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Effects of levothyroxine therapy on bone and mineral metabolism in hypothyroidism: a systematic review and meta-analysis

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Abstract

Background Thyroid hormone plays an important role in accumulating bone development and regulating bone metabolism. It is established that hypothyroidism is linked to increased risk of osteoporosis and fracture. However, the effects of levothyroxine (LT4) treatment on bone for hypothyroid patients remain controversial.

Methods A systematical search was conducted of several databases, from inception until December 9, 2022, and updated the search using the same search strategy on October 30, 2024, for studies evaluating the effects of LT4 treatment on bone in hypothyroidism including subclinical hypothyroidism (SCH) and overt hypothyroidism (OH). The data were reported using a random-effects model with a standardized mean difference (SMD) and 95% conference interval (CI).

Results Thirteen of the 5996 published articles were included in this meta-analysis. No significance was found in bone mineral density (BMD) at the lumbar spine between SCH patients treated with LT4 and control group either at baseline or after intervention. For OH, BMD at the lumbar spine was statistically lower in LT4 treatment group compared with healthy controls (HCs) (SMD: -0.28, 95%CI: -0.55, -0.02, $P=0.040$, $I^2=52\%$). There were no differences in BMD at the femoral neck, trochanter, and Ward's triangle between OH patients treated with LT4 and HCs. In addition, BMD at the lumbar spine was significantly lower in males with OH undergoing LT4 treatment for a duration of less than five years compared to those treated over five years. Nevertheless, no significant differences were found in bone metabolism biomarkers between OH patients treated with LT4 and HCs.

Conclusion This systematic review and meta-analysis demonstrated that there is a slight adverse effect of LT4 replacement therapy on bone and mineral metabolism in patients with OH, while no observed effect was found in SCH patients.

Keywords Bone mineral density, Bone turnover, Hypothyroidism, Thyroid hormone, Levothyroxine

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Introduction

Hypothyroidism, a common endocrine disorder caused by thyroid hormone deficiency, is classified as subclinical hypothyroidism (SCH) and overt hypothyroidism (OH) [1]. SCH is defined as elevated level of thyroid stimulating hormone (TSH) in combination with the normal range free thyroxine (FT4), and OH is characterized as the elevated TSH level with lower FT4 level than the reference range [2]. Thyroid hormones have profound effects on the skeletal development and bone maintenance, affecting not only the function of osteoclasts and osteoblasts but also participating in the regulation of bone metabolism [3–5]. Additionally, it has been found that TSH can promote the proliferation and differentiation of osteoblasts in rat primary osteoblasts [6]. Previous studies have indicated that hypothyroidism can be accompanied by decrease of bone mineral density (BMD), osteoporosis, even fracture [7–9]. However, the effects of levothyroxine (LT4) treatment on bone metabolism for patients with hypothyroidism remain controversial.

LT4 treatment, as the most important therapy for hypothyroidism, aims to improve the symptoms related to hypothyroidism like fatigue, constipation, and weight gain [10] and to normalize levels of TSH and thyroid hormones [11]. Long-term use of LT4 has been identified as a significant risk factor for the incidence of osteoporosis and bone fractures [12, 13]. And overtreatment of LT4 is associated with adverse effects on bone [14, 15]. Mazziotti et al. [14] demonstrated that women with differentiated thyroid carcinoma treated with long-term LT4 suppression therapy have a higher prevalence of vertebral fractures. Similarly, the results of a meta-analysis [15] involving 1824 participants showed that postmenopausal women with thyroid cancer receiving TSH suppression therapy may have a risk for lower BMD compared with those who did not. In addition, LT4 treatment may be associated with increased risk of osteoporosis in elderly females [16]. However, the effects of LT4 replacement, rather than suppression treatment on bone remain unclear.

Several studies have illustrated that bone turnover markers, such as bone alkaline phosphatase (ALP), C-telopeptide of type I collagen (CTX) and osteocalcin (OC), significantly increased in patients of SCH or OH after restoring euthyroid through LT4 treatment compared with controls [17–19]. Decreased BMD at some sites was also found in patients with hypothyroidism undergoing LT4 treatment. Conversely, other studies [20–22] have failed to determine changes in BMD and bone metabolism in patients with hypothyroidism receiving LT4 replacement therapy.

In this study, we conducted a systematic review and meta-analysis of the current studies to comprehensively evaluate the effects of LT4 replacement therapy on BMD and bone metabolism biomarkers in SCH and OH patients, and hope to provide evidence on the bone safety of LT4 treatment for hypothyroidism.

Methods

We reported this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [23] and registered the study protocol online in the International Prospective Register of Systematic Reviews (PROSPERO CRD42023390228).

Search strategy and study selection

Our study focused on the association between LT4 treatment and bone metabolism in hypothyroid patients. We conducted a comprehensive search of eight databases were systematically searched, including PubMed, Web of Science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wang Fang Database, China Science and Technology Journal Database, and China Biology Medicine Disc, from inception until December 9, 2022. And updated the search using the same search strategy on October 30, 2024. Two investigators (XL and TZ) independently selected articles using the following terms. The core search terms include ("hypothyroidism" OR "thyroid" OR "thyroid deficiency") AND ("thyroxine" OR "thyroid hormone" OR "levothyroxine") AND ("bone mineral density" OR "bone metabolism" OR "bone markers"). The full search strategy is shown in the supplementary material. Initially, the investigators screened the retrieved studies based on titles and abstracts and then reviewed the full text to determine the final inclusion of studies based on predefined criteria. To include eligible literature as much as possible, we also manually searched the references of relevant papers obtained from systematic search, as well as relevant conferences and registered clinical trials.

