Skeletal Effects of Levothyroxine for Subclinical Hypothyroidism in Older Adults: A TRUST Randomized Trial Nested Study

Elena Gonzalez Rodriguez,[1,2] Mirah Stuber,[3] Cinzia Del Giovane,[3] Martin Feller,[3,4] Tinh-Hai Collet,[2] Axel L. Löwe,[3,4] Manuel R. Blum,[4] Nicolien A. van Vliet,[5] Diana van Heemst,[5] Patricia M. Kearney,[6] Jacobijn Gussekloo,[7] Simon Mooijaart,[7] Rudi G. J. Westendorp,[8] David J. Stott,[9] Daniel Aeberli,[10] Douglas C. Bauer,[11] Didier Hans,[1,*] and Nicolas Rodondi[3,4,*]

[1]Center of Bone Diseases, Rheumatology Unit, Bone and Joint Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [2]Service of Endocrinology, Diabetes and Metabolism, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [3]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland; [4]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [5]Department of Internal Medicine, Section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands; [6]School of Public Health, University College Cork, Cork, Ireland; [7]Departments of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, Netherlands; [8]Department of Public Health and Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark; [9]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [10]Department of Rheumatology and Clinical Immunology/Allergology, Inselspital, Bern University Hospital, Bern, Switzerland; and [11]Departments of Medicine, Epidemiology and Biostatistics, University of California, San Francisco, US

ORCiD number: 0000-0001-6512-6008 (Elena Gonzalez Rodriguez).

Context: Both thyroid dysfunction and levothyroxine (LT4) therapy have been associated with bone loss, but studies on the effect of LT4 for subclinical hypothyroidism (SHypo) on bone yielded conflicting results.

Objective: To assess the effect of LT4 treatment on bone mineral density (BMD), Trabecular Bone Score (TBS), and bone turnover markers (BTMs) in older adults with SHypo.

Design and Intervention: Planned nested substudy of the double-blind placebo-controlled TRUST trial. Participants with SHypo were randomized to LT4 with dose titration versus placebo with computerized mock titration.

Setting and Participants: 196 community-dwelling adults over 65 years enrolled at the Swiss TRUST sites had baseline and 1-year follow-up bone examinations; 4 participants withdrew due to adverse events not related to treatment.

Main Outcome Measures: One-year percentage changes of BMD, TBS, and 2 serum BTMs (serum CTX-1 [sCTX] and procollagen type 1 N-terminal polypeptide [P1NP]). Student's *t*-test for unadjusted analyses and linear regression adjusted for clinical center and sex were performed.

Results: Mean age was 74.3 years ± 5.7, 45.4% were women, and 19.6% were osteoporotic. The unadjusted 1-year change in lumbar spine BMD was similar between LT4 (+0.8%) and placebo-treated groups (–0.6%; between-groups difference +1.4%: 95% confidence interval [CI] –0.1 to

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 11 July 2019. Accepted 27 September 2019.
First Published Online 8 November 2019.

*Didier Hans and Nicolas Rodondi are both equally lead authors for this study.

2.9, $P = .059$). Likewise, there were no between-group differences in 1-year change in TBS (–1.3%: 95% CI –3.1 to 0.6, $P = .19$), total hip BMD (–0.2%: 95% CI –1.1 to 0.1, $P = .61$), or BTMs levels (sCTX +24.1%: 95% CI –7.9 to 56.2, $P = .14$), or after adjustment for clinical centers and sex.

Conclusions: Over 1-year levothyroxine had no effect on bone health in older adults with SHypo. (***J Clin Endocrinol Metab* 105: 336–343, 2020)**

Registration: ClinicalTrial.gov NCT01660126 and NCT02491008

The prevalence of subclinical hypothyroidism (SHypo), defined as an elevated thyrotropin (thyroid-stimulating hormone [TSH]) level with free thyroxine (FT4) within the reference range, increases with age, reaching >10% in men >65 years and up to 21% in women ≥75 years (1, 2). Increasing evidence suggests that treating SHypo with levothyroxine (LT4) does not confer clinical benefit (3, 4). Although recent UK guidelines recommend against LT4 therapy except in very specific clinical conditions (5), others propose LT4 for adults with SHypo and a TSH >10.0 mIU/L (6, 7) and up to 9 out of 10 women with SHypo and a TSH concentration between 5.5 and 10 mIU/L should be treated if some of these guidelines were followed (8).

