

Low bone mineral density is related to high physiological levels of free thyroxine in peri-menopausal women

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Abstract

Objective: To determine whether thyroid hormone (free thyroxine (fT_4)) rather than TSH is directly related to bone mineral density (BMD).

Design: Cross-sectional population cohort study of peri-menopausal women.

Methods: Of a sample of 6846 peri-menopausal Dutch women who participated in an osteoporosis-screening programme, a cohort of 2584 was randomly selected for the assessment of thyroid function (TSH, fT_4 and thyroid peroxidase antibodies (TPO-Abs)). TPO-Ab-positive women, with a previous history of thyroid dysfunction, overt thyroid disease, subclinical hypothyroidism, osteoporosis or bilateral oophorectomy and those receiving thyroid hormone or hormone replacement therapy were excluded. Of 1477 eligible women, 1426 had TSH and fT_4 within the reference range and 51 had low or undetectable serum TSH. BMD was measured at the lumbar spine and low BMD was defined as <0.937 g/cm².

Results: The mean BMD in the 51 women with low or undetectable serum TSH was 0.984 g/cm² compared with 1.001 g/cm² in the remaining 1426 ($t=0.94$, $P=0.35$); 33% of women with low or undetectable serum TSH had low BMD compared with 34% in 1426 euthyroid women. High fT_4 but not low TSH in euthyroid women was related to low BMD by multiple logistic regression corrected for age, BMI and smoking (OR, 1.30; 95% CI, 1.02–1.69).

Conclusions: Higher fT_4 levels within the normal reference range but not low or undetectable serum TSH were independently related to decreased BMD at lumbar spine in peri-menopausal women.

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Introduction

Subclinical thyroid dysfunction is a biochemical disturbance in which the thyrotrophin (TSH) level is outside the reference range while 3,5,3',5'-L-tetraiodothyronine (thyroxine (T_4)) levels lie within normal limits (1). The concept of subclinical thyroid dysfunction has been subject to a prolonged debate and was discussed in a dedicated workshop at the International Thyroid Congress in 2010 (2). A previous expert review concluded that there is little evidence to support an association between subclinical thyroid dysfunction and adverse clinical outcome, and no evidence to indicate clear benefit of treatment (1). These conclusions were reinforced by Biondi & Cooper (3, 4).

Although TSH stimulates T_4 secretion by thyroid follicular cells (5, 6), it has only recently been accepted that the effects of the hypothalamic–pituitary–thyroid (HPT) axis on its end organs are ultimately related to levels of thyroid hormones and to the activities of the deiodinase enzymes that regulate the local concentration of 3, 5, 3'-L-triiodothyronine (T_3). Thus, T_4 is a pro-hormone of the biologically active T_3 (5, 6). Furthermore, the HPT axis setpoint varies in a population to a much greater extent than in individuals (7) because, in an individual, it is largely genetically determined (8). Thus, factors that control circulating thyroid status are likely to differ from those

that determine thyroid hormone concentrations in individual tissues; TSH has an inverse logarithmic relationship to free T_4 (fT_4), and this is determined in the pituitary and hypothalamus, therefore the circulating TSH level is sensitive to the pituitary thyroid status but is not necessarily related to thyroid status in peripheral target tissues. In addition, the type 2 deiodinase, which controls the intracellular availability of T_3 in target cells, is regulated by substrate concentration: when T_4 availability is high, the enzyme activity is reduced and *vice versa*. This represents a local control mechanism that can be 'set' to optimise the intracellular T_3 concentration in a particular target cell (9). These issues suggest: i) that serum hormone levels do not reflect tissue levels; ii) fT_4 is much more likely than TSH to be an indicator of tissue thyroid hormone responsiveness; and iii) small variations in fT_4 over a long period of time may have detrimental consequences including important effects on bone mineral density (BMD), the cardiovascular and CNS and the metabolic syndrome.