Eligibility criteria

The inclusion criteria were as follows: (1) Participants. Individuals who were diagnosed as SCH or OH; (2) Interventions. Patients who received LT4 treatment only for primary hypothyroidism without any restrictions on the dosage and duration and recover to euthyroid after LT4 treatment; (3) Outcomes. At least one of the following parameters should be measured in the study: BMD at various sites, serum calcium, phosphorus, ALP, CTX, or OC. (4) Comparison. SCH patients received a placebo or without treatment; euthyroid participants.

Exclusion criteria were as follows: (1) Participants. patients with congenital hypothyroidism, central hypothyroidism, or pregnant women; studies included participants younger than 18 years old; studies included patients who received suppressed LT4 treatment due to

thyroid cancer post-thyroidectomy or thyroid goiter; (2) Intervention. Studies on LT4 combined with other drugs, patients were taking drugs that may affect bone metabolism (e.g., bisphosphonates, estrogens, parathyroid hormone, etc.) at any time point during observation time; (3) Comparison. No control groups.

Data extraction and quality assessment

The extracted information includes the first author's name, publication year, study country, study design, participants' characteristics (sample numbers, sex ratio, age), thyroid function, duration and dosage of the LT4 therapy, BMD (measurement methods and sites), calcium, phosphorus, ALP, CTX, and OC. To ensure homogeneity, BMD data measured with dual-energy X-ray absorptiometry (DXA) will be selected for meta-analysis in our study. Only the outcome with the longest intervention duration will be considered in statistical analyses if studies provide an outcome at more than one-time point during the intervention.

Two investigators (XL and TZ) assessed the risk of bias independently. Any discrepancies were addressed by re-evaluation of the original by the third author (HZ). The bias risk assessment of randomized controlled trials (RCTs) was conducted according to the Cochrane Collaboration Risk of the bias assessment tool and every article will have an entry judgment of high, low, or unclear risk. The Newcastle-Ottawa Scale (NOS) was used to evaluate the risk of bias in observational studies included in this review. We consider 0–3,4–6,7–9 stars as high, moderate, and low risk of bias respectively.

Data analysis and statistical methods

We calculated the standardized mean difference (SMD) with a 95% confidence interval (CI) to evaluate the pooled effect size using a random-effect model. For studies in which multiple intervention groups were present, we used the calculator provided by the Cochrane Library for data pooling.

The overall variation among studies termed as heterogeneity is calculated by I^2 statistics. Statistical heterogeneity is tested using I^2 with $P<0.05$ considered significant. I^2 <25%, 25-50%, 50-75%, or 75-100% are considered to have no, low, moderate, or high heterogeneity, respectively. Sensitivity analyses will be used to evaluate the robustness of findings by excluding studies with a high risk of bias. Moreover, the possibility of publication bias was evaluated using Egger's test. $P<0.05$ was considered indicative of statistically significant publication bias. Statistical analysis was performed with RevMan 5.4 and Stata 17.0.

Results

Characteristics of the included studies

The details of the study selection process are presented in Fig. 1. A comprehensive search strategy was implemented to retrieve a total of 5996 studies from various databases. Among these studies, 595 duplicates were excluded. Two reviewers then screened 5401 articles for potential eligibility according to title and abstract. Subsequently, 55 potentially eligible studies were further evaluated by the same reviewers through a full-text assessment, resulting in the exclusion of 42 studies that did not meet the inclusion criteria. Ultimately, 13 studies were deemed eligible for inclusion in this study. Due to the limited availability of RCT investigating the association between LT4 replacement treatment and bone metabolism in OH, observational studies were also included. Of the 13 studies, five were RCTs focusing on SCH, while the remaining eight were observational studies on OH.

The general information of each study is depicted in Tables 1 and 2. A total of 1135 participants were included in this study. Among these studies, the majority of SCH and OH patients were female, with mean ages ranging from 32.8 to 74.3 years. The duration of LT4 treatment varied across studies, ranging from 4 months to 12.5 years across studies. The risk of bias evaluation for the RCTs is shown in the supplementary Fig. 1. Of the eight included observational studies on OH, most of them rated eight scores [18, 24–26], one studies received nine scores [19], two studies received seven scores [27, 28]and the rest one studies received five scores [29].

SCH

Five studies focused on BMD in SCH patients were included in this study. Four studies [17, 21, 31, 32] of included studies were placebo-controlled and the remaining study [30] assessed the BMD between LT4 treatment and no treatment group in SCH patients. BMD was measured at several sites in these studies. A meta-analysis was conducted on BMD at lumbar spine measured by DXA, while no analysis was performed at other sites due to insufficient data and different measurement methods of BMD. As shown in Fig. 2, no significant difference was found in the BMD of the lumbar spine between the treatment and control groups, either at baseline (SMD: 0.11, 95% CI: -0.14, 0.36, $P=0.370$, $I^2=2\%$) or after intervention (SMD: 0.04, 95% CI: -0.25, 0.34, $P=0.780$, $I^2=0\%$). Additionally, there was also no difference in the BMD at lumbar spine in LT4 treatment group before and after therapy (SMD: -0.01, 95% CI: -0.26, 0.23, $P=0.930$, $I^2=0\%$). Besides, in some of the included studies, BMD was also measured at other sites, including radius [31], femur neck [21], and wrist [30], but no significant changes were found between the LT4 treatment

