



Thyroid-stimulating hormone is associated with trabecular bone score and 5-year incident fracture risk in euthyroid postmenopausal women: the OsteoLaus cohort

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Received: 23 April 2021 / Accepted: 21 July 2021
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Abstract

Summary Thyroid-stimulating hormone (TSH) excess or deficiency influences bone density and fracture risk. Nevertheless, does TSH in the reference range influence bone health? In euthyroid postmenopausal women, TSH levels in the reference range were positively associated with trabecular bone score and negatively with incident fractures, without affecting BMD.

Purpose Subclinical hyperthyroidism is associated with low bone mineral density (BMD) and increased fracture risk. In healthy postmenopausal women, association between thyroid-stimulating hormone (TSH) in the normal range and BMD is contradictory. Trabecular bone score (TBS), an index of bone micro-architecture, is often decreased in secondary osteoporosis (OP). The aim was to determine the association between thyroid hormones (TSH, fT4) and BMD, TBS, and the incident 5-year OP fractures, in euthyroid post-menopausal women.

Methods We assessed 1475 women of the CoLaus/OsteoLaus cohort. We evaluated BMD at lumbar spine, femoral neck and total hip, lumbar spine TBS, and vertebral fracture with DXA. Incident major OP fractures were evaluated 5 years later by questionnaire and DXA. Women with anti-osteoporotic, antidiabetic, thyroid-modifying, hormone replacement, or systemic corticoid treatment were excluded.

Results Five hundred thirty-three women (age 68.4 ± 7.3 years, BMI 25.9 ± 4.6 kg/m², TSH 2.03 ± 0.87 mU/l, fT4 15.51 ± 1.85 pmol/l) met the inclusion criteria. There was no significant association between TSH or fT4 and BMD measures at any site. A positive association was found between TSH and TBS ($\beta = 0.138$, $p < 0.01$), even after adjusting for age, BMI, and duration of menopause ($\beta = 0.086$, $p < 0.05$). After a 5-year follow-up, women with incident major OP fractures had lower TSH levels (1.77 ± 0.13 vs. 2.05 ± 0.04 mU/l, $p < 0.05$) than women without fractures, while no difference was found for fT4.

Conclusion In euthyroid postmenopausal women, TSH levels were positively associated with TBS and negatively with incident fractures, without affecting BMD. Further studies are needed to evaluate the influence of thyroid hormones on TBS.

Keywords Thyroid hormones · Fractures · Osteoporosis · Bone mineral density · Trabecular bone score

Introduction

Osteoporosis is characterized by a deterioration of bone microarchitecture and a loss of bone mineral density (BMD), leading to an increase of fracture risk. Worldwide, about 50% of women and 20% of men over 50 years will be affected by an osteoporotic fracture [1]. However, half of fractures occurs in women and men who do not have a low BMD [2–4]. The FRAX® tool includes clinical data to predict the 10-year fracture risk [5], while the trabecular bone score (TBS) is a clinical tool to quantify the texture variations extracted from the lumbar spine dual-energy X-ray absorptiometry (DXA) [6]. TBS provides information on bone micro-architecture that is complementary to BMD and

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FRAX®, and independently and significantly predicts fracture [7]. TBS is slightly associated with BMD but not with degenerative disease or osteoarthritis [8]. TBS also gives an accurate result of bone texture in patients aged over 60 years, where the lumbar spine BMD tend to be overestimated [9].

Thyroid function is one of the multiple risk factors for osteoporosis. Thyroid dysfunction is common in the general population, especially in postmenopausal women, and increases with age. Hypothyroidism is present in 4.6% of the US population and hyperthyroidism in 1.3% [10]. The prevalence of subclinical hypothyroidism (defined by an elevated thyroid-stimulating hormone (TSH) level with free thyroxine (fT4) within the reference range) in the adult population ranges from 4 to 20%, depending on age, sex, body mass index (BMI), race, dietary iodine intake, and threshold serum TSH levels used [11]. Hypothyroidism results in low bone turnover with a decrease of bone formation and resorption, but the consequences on BMD in adults are debated. In a meta-analysis including 313,557 individuals, subclinical hypothyroidism was associated with an increased femoral neck BMD in women [12], while in another meta-analysis including 762,401 person-years follow-up, there was no association between subclinical hypothyroidism and fracture [13]. Hyperthyroidism is a well-known cause of excessive bone remodeling, associated with accelerated bone loss leading to osteoporosis. The prevalence of subclinical hyperthyroidism varies between 1 and 9.8% [11]. Compared to euthyroidism, subclinical hyperthyroidism is associated with an increased bone loss at the femoral neck [14]. The negative effect on lumbar spine BMD and total hip BMD was only present at the lowest TSH values. High thyroid function, even at high-normal levels, increases fracture risk [13, 15].