Apart from co-morbid disorders resulting in non-thyroidal illness, it is unclear whether symptoms or biological effects ascribed to subclinical hyper- or hypothyroidism are related to fT_4 levels in the upper or lower limits of the normal range rather than to decreased or increased TSH concentrations. Only a few studies have investigated a possible effect of the fT_4 concentration in subclinical thyroid dysfunction (10, 11, 12), which by definition lies within the reference range. Moreover, it is possible that the subjects with subclinical hyperthyroidism and a fT_4 level in the upper normal range have more adverse clinical outcomes than the subjects with subclinical hyperthyroidism and fT_4 levels in the middle or lower reference range, or compared with euthyroid individuals (3). It is important, therefore, to determine whether the fT_4 concentration or the TSH level in subclinical thyroid disease is related to adverse long-term consequences in the target organs such as the skeleton.

Studies of BMD in euthyroid populations indicate that thyroid hormone regulates bone turnover (1, 5, 6, 13, 14, 15). Murphy *et al.* (10) showed that low BMD in a euthyroid population of postmenopausal women was associated with fT_4 and free T_3 (fT_3) levels but not with TSH. These findings were supported by extensive data on mutant mice and other animals (16). In Nicholls' recent review, the authors highlight that the HPT axis setpoint at the upper end of the reference range is associated with reduced BMD and increased susceptibility to fracture, and discuss whether fT_4 is the predominant determinant of the skeletal response to altered thyroid status (13). They concluded that the HPT axis

setpoint should be considered as a whole and that, because of the reciprocal relationship between T_4 and TSH, it is difficult to determine whether high/normal fT_4 or low/normal TSH is the major determinant.

In the current study, we investigated BMD in peri-menopausal women with: i) low or undetectable serum TSH levels irrespective of where the fT_4 concentration lies within the reference range; ii) low or undetectable serum TSH levels and fT_4 levels in the highest quartile of the reference range; iii) low or undetectable serum TSH levels and fT_4 in the lower three quartiles of the reference range; and iv) euthyroidism.

Subjects and methods

Participants

Subjects were part of the Eindhoven Perimenopausal Osteoporosis Study (EPOS) cohort described previously (17, 18). All women born between 1941 and 1947 ($n=8503$) in Eindhoven, The Netherlands, were invited for the measurement of BMD (17). A total of 6846 women (78%) gave their consent and data on menstrual, gynaecological and medical history (including prior and family history of thyroid dysfunction, osteoporosis and fracture) and life style (smoking, alcohol and BMI) were also collected. Blood samples were collected and stored at -80°C . Subsequently, a cohort of 2584 women was randomly selected for the assessment of thyroid function (TSH, fT_4 and thyroid peroxidase antibody (TPO-Ab)) (18) (Fig. 1).

Exclusion criteria included the following (Fig. 1): women receiving thyroid ($n=67$) or osteoporosis ($n=13$) medication or hormone replacement therapy ($n=596$), with a previous history of thyroid dysfunction ($n=236$), with elevated titres of TPO-Ab ($n=245$; many women receiving T_4 were also TPO-Ab-positive) or with a prior history of bilateral oophorectomy ($n=78$). Therefore, 1489 peri-menopausal (i.e. premenopausal, normal menstruation pattern; menopausal, irregular menstruation pattern or postmenopausal, >2 years after last menstruation) women were included (Table 1).

This study was approved by the Medical Ethics Committee, Maxima Medical Centre of Veldhoven Hospital and written informed consent was obtained from all participants.

Thyroid function

Thyroid function was assessed by measurement of TSH (reference range: 0.4–6 mU/l, Abbott), fT_4 (reference range:

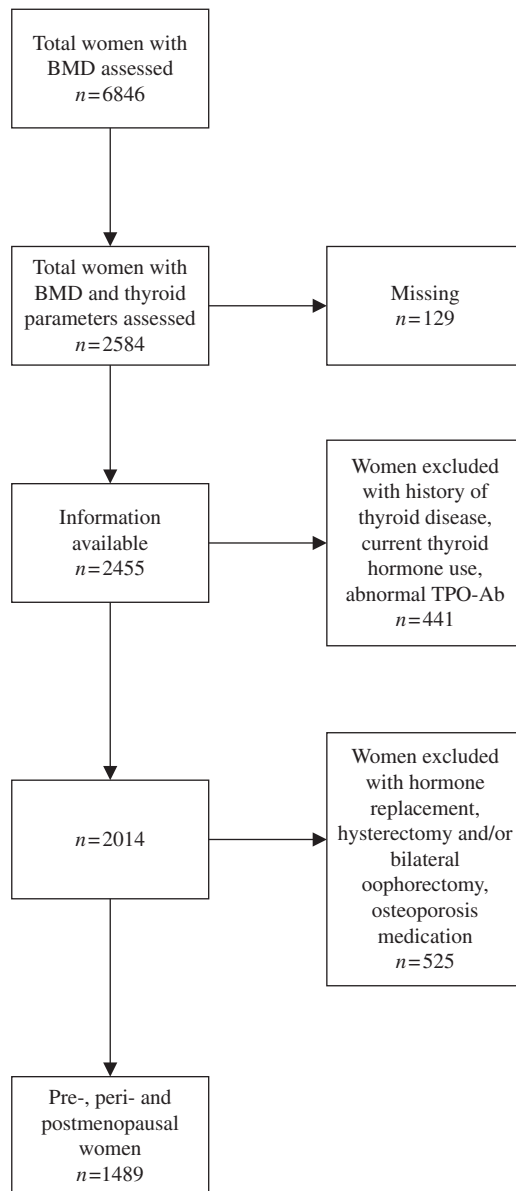


Figure 1
Flow chart of the study population.

8–26 pmol/l; Abbott) and TPO-Ab (Cambridge Life Sciences, Cambridge, UK). A non-fasting venous blood sample was drawn from all participants. Coefficients of variation for fT_4 were 6.8, 8.2 and 6.7% at concentrations of 6.4, 18 and 30 pmol/l respectively; for TSH 9.8, 4.8, 3.9 and 3.1% at the concentrations of 0.06, 0.75, 6.8 and 30 mU/l respectively; and for TPO-Ab 9.6% at a concentration of 231 U/ml (17). A TPO-Ab level >100 U/ml was defined as positive (18).

Bone mineral density

BMD was measured at the lumbar spine (L1–L4) by dual-energy X-ray absorptiometry (S.A. Hologic Europe, Brussels, Belgium) as described (17). Osteopenia is defined as a BMD 1–2.5 s.d. below the young adult mean (T -score). T -score values <2.5 s.d. are defined as osteoporosis (19). According to Hologic reference data, the mean (+s.d.) BMD at L1–L4 in 650 healthy women studied at the University of San Diego was 1.047 ± 0.110 g/cm². Osteopenia is therefore defined as a value between 0.937 and 0.772 g/cm², and osteoporosis as a value below 0.772 g/cm². The mean BMD of 232 premenopausal women in this study was 1.056 ± 0.123 g/cm². The BMDs equivalent to <1 and <2.5 s.d. were 0.927 and 0.734 g/cm² respectively. Low BMD was defined as <0.937 g/cm².

Statistical analysis

Analyses were performed using Statistical Products and Service Solutions Software (SPSS-19, IBM). BMD data were normally distributed and the differences between groups were analysed by χ^2 and Student's t -tests. Quartiles of logTSH and fT_4 were calculated and the differences in mean BMD and prevalence of osteopenia were analysed using ANOVA and χ^2 . Effect sizes were calculated according to Cohen, and coefficients below 0.32, between 0.33–0.55 and >0.55 are regarded as small, medium and large, respectively, with medium and large effect sizes being clinically relevant (20). Multiple logistic regression (OR, 95% CI) was performed with low BMD as a dependent variable and low TSH (lowest quartile) and high fT_4 (highest quartile) as independent variables adjusted for BMI, age, smoking and alcohol intake. Power calculations were performed to determine adequacy of cohort size. Using a significance threshold (α) of 0.05 and power ($1 - \beta$) of 0.80, a sample size of 1026 subjects would be sufficient to detect a 10% difference in prevalence of low BMD between women with or without fT_4 in the highest quartile. Using the same parameters to model multiple linear regression analyses, a sample size between 1057 and 172 is required for 80% power to identify a Cohen's effect size coefficient (d) between 0.2 (small) and 0.5 (medium) at a significance level of $P < 0.05$ (21). These calculations indicate that the analysis of the final cohort of 1477 subjects is adequate.