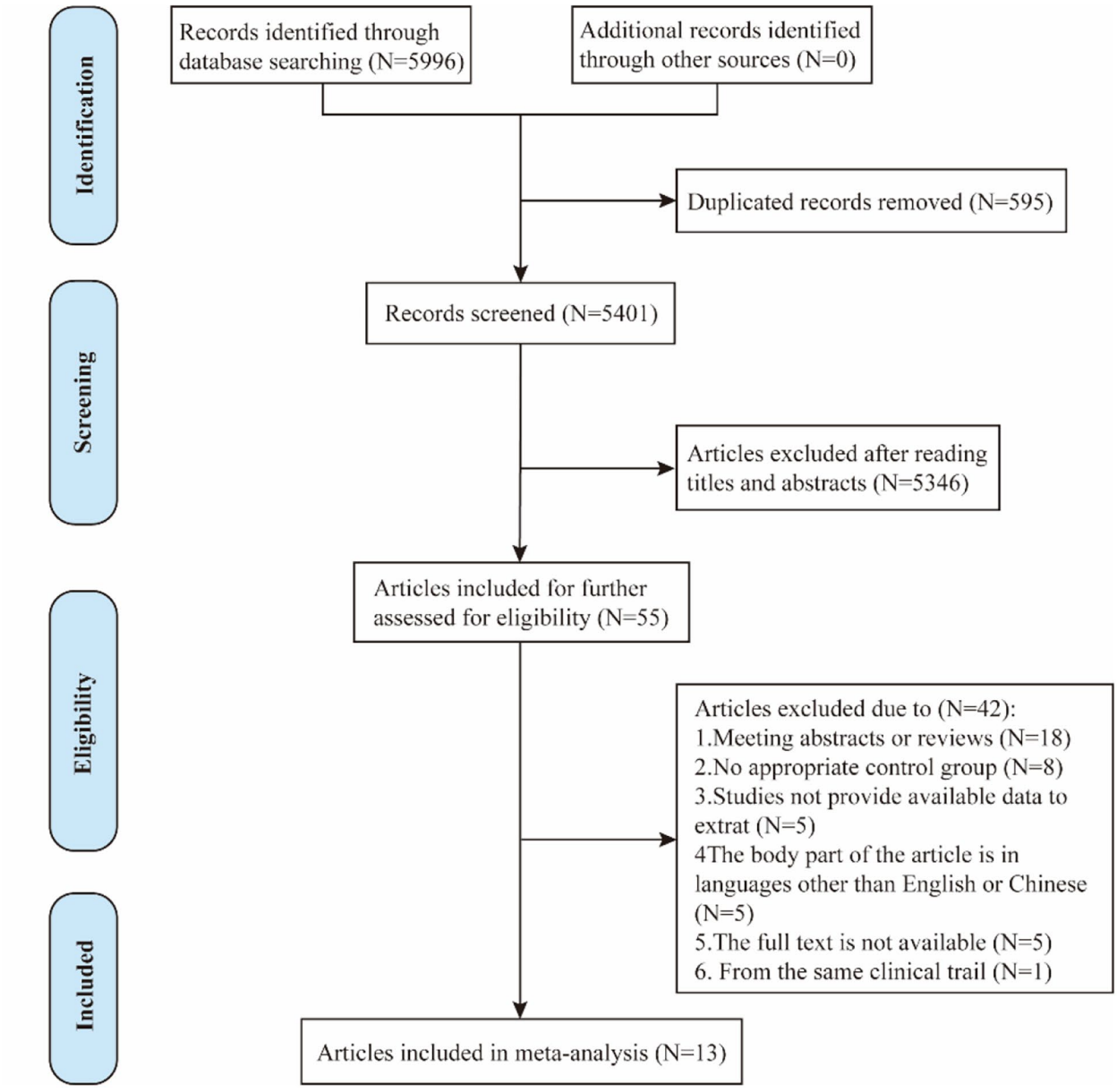

Fig. 1 Study flow diagram

and control group whether before or after intervention in their studies.

OH

BMD

Five [24, 26–28, 19] of the included studies investigated the effects of LT4 treatment on the BMD of the lumbar spine and femoral neck in patients with OH, Four of these studies, except for the study by Obling et al. [26], also assessed BMD at trochanter and Ward's triangle. Lumbar spinal BMD was found significantly lower in OH patients who received LT4 therapy compared with that in healthy controls (HCs) (SMD: -0.28, 95%CI: -0.55, -0.02, $P = 0.040$, $I^2 = 52\%$). However, there were no significant differences in BMD at the femoral neck, trochanter and Ward's triangle between patients treated with LT4 and HCs (SMD for femoral neck: -0.26, 95%CI: -0.62, 0.10, $P = 0.150$, $I^2 = 74\%$; SMD for trochanter: -0.58, 95%CI: -1.33, 0.16, $P = 0.120$, $I^2 = 93\%$; SMD for Ward's triangle: -0.46, 95%CI: -1.05, 0.13, $P = 0.130$, $I^2 = 89\%$, respectively) (Fig. 3).