The deleterious effect of high thyroid function on bone, even at high-normal levels (9, 10) is well established. On the contrary, studies have found no association between SHypo and bone mineral density (BMD) changes (11, 12); a meta-analysis of individual participant data found no association between SHypo and fracture risk (10). Concerns have been raised on the impact of LT4 on bone (13), but data on the effects of LT4 replacement on bone in SHypo are scarce and conflicting. Three small ($n = 17$ to 66) randomized clinical trials (RCTs) showed either no difference (14, 15) or a small yet not clinically significant bone loss in the LT4-treated group (16). Only one RCT analyzed bone turnover markers (BTMs), which increased transiently at 24 weeks in the LT4-treated group (between 7.7% for alkaline phosphatase and 29.9% for serum CTX-1 [sCTX]), during a 48 weeks treatment with LT4 (16). No study has analyzed the effect of LT4 substitution on Trabecular Bone Score (TBS), a textural index that evaluates pixel gray-level variations in the lumbar spine dual energy X-ray absorptiometry (DXA) image and provides an indirect index of trabecular microarchitecture, independent of bone density (17).

The Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism (TRUST) trial was a multicenter, international, double-blind parallel-group RCT of LT4 versus placebo (4, 18) and showed no apparent benefits of treatment on either primary objectives (Hypothyroid Symptoms or Tiredness score) or secondary outcomes. Since there was scarce evidence on the effect of SHypo treatment by LT4 on bone health, we measured BMD, TBS, and BTM in participants in Swiss centers at baseline and follow-up of the TRUST trial to assess the effect of LT4 on bone.

Methods

Study population

This nested study focused on skeletal outcomes of participants in the Swiss centers (Bern and Lausanne) of the TRUST trial (clinicaltrials.gov NCT02491008, NCT01660126) (4, 18). It included community-dwelling individuals aged ≥65 years with persistent SHypo. Briefly, as previously described (4), persistent SHypo was diagnosed by elevated TSH levels (≥4.6 and ≤19.9 mIU/L) on at least 2 measurements at least 3 months apart and FT4 levels within the assay reference range. Exclusion criteria included use of LT4, antithyroid, amiodarone, or lithium treatment within 12 months; thyroid surgery or radio-iodine; severe acute comorbidities; dementia; terminal illness; or galactose intolerance (4). For this bone study, among the 217 participants of the TRUST trial in Switzerland, 21 participants lacked measurements at 1-year follow-up. Four participants withdrew due to adverse events not related to treatment: 3 on the treatment arm, and 1 on the placebo arm. This analysis focused on the 196 participants who had baseline and 1-year follow-up DXA and/or BTMs values. Of these, 79 had no DXA exam at baseline or 1-year, so there were 117 participants left with both DXA exams (Fig. 1). Of the 196 participants, 6 had no BTMs measures at either baseline or 1-year follow-up for technical reasons, so 190 BTMs (sCTX and procollagen type 1 N-terminal polypeptide [P1NP]) were available for analysis.

The trial was approved by the local institutional review boards, and written, informed consent was obtained from all participants. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Intervention

Briefly, as previously described (4), treatment started with LT4 50 µg daily (25 µg in individuals <50 Kg body weight or with known coronary heart disease). Dose was titrated in the active treatment group according to target TSH levels ≥0.4 and <4.6 mIU/L and a computerized mock titration in the placebo group.

Clinical data

We recorded baseline age, sex, current smoking and alcohol consumption, history of osteoporosis and diabetes mellitus, and all ongoing treatments. Bone-affecting treatments were classified in 2 categories. Beneficial treatments included antiosteoporotics (raloxifene, bisphosphonates,