Results

Two women with thyroid dysfunction, five women with fT_4 concentrations outside the reference range and five

Table 1 Characteristics of a sample of 1489 white Caucasian peri-menopausal women without TPO-Ab and not on thyroid medication or hormone replacement therapy.

	n (%)	Mean \pm s.d.	Median (range)
Age (years)		50.3 \pm 2.4	46–57
Educational level			
Primary school	425 (28.5)		
Secondary school	520 (34.9)		
Low college degree	386 (25.9)		
High college degree	141 (9.5)		
Academic degree	30 (2.0)		
Lifestyle habits			
Currently smoking	509 (34.2)		
Regular alcohol intake	538 (36.1)		
BMI (kg/m ²)		25.4 \pm 4.2	
WHO–BMI classes			
I, <18.50	19 (1.3)		
II, 18.50–24.99	774 (52)		
III, 25.00–29.99	511 (34.3)		
IV, \geq 30.00	185 (12.4)		
BMD (g/cm ²)		1.002 \pm 0.141	
Osteopenia ^a	422 (28.3)		
Osteoporosis ^b	78 (5.2)		
Thyroid parameters			
TSH mU/l			1.29 (<0.01–55)
fT_4 pmol/l			15.3 (6.5–39)
<8	1 (0.07)		
>26	4 (0.27)		
Clinical			
Hyperthyroidism	1 (0.07)		
Hypothyroidism	1 (0.07)		
Subclinical			
Hyperthyroidism ^c	51 (3.4)		
Hypothyroidism ^d	5 (0.34)		

^aBMD >1–2.5 s.d. below mean = 0.772–0.937

^bBMD >2.5 s.d. below mean <0.772

^cTSH <0.4 mU/l

^dTSH >6 mU/l

women with subclinical hypothyroidism were excluded from the analysis (Table 1). Of the 1477 women analysed, 1426 had TSH and fT_4 levels within the reference range, 51 had low or undetectable serum TSH, 420 had osteopenia and 77 had osteoporosis. LogTSH was correlated inversely with fT_4 ($r = -0.18$, $P < 0.001$, effect size: $r = 0.38$). BMD did not correlate with logTSH ($r = 0.03$, $P = 0.34$), but correlated inversely with fT_4 ($r = -0.06$, $P = 0.03$, effect size: $r = 0.15$).

Thyroid function in relation to BMD

The analysis subgroups were defined according to thyroid function: Group I, low or undetectable serum TSH levels irrespective of fT_4 concentration; Group II, low or undetectable serum TSH levels and fT_4 in the highest quartile; Group III, low or undetectable serum TSH levels and fT_4 in the lower three quartiles; and Group IV, euthyroid women. The mean BMD in 51 women with low or undetectable serum TSH levels (Group I) was 0.984 g/cm² compared with 1.001 g/cm² in the remaining 1426 (Group IV) women ($t = 0.94$, $P = 0.35$). The number of women with low BMD in Group I was 17 (33%) compared with 480 (34%) in Group IV. Table 2 shows quartiles for logTSH and fT_4 in 1426 euthyroid women with normal TSH and fT_4 . Low logTSH was defined as a value in the lowest quartile (<0.032 mU/l) and high fT_4 was defined as value in the highest quartile (>16.7 pmol/l).

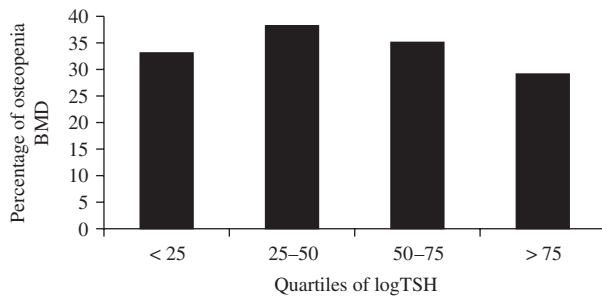
When mean BMD was compared among quartiles of logTSH concentration, no difference was identified ($F = 1.4$, $P = 0.24$). There was, however, a significant difference in mean BMD among quartiles of fT_4 (Table 2, $F = 3.9$, $P = 0.009$). *Post-hoc* analysis indicated the highest quartile differed significantly from the lower three quartiles. In Fig. 2, the percentage of women with low BMD in each logTSH quartile is shown; the prevalence of low BMD was 33% in the lowest quartile and 29% in the highest quartile ($\chi^2 = 6.4$, $df = 3$, $P = 0.10$). The prevalence of low BMD (osteopenia) among fT_4 quartiles excluding women with low or undetectable serum TSH levels is shown in Fig. 3.