Table 1 Characteristics of included studies about SCH

Study	Country	Study design	Intervention (T/C)	Etiology	Sample (F, %)	Age (T/C)	TSH value ((mIU/l) (T/C)		Initial dosage of LT4 (μg/d)	Follow-up periods	BMD measurement methods
							Baseline value	After intervention			
Ross et al., 1993 [30]	American	RCT	LT4 treatment/ No treatment	Primary hypothyroidism	17 (100)	68±6/ 60±5	9.80±3.30/ 8.40±2.70	2.70±1.50/ 8.50±10.20	50	14 m	SPA, DEXA
Chen et al., 2003 [31]	China	RCT	LT4 treatment/ Placebo	Autoimmune thyroiditis, Graves' disease treated with radioiodine or surgery	78 (79.5)	65±5.1[a]	10.60±1.90/ 10.50±1.70	4.10±0.80/ 10.70±2.30	12.5	12 m	SPA
Meier et al., 2004 [17]	American	RCT	LT4 treatment/ Placebo	Autoimmune thyroiditis; Graves' disease (treated with radioiodine or surgery or carbimazole); toxic multinodular goiter (treated with radioiodine), surgically resected goiter and idiopathic	66 (100)	57.10±1.80/ 57.10±1.90	14.40±1.70/ 11.30±1.00	3.10±0.30/ 9.9±0.6	N/A	48 w	DXA
Nie et al., 2016 [32]	China	RCT	LT4 treatment/ Placebo	Primary hypothyroidism	72 (65.3)	69.40±4.30/ 69.70±5.00	N/A[b]	N/A[b]	12.5–25	16 w	DXA
Gonzalez Rodriguez et al, 2020 [21]	Switzer-land	RCT	LT4 treatment/ Placebo	Primary hypothyroidism, exclude thyroid surgery or radioiodine therapy	196 (45.4)	74.30±5.30/ 74.20±6.10	6.30±1.90/ 6.50±2.20	3.20±1.50/ 5.60±2.40	50	12 m	DXA

Data in the table are presented as mean or mean ± SD

C control, *DXA* dual-energy X-ray absorptiometry, *F* female, *LT4* levothyroxine, *m* months, *N/A* not available, *RCT* randomized control trial, *SCH* subclinical hypothyroidism, *SPA* single photon absorptiometry, *T* treatment, *TSH* thyrotropin, *w* weeks, *y* years

[a] It refers to the age of all subjects

[b] The data of TSH at baseline and after treatment were not available, SCH is diagnosed when TSH is greater than 4 mIU/L and FT4 is within the normal range in this study, and TSH below 4.0 mIU/L after LT4 treatment

Table 2 Characteristics of included studies about OH

Study	Country	Study design	Etiology	Sample (F, %)	Age (T/HCs)	TSH (mIU/l) (T/HCs) [a]	FT4 (pmol/l) (T/HCs) [a]	LT4 dosage (μg/d)	Treatment periods	Scale of quality score
Kung et al., 1991 [27]	China	cross-sectional	Hashimoto's thyroiditis	120 (100)	32.80 ± 6.40/ 32.60 ± 6.70	2.20 ± 1.40/ 2.40 ± 0.90	N/A	106 ± 37	7.5 y	7
Franklyn et al., 1994 [24]	UK	case-control	Hashimoto's thyroiditis, atrophic thyroiditis, a past history of radioiodine treated thyrotoxicosis	109 (100)	56.30/ N/A	1.24 ± 1.29/ 1.73 ± 0.96	21.54 ± 5.27/ 15.03 ± 2.17	148.67	7.2 y	8
Langdahl et al., 1996 [28]	Denmark	cross-sectional	Primary idiopathic (autoimmune) hypothyroidism	116 (86.2)	56 ± 12/ 56 ± 11	0.04(0.00-5.20)/ 1.00(0.01–3.50)	115 ± 25/ 88 ± 11	163 (75–300)	13 y	7
Chai et al., 1999 [19]	China	case-control	Primary hypothyroidism	66 (100)	48.80 ± 12.80/ 48.40 ± 10.30	3.79 ± 2.36/ N/A	16.76 ± 4.68/ 18.50 ± 7.25	92 ± 13	11.5 ± 2.5 m	9
Liu et al., 2011 [29]	China	case-control	Primary hypothyroidism	30 (100)	36.07 ± 6.65/ 36.47 ± 5.78	2.49 ± 0.95/ 2.38 ± 0.94	16.43 ± 2.37/ 24.07 ± 2.44	N/A	N/A	5
Christy et al., 2014 [25]	India	case-control	Primary hypothyroidism	56 (100)	40.25 ± 5.31/ 37.96 ± 6.34	3.91 ± 2.88/ 2.42 ± 0.83	N/A	100–200	≥ 5 y	8
Babu et al., 2015 [18]	India	case-control	Primary hypothyroidism	50 (100)	40.40 ± 5.09/ 38.08 ± 6.06	3.93 ± 2.99/ 2.40 ± 0.85	N/A	125	≥ 5 y	8
Obling et al., 2021 [26]	Denmark	case-control	Hashimoto's thyroiditis	59 (100)	47 ± 12/ 47 ± 12	2.14(0.58–4.32)/ N/A	2.14 (0.58–4.32)/ N/A	N/A	15 (14–23) m	8

Data in the table are presented as mean or mean ± SD or median (interquartile range) which depends on data provided by the original studies

F female, *FT4* free thyroxine, *HCs* healthy controls, *LT4* levothyroxine, m months, *N/A* not available, *OH* overt hypothyroidism, *T* treatment, *TSH* thyrotropin, *y* years

[a] TSH, FT4 refers to the value after receiving treatment

Bone metabolism biomarkers

In terms of bone metabolism biomarkers, six [18, 25, 27–29, 19] of included studies investigated the effects of LT4 treatment on these biomarkers in OH patients. After analysis, serum calcium, phosphorus, and CTX did not show any significant differences between OH with the LT4 treatment group and HCs. However, there was a trend towards increased levels of serum OC and ALP in the LT4 treatment group, although the differences were not statistically significant (SMD for OC: 0.51, 95%CI: -0.03, 1.06, $P = 0.070$, $I^2 = 76\%$; SMD for ALP: 0.38, 95%CI: -0.02, 0.78, $P = 0.060$, $I^2 = 44\%$) (Table 3).