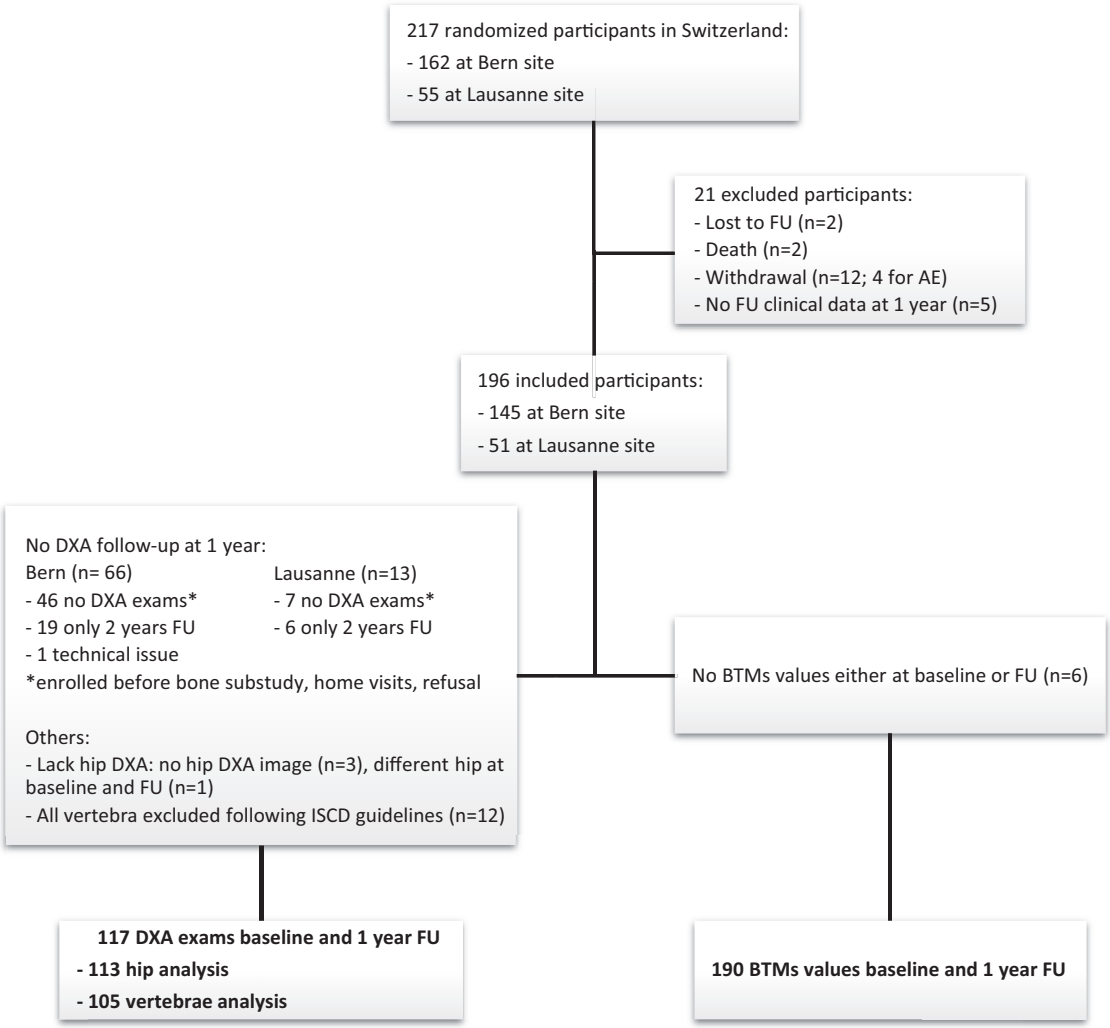

Figure 1. Flowchart of the nested TRUST bone study.
Abbreviations: FU, follow-up; AE, adverse events; DXA, dual-X-ray absorptiometry; ISCD, International Society for Clinical Densitometry; BTMs, bone turnover markers.

denosumab, or teriparatide), hormonal replacement therapy, and hydrochlorothiazide. Deleterious bone treatments included systemic or topical glucocorticoids, proton pump inhibitors, aromatase inhibitors, serotonin recapture inhibitors, and antiepileptic treatments. Incident fractures were prospectively recorded.

BMD and TBS measures

Participants had serial BMD and TBS measurements by DXA on a GEHC-Lunar Prodigy (GEHC, Madison, WI, USA) at the Bern study site, and on a GEHC-Lunar iDXA (GEHC, Madison, WI, USA) at the Lausanne site. The 2 machines were cross-calibrated at the beginning of the trial for both BMD and TBS using the appropriate phantom and benefited from a daily on-site quality control with the dedicated phantom supplied by the manufacturer. No statistical differences were observed between the 2 DXA machines; no longitudinal changes were observed during the study period. BMD measures least significant change values are (i) for the GEHC-Lunar Prodigy, 0.030 g/cm^2 at the lumbar spine (L1–L4) and 0.018 g/cm^2 at the total hip, and (ii) for the GEHC-Lunar iDXA, 0.028 g/cm^2 at the lumbar spine (L1–L4) and 0.033 g/cm^2 at the total hip. Manufacturer recommendations were followed for DXA scans at baseline and follow-up; quality assurance review was performed centrally at Lausanne for both the BMD and TBS parameters. BMD was measured at the lumbar spine (antero-posterior projection of L1 through L4) and the proximal femur (neck and trochanteric regions). Recorded images were reanalyzed for 5 individuals because there were inconsistencies within vertebral readings. Individual vertebrae were excluded if there were fractures or degenerative changes, in accordance with the International Society for Clinical Densitometry rules for excluding individual vertebrae (19) and if considered outliers (T-score ≥ +3.0 standard deviation [SD]). The same vertebrae were excluded at different time points, and mean lumbar spine T-score was calculated as the mean of the included vertebra T-score values. Participants were excluded if only 1 vertebra remained for analysis. TBS of the spine was centrally assessed at the Lausanne center (blinded from clinical outcomes) with a modified version of TBS iNsight v3.0, which accounts for tissue thickness (Medimaps Group, Geneva, CH) by the Lausanne center. Region of interest for TBS were (i) all vertebrae, because TBS is minimally affected by degenerative changes (20), and (ii) the same region used for spine BMD (eg, the same included/

excluded vertebrae). TBS least significant change is 3.88%. Left femur measurements were used unless precluded by prosthetic material.