The prevalence of osteopenia was 30% in the lower three quartiles but was higher at 40% in the upper fT_4 quartile ($\chi^2 = 9.2$, $df = 3$, $P = 0.027$, effect size: $w = 0.35$). In 51 women with low or undetectable serum TSH levels, 39% had fT_4 concentrations in the highest quartile (Group II) and 61% had fT_4 levels in the three lower quartiles (Group III). The mean BMD in women in Group II was 0.979 g/cm², compared with 0.987 g/cm² in Group III. The number of women with low BMD in Group II was 7 (35%) compared with 10 (32%) in Group III.

Table 2 Quartiles of fT_4 and logTSH of 1427 euthyroid women around menopausal age in relation to mean BMD.

	fT_4 (pmol/l)	Mean BMD*	s.d.	LogTSH (mU/l)	Mean BMD [†]	s.d.
<25th Percentile	<14.1	1.0084	0.133	<0.032	1.0068	0.148
25th–50th Percentile	14.1–15.3	1.0088	0.142	0.032–0.11	0.9922	0.145
51–75th Percentile	15.4–16.7	1.0063	0.143	0.12–0.26	0.9972	0.135
>75th Percentile	>16.7	0.9703	0.147	>0.26	1.0146	0.139

*ANOVA, $F = 3.9$, $P = 0.009$. [†]ANOVA, $F = 1.4$, $P = 0.24$.

**Figure 2**

The prevalence of low BMD (> 1 s.d. $< Mn$ = osteopenia) in 1426 euthyroid women around menopause according to TSH quartiles ($\chi^2=6.4$, $df=3$, $P=0.10$).

Osteopenia and osteoporosis in relation to thyroid function

Of the total number of 1477 women, 978 had normal BMD, 420 had osteopenia and 77 had osteoporosis. In the subgroup of women with fT_4 in the highest quartile, 217 had normal BMD, 121 had osteopenia and 27 had osteoporosis, which was significantly different ($\chi^2=11.1$, $df=2$, $P=0.004$, effect size: $w=0.59$). In women with logTSH in the lowest quartile, there was no difference in proportions of women with normal BMD, osteopenia and osteoporosis ($\chi^2=0.27$, $df=2$, $P=0.87$). Furthermore, the mean fT_4 concentrations differed in women with normal BMD, osteopenia and osteoporosis (15.4, 15.8 and 16.9 pmol/l respectively ($F=3.4$, $P=0.03$)), whereas there were no differences in mean logTSH concentrations between the subgroups.

Independent relation between thyroid function and BMD

Subsequently, multiple logistic regression analysis was performed (Table 3), adjusting for age, smoking, BMI and alcohol intake. There were 32 women (2.1%) using a beta-blocking drug which might interfere with thyroid function. Therefore, we also adjusted for beta-blocking drug intake.

As can be seen in Table 3, low BMI, higher age, smoking and fT_4 in the highest quartile were independently related to low BMD (OR, 1.53; 95% CI, 1.11–2.10), but there was no relationship between low BMD and low logTSH (Table 3) or beta-blocking agents intake. When data were analysed by multivariate linear regression (Table 4) including BMD as continuous dependent variable, a similar model was found ($F=22$, $P<0.001$, $r=0.31$, effect size: 0.68), with higher age, smoking, low

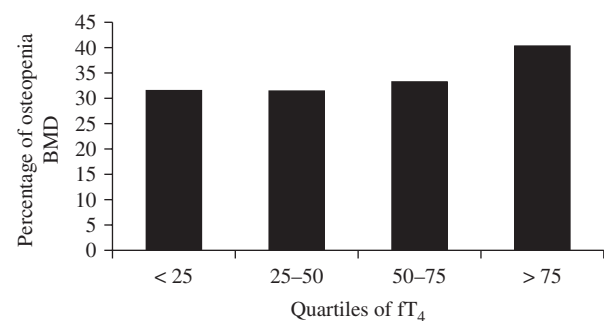
BMI and fT_4 in the highest quartile predicting low BMD with no effect of low logTSH or beta-blocking agents.

Discussion

This study demonstrates that higher fT_4 concentrations within the physiological reference range are independently related to low BMD in peri-menopausal women. There was no relationship between TSH concentration and BMD. The lack of association between low TSH and low BMD even in individuals with low or undetectable serum TSH levels is likely to be because only 39% of these women also had fT_4 levels in the upper quartile of the reference range.