Subgroup analysis

Subgroup analyses were conducted by considering sex, intervention periods and menopausal state. The subgroup analyses were only performed on the primary outcomes (Table 4).

Sex

As shown in Table 4, after stratifying by sex, there was a near statistical decrease in BMD at the lumbar spine in OH males compared with HCs (SMD: -0.88; 95%CI: -1.77, 0.02, $P = 0.050$), whereas females were not (SMD: -0.26; 95%CI: -0.55, 0.02, $P = 0.070$, $I^2 = 56\%$). No significant differences in BMD were found at other sites for both males and females.

Intervention periods

As shown in Table 4, there was a statistically significant decrease in lumbar spinal BMD in the LT4 treatment group when the intervention period was less than 5 years (SMD: -0.56; 95%CI: -1.06, -0.06, $P = 0.030$, $I^2 = 48\%$). Additionally, BMD at the trochanter and Ward's triangle also showed a statistically significant decrease in studies with an intervention time less than 5 years (SMD for trochanter: -0.69, 95%CI: -1.19, -0.18, $P = 0.007$; SMD for Ward's triangle: -0.70, 95%CI: -1.21, -0.20, $P = 0.006$, respectively). However, no significant differences in BMD were observed at these four sites when the intervention period was equal to or greater than 5 years.

Menopausal status

As shown in Table 4, no significant differences were found in BMD at any site in LT4 treatment group compared with HCs, regardless of whether participants were pre- or postmenopausal.

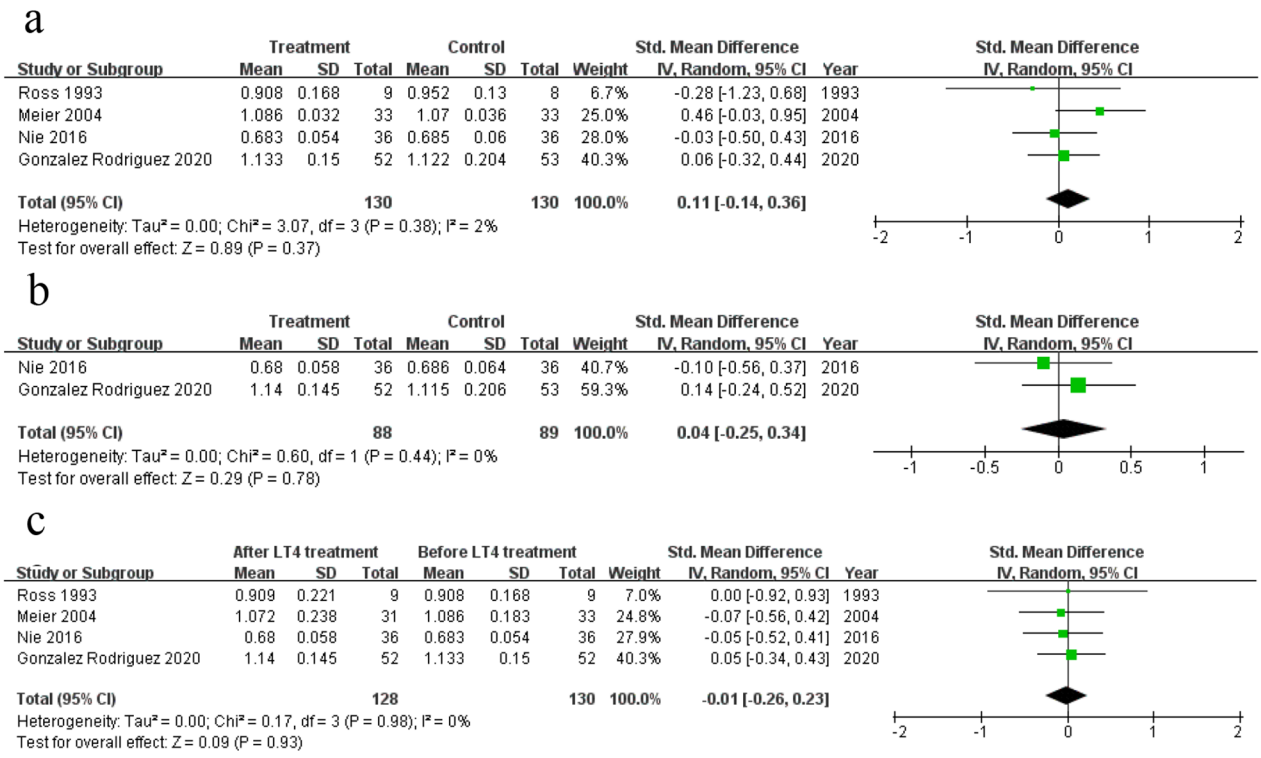

Fig. 2 Comparisons of bone mineral density at lumbar spine in subclinical hypothyroidism. (**a**) At baseline (**b**) After intervention (**c**) Before and after LT4 treatment for subclinical hypothyroidism. Treatment: levothyroxine-treated group, Controls: receiving placebo or untreated group

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by eliminating each study to determine whether the results were robust. The sensitivity analyses of each outcome did not change the results. Publication bias for each outcome was conducted using Egger's test, and the results showed that no publication bias was found in each outcome.