In euthyroid adults, the combination of a TSH in the lower normal reference range and a fT4 in the higher normal reference range are associated with an increased risk of hip fracture [15]. Published studies in euthyroid individuals suggest that fT4 influences BMD, but only in case of high value and only on some measurement sites. There is some controversy as to whether alterations in TSH, or peripheral hormones, or both, are necessary to affect bone homeostasis. TBS is often decreased in secondary osteoporosis [16]. To date, only one study has characterized the relationship between thyroid function and TBS in euthyroid men and postmenopausal women [17]. Higher fT4 levels within the normal reference range were associated with deterioration of TBS in healthy euthyroid postmenopausal women, without affecting the BMD. In the TRUST study, a one-year levothyroxine treatment had no effect on TBS in older adults with subclinical hypothyroidism [18].

Hence, this study aimed to determine the association between TSH and fT4 in the normal range and BMD, TBS, and incident fractures at 5 years in a cohort of Caucasian postmenopausal women: the OsteoLaus study.

Materials and methods

Settings

OsteoLaus is a sub-study of the CoLausPsyCoLaus study, an ongoing prospective study aiming to assess the determinants of cardiovascular and psychiatric diseases using a population-based sample [19, 20]. Information on the methodology of the CoLausPsyCoLaus study can be obtained at www.colaus-psycolaus.ch. Briefly, the CoLaus study was initiated in 2003; it included 6733 men and women aged 35 to 75 years living in the city of Lausanne, Switzerland. Follow-up has been done every 5 years, first in 2009, second in 2014, and third in 2018.

The goal of OsteoLaus is to obtain more precise fracture risk models and to evaluate the link between cardiovascular diseases and osteoporosis [21]. Between September 2009 and September 2012, all women aged between 50 and 80 years from the CoLausPsyCoLaus study were invited to participate in OsteoLaus. Of the initial 1704 women invited, 1500 (88%) accepted, and 1475 were included; 98.4% were Caucasian. Follow-up of OsteoLaus has been done every 2.5 years, first in 2012, second in 2015, and third in 2018.

Participants

The study was retrospective. Participants in the 5-year follow-up of OsteoLaus were included ($n = 1212$). Blood TSH and free T_4 were assessed at the first CoLaus follow-up, corresponding to the baseline OsteoLaus visit. Participants were sequentially excluded if they 1) had any anti-osteoporotic, antidiabetic, thyroid-modifying, hormone replacement or systemic corticoid treatment; 2) had no TSH or fT4 data, or no covariates; 3) presented with TSH or fT4 levels outside the normal reference values, and 4) had no densitometry or TBS data.

The primary endpoint of this study was to analyze the relation between fT4 and TSH in the normal range and bone measurements parameters (lumbar spine BMD, femoral neck BMD, total hip BMD, and TBS). The primary endpoint included an exploratory comparison of two subgroups divided by the medians of TSH and fT4: high fT4/low TSH and low fT4/high TSH. The secondary endpoint was to analyze the association between fT4 and TSH measured at baseline and the incidence of major osteoporotic fracture 5-year later.

Bone parameters

BMD, TBS, and prevalence of fractures were assessed at baseline OsteoLaus visit using the following: (1) a

questionnaire on potential clinical risk factors for fracture/osteoporosis, and on conditions affecting bone metabolism; (2) a spine (L1 to L4) and femur dual DXA scan using the Discovery A System (Hologic, Waltham, MA, USA); (3) a blind central processing of TBS (TBS iNsite® v3.03, Med-Imaps, Mérignac, France) based on the previously acquired antero-posterior spine DXA scan; (4) a vertebral fracture assessment (VFA) by two experienced clinicians using the semiquantitative approach of HK Genant [22]. Spine and femur DXA were analyzed according to the International Society for Clinical Densitometry (ISCD) recommendations [23]. The current TBS software is based on an algorithm accounting for BMI. We also used the research TBS algorithm which takes into account the soft tissue thickness TBS TTH [24]. Major osteoporotic fractures included vertebrae (clinical or radiologic grade 2/3 on VFA), hip, pelvis, humerus and radius, occurring spontaneously or after falling from the patient's own height. Incidence of major osteoporotic fractures was assessed similarly during the second OsteoLaus follow-up after 5 years.