The characteristics of the cohort investigated in the current study are similar to the original total EPOS population (17). The fact that so few women with low or undetectable serum TSH levels were present is because TPO-Ab-positive women, who are well known to be at particular risk for developing subclinical and overt hypothyroidism, were excluded (1). The finding that higher age, low BMI and smoking were independently related to low BMD is in accordance with previous reports (22, 23, 24).

The strength of the current study is that all participants were peri-menopausal women within a narrow age range (11 years) and they were not receiving hormone replacement therapy or osteoporosis medication. Moreover, women with previous thyroid disease, on thyroid medication and at risk of thyroid dysfunction (TPO-Ab-positive) were excluded. High TPO-Ab titers are associated with higher TSH and lower fT_4 levels. In the excluded 245 TPO-Ab-positive women (10% of the

**Figure 3**

The prevalence of low BMD (> 1 s.d. $< Mn$ = osteopenia) in 1426 women around menopause according to fT_4 quartiles, excluding 51 women with sub-clinical hyperthyroidism ($\chi^2=9.2$, $df=3$, $P=0.027$).

Table 3 Multiple logistic regression (OR, 95% CI) in peri-menopausal women. Dependent variable: low BMD (<0.937 g/cm²; BMD >1 s.d. $<$ mean = osteopenia), independent variable: thyroid function, taking into account several confounders of low BMD.

Parameter	OR (95% CI)	P
Low logTSH ^a	0.86 (0.66–1.25)	0.26
FT_4 in highest quartile ^b	1.30 (1.02–1.69)	0.041
High age	1.19 (1.14–1.25)	<0.001
Smoking	1.34 (1.06–1.69)	0.015
Alcohol intake >2 units/week	1.23 (0.97–1.56)	0.08
BMI	0.89 (0.87–0.92)	<0.001

^aLow logTSH, TSH \leq lowest quartile ≤ -0.032 IU/l.

^b FT_4 in the highest quartile ≥ 16.7 pmol/l.

original cohort in which thyroid parameters were assessed, which is consistent with previous data (3)), TSH was significantly higher and ft_4 was significantly lower compared with TPO-Ab-negative women ($P < 0.001$, Mann-Whitney U test). However, most women with elevated TPO-Ab titers are not recognized and if such women had been included, their thyroid function could have affected BMD. Nevertheless, TSH did not correlate with BMD, whereas ft_4 was weakly but significantly inversely correlated with BMD. According to Cohen's coefficient, the effect size of this correlation ($r = 0.06$, effect size = 0.18) was below 0.33, which is considered to indicate a moderate clinically relevant effect size (20). Further analysis revealed that when ft_4 concentration was grouped by quartiles, only the highest quartile included a significantly higher proportion of women with osteopenia or osteoporosis whereas each of the lower three quartiles had a similar prevalence of low BMD.

Murphy *et al.* (10) similarly demonstrated an independent relationship between ft_4 in the highest quintile of the reference range and low BMD in healthy euthyroid postmenopausal women, and they also found no relationship between TSH and BMD. When we analysed the current data using quintiles of ft_4 , we found an even higher independent effect of ft_4 in the upper normal range (1.35, 95% CI, 1.02–1.79, $P = 0.036$). Similar to the current study, Murphy *et al.* also reported an inverse correlation between ft_4 and BMD by multiple linear regression. Other studies have also demonstrated that women with higher ft_4 levels within the normal reference range have lower BMD, but they found little or no association between BMD and TSH (10, 11, 12, 25). Interestingly, in a study from Taiwan using a similar cross-sectional design in women of comparable age to the current study, no relation was

demonstrated between TSH and BMD, while the authors found a significant but weak correlation between BMD and ft_4 in postmenopausal women (11). However, because of the inverse relationship between TSH and T_4 that results from negative feedback regulation of the HPT axis (as reviewed elsewhere (5, 10)), it is not possible to make a distinction between the physiological importance of higher ft_4 levels compared with lower TSH levels.