Discussion

In this study, we aimed to examine the effects of LT4 replacement therapy on bone and mineral metabolism in hypothyroidism. Our findings indicated that there were no significant differences in BMD at lumbar spine for SCH between the treatment and control groups whether at baseline or after intervention. Conversely, lumbar spinal BMD of OH patients was observed a reduction following LT4 replacement treatment compared with HCs. Nevertheless, BMD at other skeletal sites and bone metabolism biomarkers did not exhibit any significant difference between individuals with LT4-treated OH and HCs.

Our study did not find any significant difference in BMD at lumbar spine between LT4-treated SCH patients and controls. These results are in accordance with a previous meta-analysis [33]. Additionally, Büchi et al. [34] indicated that LT4 therapy did not affect bone microarchitecture, which supports our findings. Due to limited available data, it was difficult to conduct a quantitative analysis of changes in bone metabolic biomarkers in SCH patients treated with LT4. It has been indicated in previous studies [17, 21] that LT4 replacement doses do not impact bone metabolism biomarkers. It is also supported that LT4 may have little effect on bone in SCH patients. This finding may suggest that LT4 low-dose treatment for SCH patients is safe in terms of bone metabolism. However, these results were not stable due to the smaller number of included studies that reported the effects of SCH on BMD. It is worth noting that the effects of LT4 on bone metabolism in SCH patients may be influenced by factors such as treatment dose, individual age, and follow-up time. Therefore, future research should consider these factors in order to provide a more comprehensive understanding of the relationship between LT4 replacement therapy and bone metabolism in SCH.

The findings of this study revealed that only lumbar spinal BMD was statistically different in the LT4-treated OH group compared with HCs. These are consistent with previous research indicating that BMD may be affected by LT4 treatment [18, 25]. TSH and thyroid hormones are negative regulators of bone remodeling via TSH receptors on osteoclast and osteoblast precursors [35]. Thyroid hormone indirectly promotes osteoclast formation and activation by inducing the expression of cytokines, prostaglandins and the receptor activator of