Blood measurements

Assays were performed by the CHUV Clinical Laboratory on fresh blood samples within 2 h after collection. TSH and fT_4 were assessed by chemiluminescence (ECLIA) on a Cobas e 602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch coefficients of variation ranging between 1.1 and 3.0% for TSH and between 2.7 and 5% for fT_4 . Technical documentation (in French) can be provided upon request. Reference ranges are 0.27 to 4.20 mU/L for TSH and 12 to 22 pm/L for fT_4 [25]. Serum and urinary creatinine were measured by the Jaffe kinetic compensated method (2.9–0.7%). Estimated glomerular filtration rate (eGFR) was computed using the MDRD equation.

Covariates

Height and weight were measured with the participant barefoot and in minimum clothing, using a portable stadiometer/electronic scale (Seca version 216, Seca, Chino, CA, USA) with a precision of 0.1 cm and 0.1 kg, respectively. BMI was calculated by dividing the individual's weight by height squared (kg/m^2). Age, history of disease, smoking status, alcohol consumption, and menopausal duration were assessed by questionnaire. Menopause duration was categorized into \leq and $>$ 10 years.

Statistical methods

Statistical analysis was conducted using Stata v.16 (Stata Corp, College Station, TX, USA). Prevalence levels and corresponding 95% confidence intervals for deteriorated TBS

(values $<$ 1.23) or BMD (values $<$ -2.5 SD) were computed using the exact binomial procedure. Bivariate associations were conducted using Spearman correlations; multivariate associations were conducted using linear regression and the results were expressed as beta standardized coefficients. Multivariate linear regression used bone measures as the dependent variable and thyroid hormones as the independent variable, with adjustment for age (continuous), BMI (continuous), and duration of menopause (categorical). Statistical significance was considered for a two-sided test with $p < 0.05$. As previous studies suggested that low-normal TSH (i.e., $<$ 1 mU/l in the normal range) may favor skeletal fragility and higher risk of fractures, a sensitivity analysis was conducted by comparing bone parameters according to three groups of TSH ($<$ 1, 1–2.5, and $>$ 2.5 mU/l). Further comparisons between participants with TSH levels below or above 1 mU/L were conducted among participants who experienced fragility fractures after 5-year follow-up. As bone parameters at baseline were strongly correlated (Spearman r ranging from 0.366 to 0.851, all $p < 0.0001$), several multivariable analyses adjusting for other covariates and for one parameter at the time were conducted.