Bone turnover markers (BTMs) measurements

Venous blood was drawn at any time during the day and without regard to fasting status. The Bern University Hospital routine laboratory quantified serum concentration of bone biomarkers P1NP, representing bone formation, and serum CrossLaps (sCTX), representing bone resorption, in blood samples at baseline and at 1-year follow-up using Roche Cobas© technology, from fresh samples (Bern participants) or from frozen samples (Lausanne participants).

Statistical analysis

We calculated we would need to include 375 participants to detect a difference in the change in total hip BMD as small as 1.3% over 2 years between groups, with power of 80% and 2-sided alpha of .05, based on the annual bone loss observed in placebo treated individuals in several US trials (21).

Descriptive results (baseline data) are expressed as number of participants (percentage) or as mean ± SD. Between-group comparisons on the difference between 1-year follow-up and baseline values were performed using Student's *t*-test for nonadjusted analyses and linear regression adjusted for clinical site and sex to account for BMD differences resulting from DXA machines and gender, but unadjusted results were similar. Results are expressed as mean percentage changes (95% confidence interval [CI]). Statistical significance was considered for *P*-values < .05. All analyses were performed using Stata version 15 (StataCorp, College Station, TX) for Windows.

Results

The mean age at inclusion was 74.3 ± 5.7 years, 45.4% were women, and participants presented with a mean body mass index of 27.5 ± 5.0 kg/m^2 (Table 1). TSH was 6.4 ± 2.0 mlU/L and FT4 13.6 ± 1.9 pmol/L before randomization, corresponding to SHypo, which evolved to the euthyroid state at 1 year in the treatment arm but not in the placebo group (TSH 3.2 ± 1.5 vs. 5.6 ± 2.4; *P* < .001). The characteristics of the 117 participants with DXA exams are detailed by treatment group in a digital research repository; (22). At the baseline DXA exam, 19.6% of the participants were osteoporotic, and 20.5% were osteopenic according to the World Health Organization definition based on the lowest T-score from lumbar spine, total hip, or femoral neck (23). Mean T-scores values were in the normal range at lumbar spine (–0.6 ± 1.5 SD) and total hip (–0.6 ± 1.2 SD) and in the osteopenic range at the femoral neck (–1.1 ± 1.1 SD). On the other hand, 26.5% had degraded TBS, and 29.1% had partially degraded TBS, according to the thresholds defined in McCloskey et al. (24). The distribution of all parameters was balanced between groups (all *P*-values > .10) both in the whole study group and the DXA data subgroup, except for deleterious treatments (including systemic or topic glucocorticoids, proton pump inhibitors, aromatase inhibitors, serotonin recapture inhibitors, and antiepileptic treatments) in the DXA data subgroup, which were more frequent in LT4 treated participants (40.7% vs. 22.4% of placebo treated participants, *P*-value = .03).

Table 1. Characteristics of included participants, by treatment group

	Placebo	LT4 treated
Sample size	96	100
Bern study site	71 (74)	74 (74)
Female	44 (45.8)	45 (45)
Age (years)	74.2 ± 6.1	74.3 ± 5.3
Weight (kg)	75.0 ± 14.8	78.2 ± 17.4
Height (cm)	166.5 ± 8.9	167.1 ± 8.6
BMI (kg/m^2)	27.0 ± 4.5	27.9 ± 5.3
Current smoking	8 (8.3)	8 (8.0)
Excess alcohol consumption	11 (11.5)	8 (8.0)
TSH (mUI/L)		
Baseline	6.5 ± 2.2	6.3 ± 1.9
Median (IQR)	5.7 (5.2–7.1)	5.8 (5.1–6.8)
Range	4.6–17.0	4.6–16.8
Free T4 (pmol/L)	13.7 ± 1.8	13.5 ± 2.0
GFR <30 ml/min	3 (3.1)	3 (3.0)
Osteoporosis history	13 (13.5)	13 (13.3)
Diabetes history	10 (10.4)	16 (16.0)
Ca supplemented	24 (25.0)	18 (18.0)
Vitamin D supplemented	23 (24.0)	32 (32.0)
Bone affecting treatments		
Anti-osteoporotic or HRT	11 (11.5)	5 (5.0)
HTZC	12 (12.5)	11 (11.0)
Systemic GC	3 (3.1)	2 (2.0)
Deleterious	28 (29.2)	40 (40.0)

Results are expressed as mean ± standard deviation for continuous variables and as number of participants (percentage) for categorical variables. Excess alcohol consumption is more than 2 units per day. Antiosteoporotic treatments are raloxifen, bisphosphonates, denosumab, or teriparatide. Deleterious includes proton pump inhibitors, systemic or topic glucocorticoids, aromatase inhibitors, serotonin recapture inhibitors, and antiepileptic treatments.

Abbreviations: BMI, body mass index; Ca, calcium; GC, glucocorticoids; HRT, hormonal replacement therapy; HTZC, hydrochlorothiazide; LT4, levothyroxine.