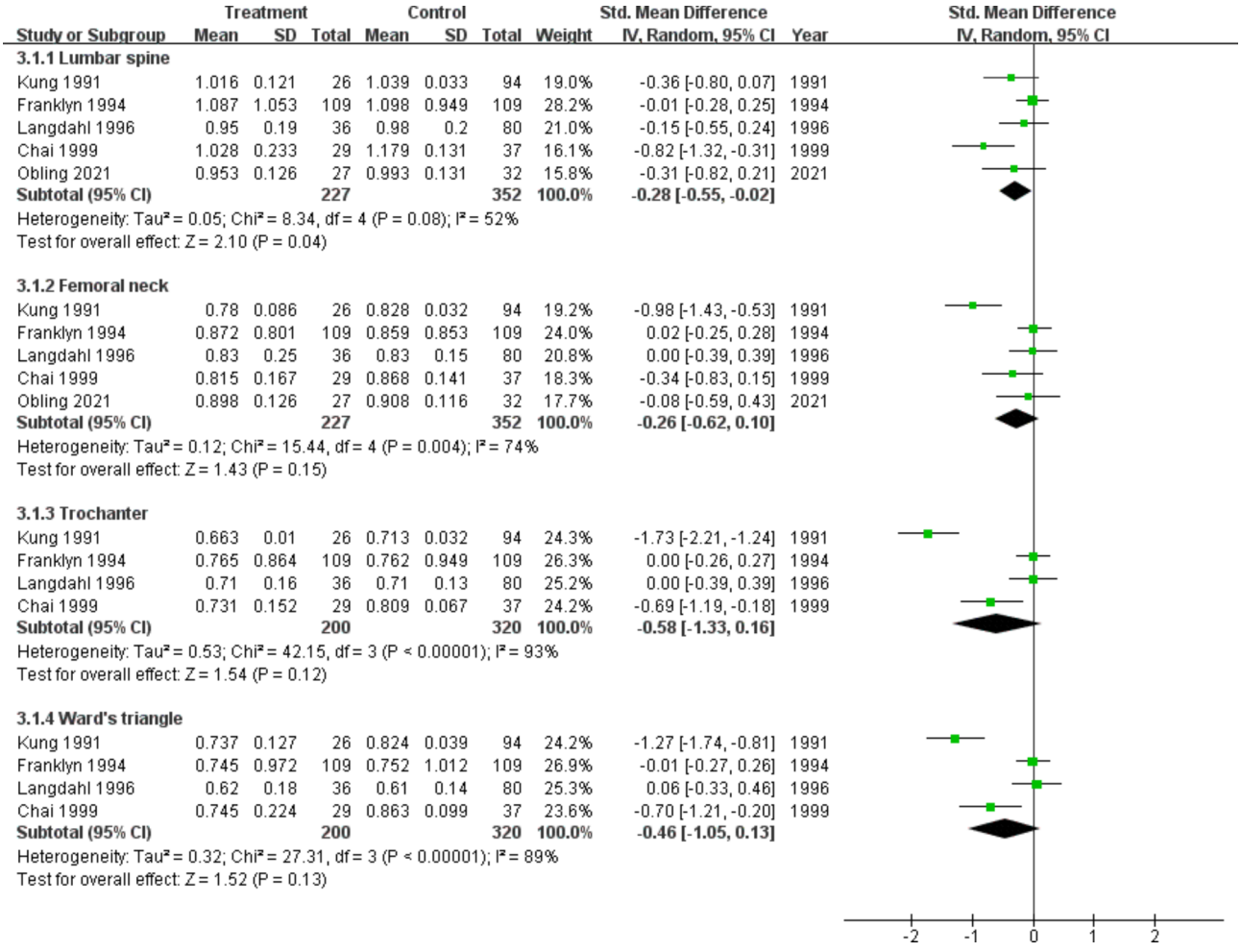

Fig. 3 Comparisons of bone mineral density at several sites in levothyroxine-treated overt hypothyroidism versus controls. Controls: healthy controls

Table 3 Bone metabolism biomarkers in OH with LT4 treatment and HCs

Outcomes	Number of studies (*n*)	Sample size (T/HCs)	SMD (95%CI)	I^2, %	*P* value
Calcium	4 [18, 19, 27, 28]	116/236	0.39 (-0.27, 1.05)	87	0.250
Phosphorus	4 [18, 19, 27, 28]	116/236	0.02 (-0.47, 0.52)	78	0.920
CTX	2 [25, 28]	64/108	0.87 (-0.39, 2.14)	92	0.180
OC	4 [18, 19, 28, 29]	105/157	0.51 (-0.03, 1.06)	76	0.070
ALP	2 [27, 28]	61/174	0.38 (-0.02, 0.78)	44	0.060

ALP alkaline phosphatase, *CI* conference interval, *CTX* C-telopeptide of type I collagen, *HCs* healthy controls, *I2* I-square, *LT4* levothyroxine, *OC* osteocalcin, *OH* overt hypothyroidism, *SMD* standardized mean difference, *T* treatment

nuclear factor NF-kB ligand [12, 36, 37]. Although current studies demonstrated that LT4 suppression therapy has adverse effects on bone [15], some researches have indicated that even euthyroid individuals receiving LT4 treatment may be susceptible to bone metabolic disorders [38, 39], and TSH and thyroid hormone levels within the normal range are negatively correlated with BMD among euthyroid adults [40, 41]. Notably, the lumbar spine is primarily composed of trabecular bone and it is structurally more fragile compared to other skeletal sites [42]. Therefore, the reduction in lumbar spinal BMD observed in our study may be due to the higher serum T4 concentrations achieved with LT4 replacement [18]. Besides, since bone remodeling cycle is often prolonged in hypothyroid patients, decreased BMD may be likely explained by an increase in the bone remodeling rate induced by the LT4 treatment [17]. In terms of bone metabolism biomarkers, from our results, the LT4 treatment group exhibited increased levels of OC and ALP, although there was no statistical difference. These findings may provide biochemical evidence supporting the impact of LT4 treatment on bone health in OH patients. And these are consistent with a study by Rosa, which reported an increase in OC levels following thyroid hormone treatment in women with nontoxic goiter, both before and after menopause [43].

Table 4 Subgroup analysis of BMD at various sites in LT4-treated OH

Sites	Factors	Subgroup	Studies (*n*)	SMD (95%CI)	I^2, %	*P* value	*P* value between subgroups
Lumbar spine	Sex	male	1 [28]	-0.88 (-1.77, 0.02)	-	0.050	0.030
		female	5 [19, 24, 26–28]	-0.26 (-0.55, 0.02)	56	0.070	
	Intervention periods (years)	< 5	2 [19, 26]	-0.56 (-1.06, -0.06)	48	0.030	0.040
		≥ 5	3 [24, 27, 28]	-0.12 (-0.31, 0.08)	0	0.240	
	Menopausal status	Pre-	4 [19, 24, 27, 28]	0.01 (-0.43, 0.46)	55	0.950	0.310
		Post-	3 [19, 24, 28]	-0.51 (-1.23, 0.21)	82	0.170	
Femur neck	Sex	male	1 [28]	-0.51(-1.37, 0.36)	-	0.250	0.110
		female	5 [19, 24, 26–28]	-0.25 (-0.63, 0.12)	75	0.180	
	Intervention periods (years)	< 5	2 [19, 26]	-0.22 (-0.57, 0.14)	0	0.230	0.150
		≥ 5	3 [24, 27, 28]	-0.30 (-0.88; 0.27)	87	0.310	
	Menopausal status	Pre-	4 [19, 24, 27, 28]	-0.33 (-0.92, 0.27)	75	0.280	0.130
		Post-	3 [19, 24, 28]	-0.29 (-0.92, 0.33)	77	0.360	
Trochanter	Sex	male	1 [28]	-0.33 (-1.19, 0.52)	-	0.180	0.110
		female	4 [19, 24, 27, 28]	-0.59 (-1.35,0.17)	93	0.130	
	Intervention periods (years)	< 5	1 [19]	-0.69 (-1.19, -0.18)	-	0.007	0.120
		≥ 5	3 [24, 27, 28]	-0.56 (-1.52, 0.41)	95	0.260	
	Menopausal status	Pre-	4 [19, 24, 27, 28]	-0.40 (-1.34, 0.53)	92	0.400	0.150
		Post-	3 [19, 24, 28]	-0.30 (-0.90, 0.29)	74	0.310	
Ward's triangle	Sex	male	1 [28]	-0.55 (-1.42, 0.31)	-	0.210	0.090
		female	4 [19, 24, 27, 28]	-0.45 (-1.07, 0.16)	89	0.150	
	Intervention periods (years)	< 5	1 [19]	-0.70 (-1.21, -0.20)	-	0.006	0.130
		≥ 5	3 [24, 27, 28]	-0.39 (-1.13, 0.35)	92	0.300	
	Menopausal status	Pre-	4 [19, 24, 27, 28]	-0.22 (-1.03, 0.59)	86	0.590	0.260
		Post-	3 [19, 24, 28]	-0.36 (-1.12, 0.39)	84	0.350	