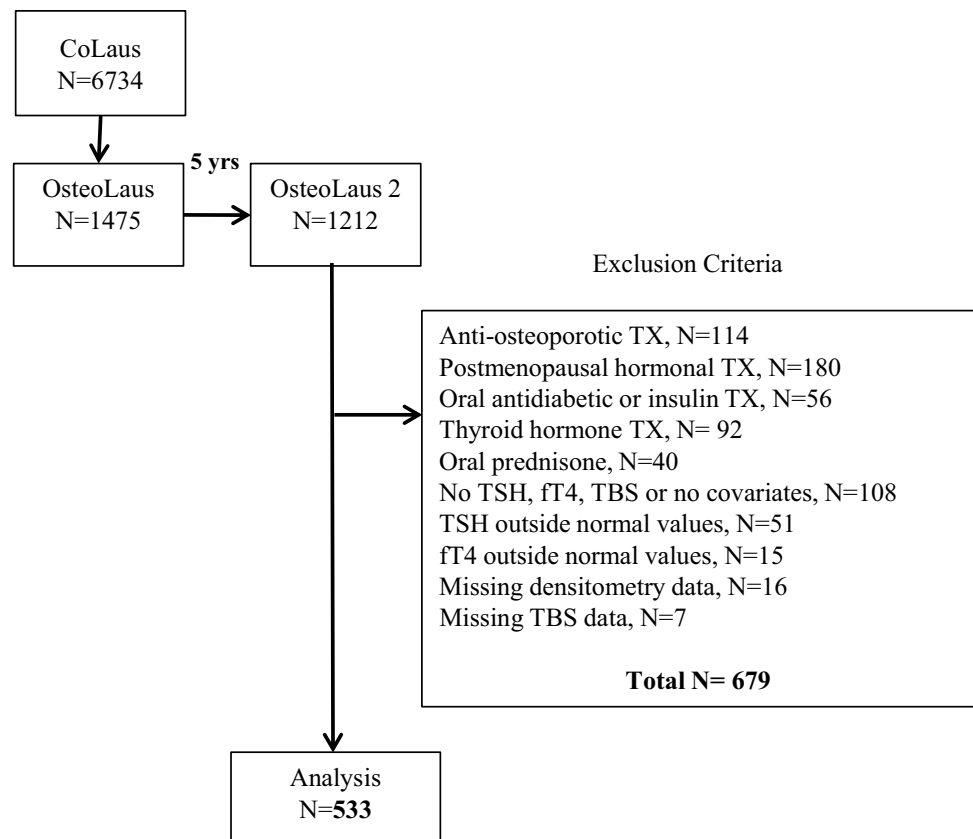
Ethics committee

The CoLaus and OsteoLaus studies were approved by the Institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (Commission cantonale d'éthique de la recherche sur l'être humain. Available from: <http://www.cer-vd.ch>). The studies were performed in agreement with the Helsinki Declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their written informed consent before entering the study.

Results

Participants' selection and characteristics

The selection procedure of the participants is shown in Fig. 1. Of the initial 1212 participants, 533 (45.6%) had normal values for TSH and fT_4 (Supplementary Material, Fig. 1). The clinical characteristics of excluded and included participants are provided in Table 1. There were no significant differences between the two groups except for age, with the excluded participants being 1.5 years older. No included participant has further confounders such as renal failure ($\text{GFR} < 15 \text{ ml}/\text{min}/1.73\text{m}^2$), anticancer drugs, genetic bone disease or malformation, inflammatory bowel disease, gastrectomy, anorexia, neoplasm

Fig. 1 Flowchart with exclusion criteria**Table 1** Baseline characteristics of included and excluded participants

	Baseline	Included	Excluded	<i>p</i> -value
<i>n</i>	1212	533	679	-
Age (year)	69.27 ± 7.38	68.44 ± 7.32	69.93 ± 7.37	0.001
BMI (kg/m ²)	26.07 ± 4.72	25.88 ± 4.55	26.22 ± 4.86	0.221
Duration of menopause (years)	20.09 ± 9.50	19.01 ± 9.34	21.20 ± 9.53	0.000
eGFR (ml/min/1.73 m ²)	71.88 ± 13.66	72.24 ± 12.90	71.59 ± 14.25	0.410
Current smoker	15.19%	14.82%	15.49%	0.749
Femoral neck BMD <i>T</i> -score	-1.225 ± 0.874	-1.285 ± 0.820	-1.177 ± 0.914	0.034
Total hip BMD <i>T</i> -score	-0.876 ± 1.014	-0.939 ± 0.970	-0.824 ± 1.046	0.053
Lumbar spine BMD <i>T</i> -score	-0.640 ± 1.640	-0.747 ± 1.572	-0.553 ± 1.690	0.043
TBS	1.314 ± 0.095	1.315 ± 0.094	1.313 ± 0.096	0.705
Fractures at 2.5 years	6.19% (75)	5.63% (30)	6.63% (45)	0.474
Fractures at 5 years	9.65% (117)	8.26% (44)	10.75% (73)	0.144

Fractures accounted are the major osteoporotic fractures: non traumatic vertebral, hip, humerus, and forearm

or other secondary osteoporosis. The prevalence of BMD < -2.5 DS was 10.9% (95% CI 8.4–13.8) at lumbar spine, 3.9% (95% CI 2.5–6.0) at total hip, and 5.3% (95% CI 3.5–7.5) at femoral neck. Deteriorated TBS was present in 18.4% (95% CI 15.2–21.9).