Table 2 shows BMD and TBS values at baseline and 1-year follow-up by treatment group. One left femur value outlier due to femur anomalies was replaced by right femur readings; femur values were excluded for 1 participant as it was measured on different sides at each exam. Three participants had no hip image because of bilateral total hip prosthesis. At baseline, BMD in the placebo group was 1.122 ± 0.204 g/cm^2, 0.963 ± 0.166 g/cm^2, and 0.890 ± 0.131 g/cm^2 in lumbar spine, total hip, and femoral neck respectively, and 1.133 ± 0.150 g/cm^2, 0.980 ± 0.167 g/cm^2, and 0.908 ± 0.160 g/cm^2, respectively, in the same sites in the LT4 treated group. At baseline, lumbar spine

Table 2. BMD (g/cm^2) and TBS values and percentage changes after 1 year of treatment, by treatment group

	Placebo	LT4 treated	LT4 treated vs. Placebo	*P*-value
Lumbar spine, sample size	53	52		
BMD				
Baseline (g/cm^2)	1.122 ± 0.204	1.133 ± 0.150		
1-year follow-up (g/cm^2)	1.115 ± 0.206	1.140 ± 0.145		
Changes after one year treatment, non-adjusted (%)	–0.6 (–1.8 to 0.6)	0.8 (–0.1 to 1.7)	1.4 (–0.1 to 2.9)	.059
TBS				
Baseline (unitless)	1.325 ± 0.113	1.307 ± 0.968		
1-year follow-up (unitless)	1.331 ± 0.098	1.299 ± 0.108		
Changes after one year treatment, non-adjusted (%)	0.7 (–0.6 to 2.1)	–0.5 (–1.9 to 0.8)	–1.3 (–3.1 to 0.6)	.19
Femur, sample size	57	56		
Total hip				
Baseline (g/cm^2)	0.963 ± 0.166	0.980 ± 0.167		
1-year follow-up (g/cm^2)	0.960 ± 0.166	0.975 ± 0.173		
Changes after one year treatment, non-adjusted (%)	–0.4 (–1 to 0.3)	–0.6 (–1.2 to 0.1)	–0.2 (–1.1 to 0.7)	.61
Femoral neck				
Baseline (g/cm^2)	0.890 ± 0.131	0.908 ± 0.160		
1-year follow-up (g/cm^2)	0.885 ± 0.131	0.901 ± 0.161		
Changes after 1-year treatment, nonadjusted (%)	–0.5 (–1.3 to 0.2)	–0.7 (–2.2 to 0.7)	–0.2 (–1.8 to 1.4)	.82

Results are expressed as mean BMD/TBS ± SD, or as mean percentage BMD/TBS change in one year (95% CI). Between-group comparisons performed using Student's *t*-test.
Abbreviations: LT4, levothyroxine; Pl, placebo; BMD, bone mineral density; TBS, trabecular bone score.

TBS was 1.325 ± 0.113 in the placebo group versus 1.307 ± 0.968 in the LT4-treated group.

BMD percentage changes after 1 year were not statistically different in placebo and LT4-treated participants in nonadjusted analyses (Table 2; Fig. 2) at lumbar spine BMD (–0.6% vs.+0.8%; between group difference +1.4%: 95% CI –0.1 to 2.9, P = .059). Likewise, there were no between-group differences in 1-year change in total hip BMD (–0.2%: 95% CI –1.1 to 0.1, P = .61) or femoral neck BMD (–0.2%: 95% CI -1.8 to 1.4, P = .82). Further adjustment for center and sex did not change the results (22). Unadjusted lumbar spine TBS percentage changes after 1 year were not statistically different between the 2 groups either (–1.3%: 95% CI –3.1 to 0.6, P = .19). We found similar results for TBS both in adjusted analyses and independent of the included vertebrae (all vertebrae, or only those included in BMD analysis after application of International Society for Clinical Densitometry guidelines). Results were similar after excluding participants receiving bone-affecting treatments.

We assessed the effect of LT4 treatment versus placebo on BTMs: There was no statistically significant difference between groups, either in unadjusted (Table 3) or adjusted analyses (22). The results were similar in sensitivity analyses by clinical site or after excluding participants who were receiving bone affecting treatments (data not shown).

In each group, 3 fractures were observed during follow-up, with no significant difference between groups.

Discussion

Our study did not show any harmful effect of LT4 replacement for 1 year on bone health, which we assessed by measuring BMD, TBS, and BTMs in community-dwelling adults aged ≥65 with SHypo. Our study is the largest randomized controlled trial for SHypo treatment to date, and no other study has analyzed SHypo treatment effect on bone microarchitecture as assessed by lumbar spine TBS.

