencing the BMD content of patients in original studies were not adjusted. Finally, the references included in this study were almost case-control studies, which would limit causal inference. Therefore, more cohort studies are needed to predict how the content of BMD in women with POI will develop over time. For these reasons, we recommend that our conclusions should be viewed conservatively.

In summary, this systematic review and meta-analysis demonstrated that the BMD content in femur neck and nondominating forearm were significantly lower in subjects with POI. These mean that women who loss of ovarian function at a very young age will lead to some degree of changes in the bone mass, increasing the risk of fracture. Therefore, we recommend that BMD should be evaluated and comprehensively studied to ensure that early medical intervention (especially HRT), and minimize the risk of fracture morbidity and mortality associated with osteopenia in patients with POI. Moreover, further studies are required to verify the relationship between the BMD content of lumbar spine, Ward's triangle, trochanter, hip and POI.

Conclusion

The BMD content altered in patients with primary ovarian insufficiency compared with healthy controls. Therefore, we recommend that early medical intervention (e.g., hormone replacement therapy) to minimize the risk of fracture morbidity and mortality associated with osteopenia in patients with POI.

AUTHOR CONTRIBUTIONS

MJ, YG, YQ, LH, HW, JG and WL: literature search, screening, and data extraction. YG, YQ, LH, HW, JG and WL: data analysis and results visualization. MJ and LH: manuscript draft. LH: manuscript modification. All authors reviewed the final version of the manuscript and approve it for publication.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

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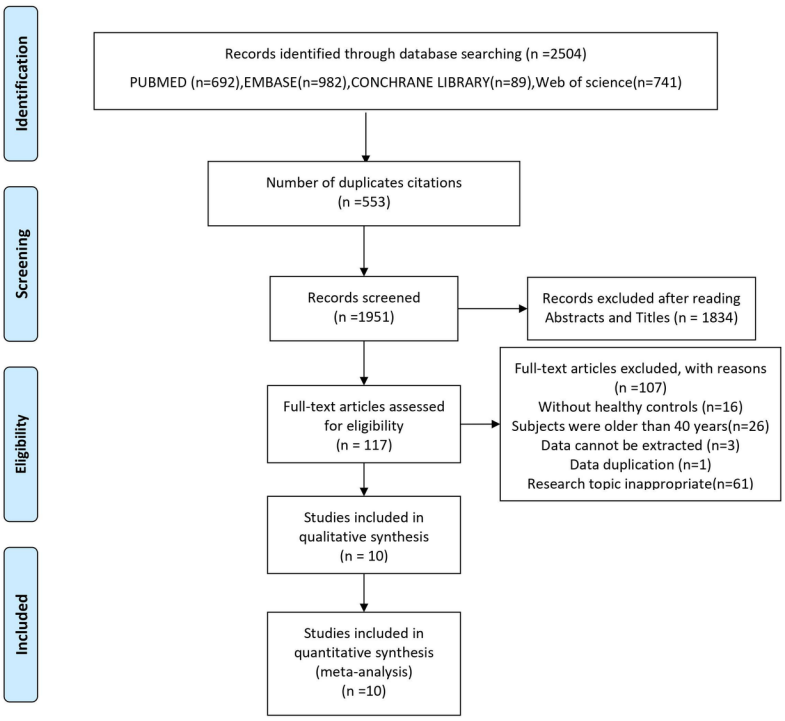

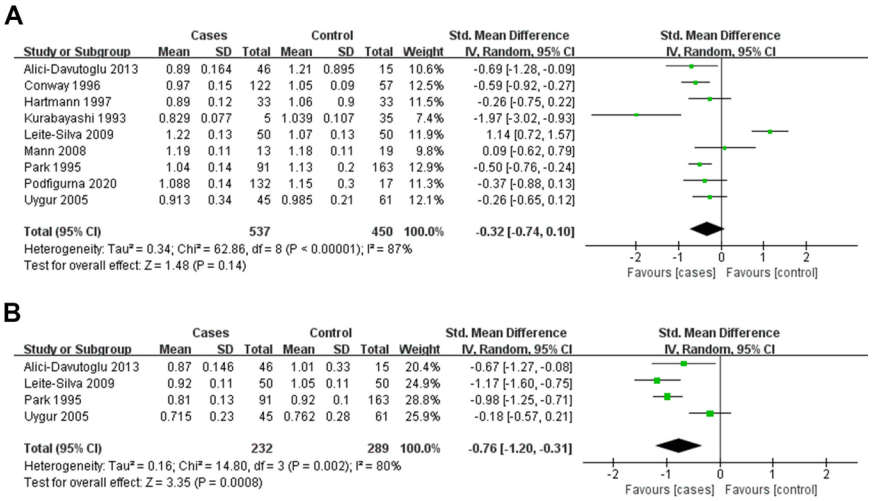

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