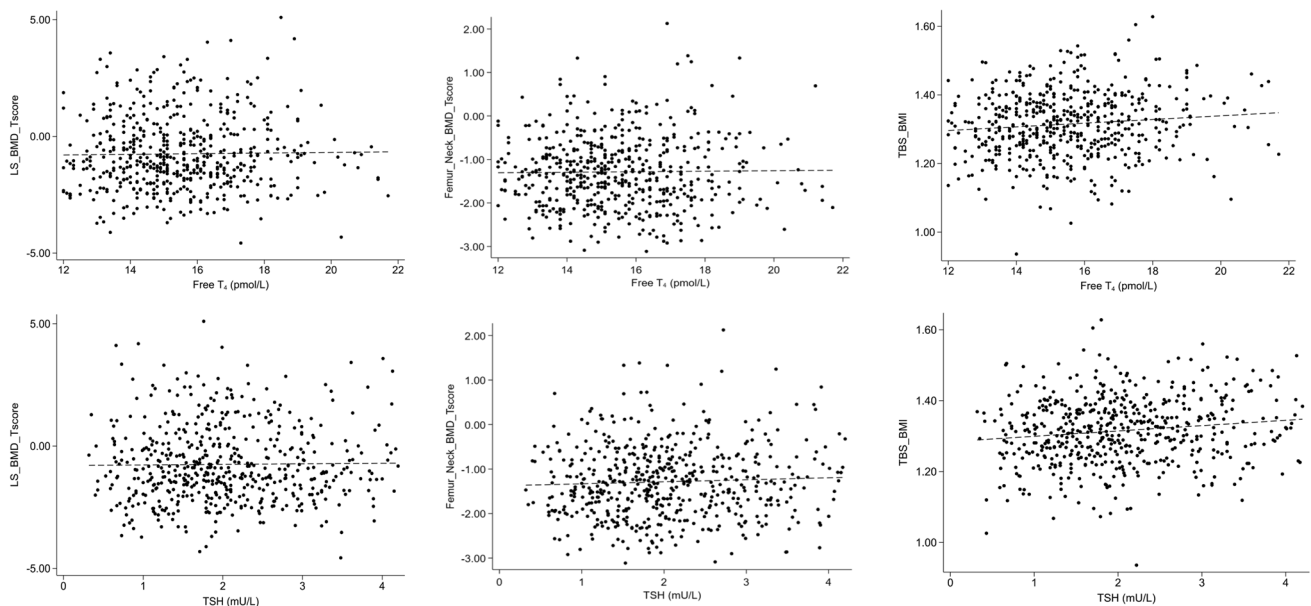
TSH, fT4, and bone parameters: main analysis

There was no association between fT4 and lumbar spine or hip BMD (Table 2 and Fig. 2). As the results for TBS and TBS TTH (algorithm used for research) were the same, we

Table 2 Association between TSH and ft4 and BMD and TBS

	Spearman	<i>p</i> -value	Beta, model 1	<i>p</i> -value	Beta, model 2	<i>p</i> -value
TSH						
Femoral neck BMD <i>T</i> -score	0.040	0.355	0.048	0.271	0.023	0.576
Total hip BMD <i>T</i> -score	0.058	0.181	0.064	0.142	0.045	0.256
Lumbar spine BMD <i>T</i> -score	0.015	0.727	0.013	0.771	0.010	0.805
TBS	0.132	0.002	0.138	0.001	0.087	0.031
ft4						
Femoral neck BMD <i>T</i> -score	-0.010	0.821	0.013	0.758	-0.014	0.732
Total hip BMD <i>T</i> -score	0.002	0.966	0.014	0.755	-0.017	0.669
Lumbar spine BMD <i>T</i> -score	0.020	0.654	0.016	0.706	0.006	0.518
TBS	0.094	0.026	0.105	0.015	0.066	0.101

Results are expressed as Spearman rank correlation or beta coefficients obtained from linear regression. Statistical analysis performed using Spearman rank correlation or linear regression. Model 1: unadjusted; model 2: adjusted for age (continuous), body mass index (continuous), and duration of menopause (\leq or $>$ 10 years)

**Fig. 2** Association between ft4 and TSH and lumbar spine (LS) BMD *T*-score, femoral neck BMD *T*-score, and TBS with regression line

give only the results for the TBS used in clinical routine. ft4 was positively associated with TBS ($\beta=0.105$, $p=0.015$) in the unadjusted model but disappeared after adjustment. TSH was positively associated with TBS ($\beta=0.138$, $p<0.01$) in the unadjusted model, and remained significant after adjustment for age, BMI and duration of menopause ($\beta=0.087$, $p=0.031$).

TSH, ft4, and bone parameters: exploratory analysis

The purpose of this exploratory analysis was to detect a difference within the extremes of the normal ft4 and TSH values. We compared two subgroups divided by the medians of TSH and ft4: high ft4/low TSH ($n=137$) and low

ft4/high TSH ($n=136$). Neither BMD values at the three measurement sites, nor TBS values differed between the two groups in the bivariate and multivariable analyses (Table 3). In the Supplementary Table 1, we analyzed TBS, BMD and fractures in subjects stratified in three groups TSH categories (TSH < 1 mU/l, TSH 1–2.5 mU/l and TSH > 2.5 mU/l). The conclusions do not change relative to the comparison between high ft4/low TSH and low ft4/high TSH groups.