Three earlier RCTs analyzed the effect of LT4 treatment of SHypo in bone with conflicting results. Similar to our study, a double-blinded (n = 31, 75% women, mean age: 68 years, follow-up 10 months) (14) and an unblinded (n = 17 postmenopausal women, follow-up 14 months) (15) RCT did not find a significant difference in BMD change between LT4- and placebo-treated individuals. Meta-analyses on the association of SHypo with fracture risk (10, 12) or BMD (11, 12) showed no difference in observed results when they included or excluded LT4-treated individuals but did not analyze outcomes specifically in this group. Only the double-blinded RCT by Meier et al. (16) reported a statistically but not clinically significant BMD loss at the lumbar

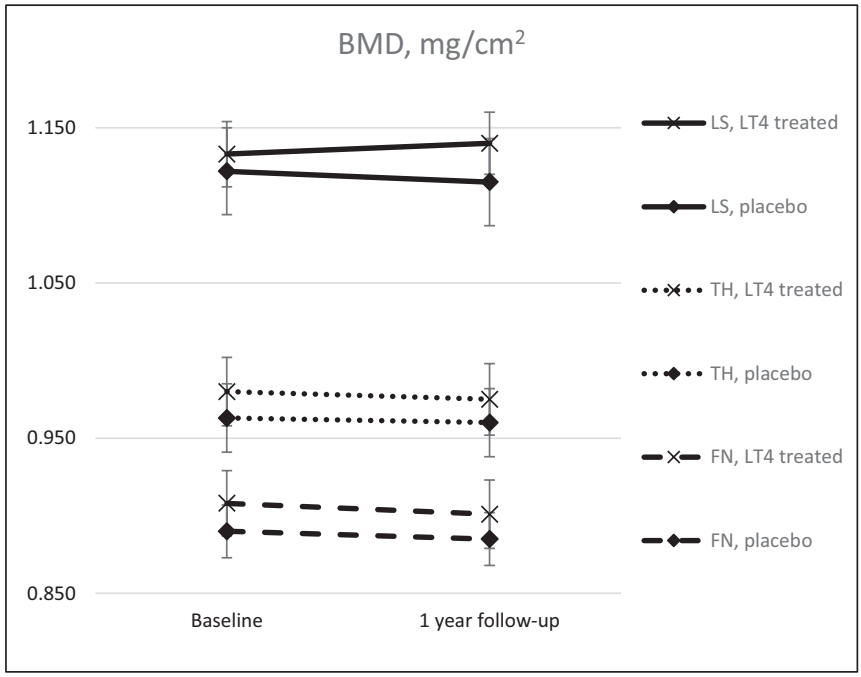

Figure 2. One-year change in bone mineral density (left) at lumbar spine (continuous line), total hip (dotted line), and femoral neck (broken line), in placebo (diamonds) and LT4-treated (cross) patients.

Abbreviations: BMD, bone mineral density; LS, lumbar spine; TH, total hip; FN, femoral neck; LT4, levothyroxine therapy.

spine when it compared treatment to placebo (–1.15%) in 66 women (56.1 years, follow-up 48 weeks). In this study, TSH at follow-up (3.1 ± 0.3 mU/L) was similar to that of our study (3.2 ± 1.5 mU/L) but was higher at baseline (12.8 ± 1.4 mU/L, as compared to 6.3 ± 1.9); a stronger change in TSH could explain the observed results. Of note, 74% were postmenopausal; 37% of these women were on hormone replacement therapy (HRT), but interaction with estrogens was not analyzed. The transient increase in BTMs in the study by Meier et al. (16) may indicate that LT4 treatment restored bone turnover to the usual early menopause values in these almost 2 decades younger participants. Pines et al. (25) reported that the beneficial effects of estrogen replacement on BMD were reduced when it was combined with LT4 replacement therapy. In our study, participants were older than in the Jaeschke et al. (14) RCT, under half were women, and very few participants were on HRT (less than 6.9%) so we could not conduct a separate analysis. Adjustment by sex did not change the magnitude or the statistical significance of the effect. Our results thus accord with those of 2 studies with a similar population (14, 15), suggesting LT4 treatment for SHypo does not harm bone health after 1 year of treatment in individuals over 65; the current study results may however not apply to a younger population.

Only 3 studies analyzed the effect of thyroid function on TBS. In 2 prospective cohorts of participants with thyroid cancer undergoing TSH suppressive therapy for 5 to 10 years (26, 27), excess LT4 treatment had a

Table 3. BTMs values, and nonadjusted percentage changes after 1-year of treatment, by treatment group

	Placebo	LT4 treated	LT4 treated vs. placebo	*P*-value
Sample size	94	96		
sCTX				
Baseline (ng/L)	247.9 ± 148.9	244.7 ± 156.1		
1-year follow-up (ng/L)	252.0 ± 166.8	259.3 ± 149.9		
Changes after one year treatment (%)	9.1 (–1.7 to 19.9)	33.2 (3.1 to 63.3)	24.1 (–7.9 to 56.2)	.14
P1NP				
Baseline (µg/L)	39.5 ± 15.9	40.0 ± 25.1		
1-year follow-up (µg/L)	39.1 ± 17.9	41.8 ± 22.8		
Changes after one year treatment (%)	2.3 (–4.1 to 8.8)	10.7 (3 to 18.3)	8.3 (–1.6 to 18.3)	.10

Results are expressed as mean sCTX/P1NP ± SD, or as mean percentage sCTX/P1NP change in 1-year (95% confidence interval). Between-group comparisons performed using Student's *t*-test.