BMD bone mineral density, *CI* conference interval, *I2* I-square, *LT4* levothyroxine, *OH* overt hypothyroidism, *SMD* standardized mean difference

Upon conducting subgroup analysis by sex, the result showed that there was a reduction in BMD at the lumbar spine in males with OH, while no significant difference was observed at other sites. This observation may be attributed to the potential absence of protective effects of estrogen, which plays a role in bone remodeling, in males compared to females [44]. Furthermore, our results indicated that LT4 replacement treatment led to a reduction in BMD at the lumbar spine in OH patients when the duration of treatment was less than five years. These findings are consistent with some studies [38, 45], suggesting that the duration of intervention may influence BMD. It is important to note that the studies included in the subgroup analysis, focusing on treatment durations of less than five years, primarily assessed BMD within approximately one year of initiating LT4 treatment. Consequently, BMD assessment shortly after the initiation of LT4 treatment may not accurately reflect the steady bone remodeling, because many new remodeling units remained in the resorptive phase at that time [44]. And no significant difference was observed in OH patents receiving LT4 treatment more than five years. A possible hypothesis may be that thyroid hormone levels have stabilized and the previous reduction of BMD during thyroid hormone deficiency has been corrected due to long-term LT4 treatment. Some studies have reported contrasting results, suggesting that long-term LT4 treatment may lead to a loss of bone mass or an increased risk of osteoporotic fractures [18, 46, 47]. These effects may be attributed to the cumulative impact of hyperthyroidism and the control level of TSH during treatment, rather than the thyroid hormone itself [9]. In this study, the menopausal status of LT4-treated OH patients did not appear to be associated with changes in BMD at any sites. These findings are consistent with some studies that focused on pre- and postmenopausal women receiving LT4 treatment, which reported no significant changes in BMD and trabecular bone score [48, 49]. However, one study [50] suggested that both pre- and postmenopausal women who received long-term LT4 treatment, whether at suppressive or normal dosages, exhibited low trabecular bone scores.

This study has some limitations. Firstly, the number of included studies was limited, which prevented further exploration of the high heterogeneity observed in certain outcomes. Secondly, the focus of the included studies was primarily on older adults with SCH, and there was a lack of comprehensive data on the association between LT4 replacement therapy and bone metabolism in adults under the age of 60. Future research should include prospective and longitudinal studies that specifically target young adults. Thirdly, the limited number of included studies precluded us from performing subgroup analyses based on menopausal status for patients with subclinical

hypothyroidism. Fourthly the majority of participants in this study were female, which limits the generalizability of the findings to male patients. Although a subgroup analysis by sex revealed a significant difference in BMD at the lumbar spine between males and females in LT4-treated individuals OH, there was only one study that included male participants in our analysis. Fifthly, the duration of LT4 intervention may have an effect on bone metabolism. However, most of the included studies on SCH had intervention durations of approximately one year in this review, and there is paucity of research on the long-term effects of LT4 therapy on bone in patients with SCH. Therefore, it is challenging to determine the effects of different LT4 intervention periods on bone metabolism in individuals with SCH. Further studies are warranted in the future to investigate the potential long-term effects of LT4 intervention on bone metabolism in this population.

Conclusion

This systematic review and meta-analysis concluded that LT4 replacement therapy has a slight detrimental effect for patients with OH on bone and mineral metabolism, while no adverse effect on SCH. However, it is necessary to conduct prospective studies or high-quality RCT studies to validate these findings and further investigate the effects of LT4 replacement treatment on bone health in patients with hypothyroidism in the future.

Abbreviations

LT4	Levothyroxine
OH	Overt hypothyroidism
SCH	Subclinical hypothyroidism
TSH	Thyroid stimulating hormone
FT4	Free thyroxine
BMD	Bone mineral density
ALP	Alkaline phosphatase
CTX	Carboxy-terminal telopeptide of type I collagen
OC	Osteocalcin
DXA	Dual-energy X-ray absorptiometry
HCs	Healthy controls
RCT	Randomized controlled trials
SMD	Standardized mean difference
CI	Conference interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01819-7.

Supplementary Material 1: Additional files: Table S1. Search strategies for PubMed Fig. S1. Risk of bias for randomized controlled trails focused on subclinical hypothyroidism.

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Author contributions

All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by XL, TZ, HZ and SL. XL and TZ contributed equally to this study. LT provided the idea for this article. All authors commented on the previous versions of the manuscript and have read and approved the final version.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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Not applicable.

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