Incident fractures

After 2.5 and 5 years, 30 and 44 participants, respectively, had a major incident osteoporotic fracture. Among these 44 participants, six had vertebral fracture and nine had

Table 3 Association between BMD and TBS with categories of ft4 and TSH

	High ft4, low TSH	Low ft4, high TSH	<i>p</i> -value
<i>n</i>	137	136	
Femoral neck <i>T</i> -score			
Model 1	-1.28±0.88	-1.23±0.77	0.637
Model 2	-1.3±0.07	-1.22±0.07	0.357
Total hip <i>T</i> -score			
Model 1	-0.92±1.04	-0.94±0.89	0.888
Model 2	-0.95±0.07	-0.90±0.07	0.631
Lumbar spine <i>T</i> -score			
Model 1	-0.71±1.64	-0.77±1.46	0.752
Model 2	-0.74±0.13	-0.74±0.13	0.988
TBS			
Model 1	1.31±0.1	1.31±0.09	0.837
Model 2	1.31±0.01	1.32±0.01	0.522

Results are expressed as average±standard deviation or as multivariable-adjusted average±standard error. Model 1: unadjusted; model 2: adjusted for age (continuous), body mass index (continuous), and duration of menopause (≤ or > 10 years)

Table 4 Association between TSH and ft4 and incident major osteoporotic fractures at 2.5 and 5 years

	<i>n</i>	TSH (mU/L)		ft4 (pmol/L)	
		Model 1	Model 2	Model 1	Model 2
2.5 years		0.074	0.134	0.494	0.613
No	503	2.05±0.86	2.04±0.04	15.5±1.9	15.5±0.1
Yes	30	1.75±0.90	1.80±0.16	15.3±1.6	15.3±0.3
5 years		0.013	0.038	0.975	0.746
No	489	2.06±0.87	2.05±0.04	15.5±1.9	15.5±0.1
Yes	44	1.72±0.83	1.77±0.13	15.5±1.8	15.6±0.3

Results are expressed as average±standard deviation or as multivariable-adjusted average±standard error. Model 1: unadjusted; model 2: adjusted for age (continuous), body mass index (continuous), and duration of menopause (≤ or > 10 years)

two major osteoporotic fractures. After a 5-year follow-up, participants with major osteoporotic fractures had lower TSH levels than participants without fracture in the bivariate analysis (1.77 ± 0.13 vs. 2.05 ± 0.04 mU/l, $p = 0.038$, Table 4); this association remained after adjusting for age, BMI, and menopause duration. No association between TSH and incident fractures at 2.5 years was detected. There was no association between ft4 and the incident fracture after 2.5 or 5 years. Among participants who experienced fragility fractures after 5-year follow-up, we provided in Supplementary Table 2 the distribution of TBS and BMD in those with TSH below 1 mU/L and in those with TSH > 1 mU/l. We chose the 5-year follow-up to have the maximum number of participants and thus the highest statistical power possible. There was no difference in BMD or TBS values. There were

strong correlations between all baseline variables (Spearman r ranging from 0.366 to 0.851, all $p < 0.0001$). Hence, to avoid collinearity, it was decided to adjust on a single variable, and several models were applied, one for each variable. The results are provided in Supplementary Table 3. The results confirm those indicated in Table 4, i.e., the probable existence of an association between TSH levels and incident fractures.

Discussion

In this cross-sectional study of postmenopausal euthyroid women, there was a positive association between TSH and TBS. In the longitudinal analysis, there was an inverse association between TSH and incident major osteoporotic fractures at 5 years.