Abbreviations: BTMs, bone turnover markers; LT4, levothyroxine; Pl, placebo; sCTX, serum C-terminal crosslinked telopeptides; P1NP, procollagen type 1 N-terminal propeptide.

deleterious effect on TBS only in women transitioning from premenopause to postmenopause (26) and no effect in postmenopausal women at treatment initiation (26, 27). But in a euthyroid cohort (28), high-normal free T4 levels, but not TSH values, were associated with low TBS only in postmenopausal women. In our study, as published, TBS changes are not associated to TSH values changes; the link to free T4 cannot be analyzed in detail, as it was not measured at follow-up.

Our conclusions are reinforced by the absence of a significant difference in BTMs changes between both groups at 1 year. Meier et al. (16) obtained similar results by measuring different BTMs, including sCTX, finding no changes at 48 weeks. They did observe a transient increase (at 24 weeks) in treated adults, which they interpreted as restoration of normal remodeling levels that had been decreased in SHypo. We did not have earlier BTMs measures to evaluate this hypothesis.

The greatest strengths of our trial were its double-blind RCT design and that it was the biggest RCT on SHypo and bone (prior studies: n = 17 to 66). Among limitations, it may still be underpowered because we were able to include only 196 individuals. However, the point estimates in the current results went in the opposite direction to published ones, with a nonsignificant BMD increase under LT4 and a slight decrease under placebo, which makes it unlikely that we would have found different results with a larger sample. This trend for an eventual benefit of LT4 treatment on lumbar spine (P = .06 for the difference in adjusted analysis) is most probably due to chance. Also the largest change included in the 95% CIs is a gain of 2.9% spine BMD or a loss of 4.0% for TBS, which makes it very unlikely that we have missed a clinically important difference. We might have been limited by the short follow-up period, although it was the longest blinded trial. Our study cannot address with appropriate power the effect in participants with more pronounced SHypo, due to the low number of participants with TSH >10 mUI/L, although this is also the case in the general population (1). In our study TSH target values were <4.6 mU/L as proposed for older persons (29), with some different expert opinions (7), and we cannot exclude that attaining lower TSH values might have a deleterious effect on bone health. Lumbar spine BMD baseline values were quite high in our participants, suggesting underlying degenerative changes that may interfere with the measures. However, degenerative changes do not affect femoral measures or lumbar spine TBS, which give similar results. Finally, sCTX preanalytical conditions were not standardized (not done fasting in the morning), explaining the large range, but P1NP, which does not depend on these preanalytical conditions, did not change over time or depending on treatment, confirming the absence of LT4 effect on remodeling at 1-year follow-up.

Our results are reassuring in the context of the large number of individuals with SHypo treated with LT4, although this trend may change in the view of latest evidence and guidelines (5). Only a large long-term, placebo-controlled trial will definitively determine if treatment of SHypo adversely affects bone health, and to the best of our knowledge, such a trial is not ongoing or planned in the near future. Until long-term safety is ascertained, we suggest that physicians who wish to treat SHypo in their older patients prescribe the lowest thyroxine dose to achieve a clinical response and keep TSH within the normal range.

Acknowledgments

Financial Support: The TRUST Thyroid trial was supported by research grant (278148) from the European Union FP7-HEALTH-2011 program and by grants from the Swiss National Science Foundation (SNSF 320030-150025 and 320030-172676 to NR), the Swiss Heart Foundation, and Velux Stiftung (grant 974a to NR). THC's research is supported by grants from the Swiss National Science Foundation (PZ00P3-167826). The study medication (levothyroxine and matching placebo) was supplied by Merck KGaA at no cost. Merck played no role in designing, analyzing, or reporting the trial.

Clinical Trial Information: The trial was registered on ClinicalTrials.gov numbers NCT01660126 (TRUST Thyroid trial) and NCT02491008 (Skeletal outcomes).

Additional Information

Correspondence and Reprint Requests: Elena Gonzalez Rodriguez, Center of Bone Diseases, Rheumatology Service, CHUV, Lausanne University Hospital, Rue Pierre-Decker 4, Lausanne, CH-1011 Switzerland. E-mail: elena.gonzalez-rodriguez@chuv.ch.