Association between ft4 or TSH and BMD or TBS in euthyroid postmenopausal women

We found a positive association between TSH and TBS in postmenopausal women. The association between ft4 and TBS on bivariate analysis disappeared on multivariable analysis. The finding of an association between TSH and TBS, but not ft4 and TBS, is probably due to the higher sensitivity of TSH as a biomarker and the insufficient power to identify an association with ft4. In a Korean study including 648 postmenopausal women, ft4 was negatively associated with TBS, while no association was found between TSH and TBS or BMD [17]. Although both studies go in the same direction (a lower thyroid function is associated with higher TBS), the difference can be due to differences in participants: ethnicity, younger age, lower BMI, the use of a different DXA facility (GE Lunar Prodigy vs. Hologic) and the exclusion criteria. Two studies of thyroid cancer patients receiving exogenous T4 treatment to suppress TSH found the same trends. In 273 postmenopausal women with differentiated thyroid carcinoma, duration of TSH suppression was negatively correlated with lumbar spine TBS levels, but not with BMD [26]. Similar results were found in 84 Spanish postmenopausal women (but not in the 61 premenopausal women) treated with thyroid suppression therapy for differentiated thyroid carcinoma [27]. The authors concluded that TBS should be considered in the evaluation of these postmenopausal women for fracture risk evaluation. This association with altered TBS, but not with altered BMD, has been described in other causes of secondary osteoporosis (type 2 diabetes mellitus, chronic kidney disease glucocorticoids, HIV) [16].

We and the previously cited studies [17, 26, 27] found no association between TSH or ft4 and BMD, contrary to other studies [12, 28–31]. Mazziotti G et al. found an

association between low-normal TSH values and high prevalence of vertebral fractures in women, independently of thyroid hormones, age and BMD [29]. In 1278, European postmenopausal women (68 ± 7 years), higher ft_4 levels within the normal range were associated with lower hip BMD [30]. There was no association between lumbar spine BMD and ft_4 . Therefore, it is possible that participants with hyper- or hypothyroidism might have been included (2.5th and 97.5th percentiles values for ft_4 and TSH). In a sample of 1426 peri-menopausal Dutch women, ft_4 levels in the highest quartile within the normal range, but not low serum TSH, were independently related to decreased BMD at lumbar spine [31]. In a meta-analysis including 313,557 individuals (mean age from 51 to 85 years), in women, subclinical hyperthyroidism was associated with lower distal forearm BMD, whereas subclinical hypothyroidism (high TSH with normal ft_4) was associated with higher femoral neck BMD [12]. The differences observed at lumbar spine between both studies may be related to the age of the participants. As TBS is not associated with degenerative disease or osteoarthritis, it gives an accurate result in patients over 60 year, where the lumbar spine BMD is overestimated [9].

The protective effect of TSH on bone has been demonstrated in in vitro studies by uncoupling bone resorption and formation, leading to an increase in bone mass [32–34]. Only one in vitro study suggested that the effect of the thyrotropic axis on bone is due to the thyroid hormone effects instead of the direct effects of TSH itself [35]. A study in 10 thyroidectomized postmenopausal women treated with a recombinant TSH injection showed an increase in bone formation markers; this result was absent in the premenopausal group [36]. Another study including women treated with L-thyroxine suppressive therapy for thyroid carcinoma found a decrease in bone resorption markers and an increase formation markers after short term recombinant human TSH stimulation in postmenopausal women but not in premenopausal women [37]. It was therefore important to exclude women taking hormone replacement therapy from our analysis. In the TRUST randomized controlled trial, after 1 year of levothyroxine daily substitution (25–50 μ g), there was no significant change on BMD and TBS in the 737 men and women included, and there was no difference to placebo-treated participants [18]. The population was older than 65 years and had a subclinical hypothyroidism [18]. This interventional study suggests that even if there is an association between TSH and/or ft_4 and BMD and/or TBS, a modest change in ft_4 and/or TSH values does not modify BMD and/or TBS in the short term. This could mean that a long-term change is needed to highlight a clinical significance.

Influence of extreme ft_4 /TSH relationships on BMD or TBS in euthyroid postmenopausal women

This exploratory analysis was performed to highlight a possible difference between women close to subclinical hyperthyroidism or sub-clinical hypothyroidism values. For this analysis, we assumed that TSH and ft_4 have an independent and inverse effect on BMD and TBS. Neither BMD values at the three measurement sites, nor TBS values differed between the two groups in the bivariate and multivariable analyses. The lack of difference observed may be due to the small sample size of the groups, or the fact that only TSH or only ft_4 influences the BMD and TBS values. In a sample of 1426 peri-menopausal Dutch women, the BMD of participants with low TSH and high ft_4 did not differ from that of other participants [29]. These results suggest that the interaction between thyroid hormones and the bone measurements in euthyroid subjects is small. It is still important to analyze these results with caution due to the potential bias from the categorization, and the unknown length of time of being in one or the other of the categories.