Disclosure Summary: EGR, MS, CDG, MF, THC, ALL, MRB, NAvV, DvH, PMK, JG, SM, RGJW, DJS, DA, DCB, and NR have nothing to declare. DH holds stock in Medimaps Group, the makers of the Trabecular Bone Score software. Merck KGaA, Darmstadt, Germany, reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

Data availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;**160**(4):526–534.
2. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;**87**(2):489–499.
3. Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA*. 2018;**320**(13):1349–1359.
4. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med*. 2017;**376**(26):2534–2544.
5. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ*. 2019;**365**:l2006.
6. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;**22**(12):1200–1235.
7. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;**2**(4):215–228.
8. Rodriguez-Gutierrez R, Maraka S, Ospina NS, Montori VM, Brito JP. Levothyroxine overuse: time for an about face? *Lancet Diabetes Endocrinol*. 2017;**5**(4):246–248.
9. Aubert CE, Floriani C, Bauer DC, et al. Thyroid function tests in the reference range and fracture: individual participant analysis of prospective cohorts. *J Clin Endocrinol Metab*. 2017;**102**(8):2719–2728.
10. Blum MR, Bauer DC, Collet TH, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA*. 2015;**313**(20):2055–2065.
11. Segna D, Bauer DC, Feller M, et al. Association between subclinical thyroid dysfunction and change in bone mineral density in prospective cohorts. *J Intern Med*. 2018;**283**(1):56–72.
12. Yang R, Yao L, Fang Y, et al. The relationship between subclinical thyroid dysfunction and the risk of fracture or low bone mineral density: a systematic review and meta-analysis of cohort studies. *J Bone Miner Metab*. 2018;**36**(2):209–220.
13. Viniol A, Hickstein L, Walker J, Donner-Banzhoff N, Baum E, Becker A. Influence of thyroid hormone therapy on the fracture rate - a claims data cohort study. *Bone*. 2016;**86**:86–90.
14. Jaeschke R, Guyatt G, Gerstein H, et al. Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med*. 1996;**11**(12):744–749.
15. Ross DS. Bone density is not reduced during the short-term administration of levothyroxine to postmenopausal women with subclinical hypothyroidism: a randomized, prospective study. *Am J Med*. 1993;**95**(4):385–388.
16. Meier C, Beat M, Guglielmetti M, Christ-Crain M, Staub JJ, Kraenzlin M. Restoration of euthyroidism accelerates bone turnover in patients with subclinical hypothyroidism: a randomized controlled trial. *Osteoporos Int*. 2004;**15**(3):209–216.
17. Shevroja E, Lamy O, Kohlmeier L, Koromani F, Rivadeneira F, Hans D. Use of Trabecular Bone Score (TBS) as a complementary approach to Dual-energy X-ray Absorptiometry (DXA) for fracture risk assessment in clinical practice. *J Clin Densitom*. 2017;**20**(3):334–345.
18. Stott DJ, Gussekloo J, Kearney PM, et al. Study protocol; thyroid hormone replacement for untreated older adults with subclinical hypothyroidism - a randomised placebo controlled trial (TRUST). *BMC Endocr Disord*. 2017;**17**(1):6.
19. Hans D, Downs RW Jr, Duboeuf F, et al. Skeletal sites for osteoporosis diagnosis: the 2005 ISCD official positions. *J Clin Densitom*. 2006;**9**(1):15–21.
20. Padlina I, Gonzalez-Rodriguez E, Hans D, et al. The lumbar spine age-related degenerative disease influences the BMD not the TBS: the Osteolaus cohort. *Osteoporos Int*. 2017;**28**(3):909–915.
21. Black DM, Thompson DE, Bauer DC, et al. FIT Research Group. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab*. 2000;**85**(11):4118–4124.
22. Gonzalez Rodriguez E, Stuber M, Del Giovane C, et al. Skeletal effects of levothyroxine for subclinical hypothyroidism in older adults: a TRUST randomized trial nested study. *Zenodo*. 2019. Deposited 18 August 2019. http://doi.org/10.5281/zenodo.3370733.
23. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int*. 1994;**4**(6):368–381.
24. McCloskey EV, Odén A, Harvey NC, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res*. 2016;**31**(5):940–948.
25. Pines A, Dotan I, Tabori U, et al. L-thyroxine prevents the bone-conserving effect of HRT in postmenopausal women with subclinical hypothyroidism. *Gynecol Endocrinol*. 1999;**13**(3):196–201.
26. De Mingo Dominguez ML, Guadalix Iglesias S, Martin-Arriscado Arroba C, et al. Low trabecular bone score in postmenopausal women with differentiated thyroid carcinoma after long-term TSH suppressive therapy. *Endocrine*. 2018;**62**(1):166–173.
27. Kim EH, Jeon YK, Pak K, et al. Effects of thyrotropin suppression on bone health in menopausal women with total thyroidectomy. *J Bone Metab*. 2019;**26**(1):31–38.
28. Hwangbo Y, Kim JH, Kim SW, et al. High-normal free thyroxine levels are associated with low trabecular bone scores in euthyroid postmenopausal women. *Osteoporos Int*. 2016;**27**(2):457–462.
29. Javed Z, Sathyapalan T. Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits. *Ther Adv Endocrinol Metab*. 2016;**7**(1):12–23.