Association between ft_4 or TSH and incident osteoporotic fractures in euthyroid postmenopausal women

We found that women in the lower normal TSH range had a higher incidence of major osteoporotic fracture 5 years later. Our results are consistent with the association found between TSH and TBS. In the OPUS 6-year prospective cohort study ($n = 1278$), higher ft_4 was associated with an increased risk of incident nonvertebral fracture, and higher TSH with a decrease of this risk [28]. In the OPENTHYRO register ($n = 222,138$, mean follow-up 7.5 years), the risk of hip fractures increased with each SD decrease of TSH in both genders, while the risk of major osteoporotic fractures increased only in women (HR 1.32, 95% CI 1.19–1.46) [38]. In a meta-analysis including 70,298 participants (mean age 64 years, 61.3% women), subclinical hyperthyroidism was associated with an increased risk of hip and other fractures, particularly among participants with TSH levels below 0.10 mU/L [13]. In another meta-analysis including 313,557 participants, subclinical hyperthyroidism was associated with a higher risk of all types of fractures [12]. Thus, there is a clear association in the literature between TSH and decreased risk of fracture [29]. However, caution should be used when interpreting the results because of the heterogeneity of the populations, and of the considered normal range for TSH values.

Strengths and limitations

The main strength of this study is the design of the OsteoLaus and CoLaus cohorts. All blood tests and DXA exams were done under the same conditions. The same thyroid hormone normal values were used for all participants. Another strength is the purity of the studied sample reached through the exclusion criteria and confounders for osteoporosis. For example, we excluded the diabetic patients whose TBS is decreased while their BMD is paradoxically increased [39]. The limitations of the study are related to the relatively small sample size. In addition, due to the exclusion criteria, the results are not generalizable to all postmenopausal euthyroid women. We have not measured thyroid autoantibodies. Autoimmunity per se may affect bone structure. We have not measured fT3, which probably has a regulatory role. This could support measurement of fT3, fT4, and TSH in future studies, to better understand the link between thyroid hormones and bone. The effect of thyroid hormones on muscle has also been documented [38, 40]. This effect could alter the association between thyroid hormones and a marker of bone health. Inherent biases are the inter/intra individual or seasonal variation and the genetic polymorphism of the thyroid hormones. Minimizing those effects was possible thanks to the study size and the systematic collection of blood samples on the same time of the day [41]. TSH values were measured at baseline and not during the follow-up. This is a potential limitation of the study because the time of exposure to low and low-normal TSH may be an important factor influencing skeletal health [42].

Conclusion

This is the first study showing an association between TSH in the normal range and TBS, and with the fracture incidence after 5 years. Lower TSH may lead to a weaker bone structure and a higher fracture incidence without affecting the BMD. Even if there is a normal BMD, the TBS can already be degraded. The TBS seems then to be a more powerful tool to assess the fracture risk for secondary osteoporosis. It could help the clinician to assess smaller change in bone microarchitecture. Larger studies are needed to evaluate the influence of TSH on bone health.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00198-021-06081-4>.

Acknowledgements The authors wish to thank all the participants of the study and the clinical teams who evaluated them.

Author contribution CV wrote most of the article; PMV collected data, made part of the statistical analysis, and wrote part of the article; OL

revised the article for important intellectual content and wrote part of the article. PMV had full access to the data. OL is the guarantor of the study. GW, EGR, and DH participated in the development of the study and revised the article.

Funding Open Access funding provided by Université de Lausanne. The OsteoLaus study is supported by research grants from Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois strategic plan funds) and the Swiss National Science Foundation (grant 32473B_156978). The CoLausIPsyCoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CS0-122661, 33CS30-139468, 33CS30-148401, and 32473B-182210).

Data availability Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References. The data presented in this study are available upon reasonable request to the corresponding author. The data are not publicly available due to the fact of confidentiality reasons.

Code availability Not applicable.

Declarations

Ethics approval and consent to participate The CoLaus and OsteoLaus studies were approved by the Institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (Commission cantonale d'éthique de la recherche sur l'être humain. Available from: <http://www.cer-vd.ch>). The studies were performed in agreement with the Helsinki Declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their written informed consent before entering the study. Informed consent was obtained from all participants involved in the study.

Consent for publication Informed consent was obtained from all participants involved in the study.

Conflicts of interest Colin Vendrami, Pedro Marques-Vidal, Elena Gonzalez Rodriguez, Gérard Waeber, and Olivier Lamy declare that they have no conflict of interest related to this manuscript. Didier Hans is a co-owner of the TBS patent and holds stock options and royalties in the Medimaps group.

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals Not applicable.

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