Importantly, the current work and other related studies are associated studies and therefore cannot demonstrate causal relationships between either ft_4 or TSH with BMD. As noted above, such studies are not able to ascribe specific and independent roles for either hormone in the regulation of bone density because of their physiological reciprocal relationship as defined by the HPT axis. A recent review of the literature showed evidence that for both 'endogenous' as well as 'exogenous' subclinical hyperthyroidism, postmenopausal women rather than premenopausal women are at increased risk for lower BMD (26). However, most if not all of the studies considered in this review failed to discriminate women with subclinical hyperthyroidism and ft_4 levels at the upper normal range from those with ft_4 levels at the lower normal range. It should be noted in the current study that women with endogenous (with elevated TPO-Ab titres) and exogenous (receiving hormone replacement therapy) subclinical hyperthyroidism were excluded from the analysis. Overall, our data indicate an inverse relation between ft_4 at the upper end of the reference range and BMD.

It is well established that thyroid hormones, acting via $TR\alpha$, promote catabolic actions on the adult skeleton (6). In hyperthyroidism, bone resorption and formation are both accelerated and the remodelling cycle is shortened. Furthermore, $TR\beta^{-/-}$ mice display osteoporosis despite elevated

Table 4 Multiple linear regression in 1477 peri-menopausal women. Dependent variable: BMD, independent variable: thyroid function, taking into account several confounders of low BMD.

	β (95% CI)	P
Low logTSH ^a	0.007 (–0.009 to 0.024)	0.39
FT_4 in highest quartile ^b	–0.02 (–0.037 to –0.004)	0.014
High age	–0.011 (–0.014 to –0.008)	<0.001
Smoking	–0.029 (–0.044 to –0.014)	<0.001
Alcohol intake >2 units/week	–0.009 (–0.010 to 0.09)	0.1
BMI	0.012 (0.008 to 0.018)	<0.001

^aLow log TSH, TSH \leq lowest quartile ≤ -0.032 IU/l.

^b FT_4 in the highest quartile ≥ 16.7 pmol/l.

concentrations of both thyroid hormones and TSH that result from dissociation of the HPT axis (6, 16), further suggesting that actions of T_3 in bone predominate over those of TSH. Human studies of siblings with isolated TSH deficiency revealed that individuals have normal BMD following thyroid hormone replacement despite a lifelong absence of TSH (27). All these observations are consistent with the outcome of the current study, which demonstrates that higher fT_4 levels, but not lower TSH concentrations, are related to reduced BMD. Nevertheless, TSH receptor expression has been documented in skeletal cells (28), although the clinical importance of this finding remains controversial. However, if TSHR expression is regulated by T_3 in skeletal cells then such a local regulatory mechanism could account for complex interplay between thyroid hormones and TSH regulation. Such a possibility could support measurement of both fT_3 and fT_4 as well as TSH in future studies, although the T_3 level in target tissues does not necessarily correlate well with its circulating concentration.

Several limitations of the study should be considered. First, a cross-sectional design was used and it was not possible to determine whether there is a relationship between fT_4 or TSH and loss of BMD or incident fracture. Second, BMD was only assessed at the lumbar spine and not at the hip or other anatomical sites. However, there is no evidence that effects of T_4 on BMD are restricted to the vertebrae: indeed, Murphy *et al.* showed that high fT_4 was related to low BMD at both the lumbar spine and hip (10). Third, only fT_4 and not fT_3 levels were assessed and bone markers were not evaluated. In addition, only a single measurement of T_4 and TSH was available; this reduces precision, but the size of the well-characterised cohort and power of the study mitigate these issues. Fourth, the Hologic thresholds for low BMD were based on a USA population, which is of different ethnic origin to the current study that contains predominantly white European Caucasian women. Finally, the presence of non-thyroidal illness was not defined as a specific exclusion criterion; some chronic conditions that cause non-thyroidal illness may also interfere with BMD and thus confound the reported findings, although the large size of the population also mitigates this potential problem. What is the clinical relevance of the current study? There is consensus that the consequences of subclinical thyroid dysfunction on symptoms and adverse clinical outcomes are minimal, although the precise outcomes of studies are variable (1, 3, 4). Most if not all studies do not take account of the fT_4 level in individuals with subclinical hyperthyroidism. By definition, women with a decreased TSH and fT_4 level in the lower reference range are categorised in the same group as women

with a decreased TSH but fT_4 level in the upper reference range. In light of the current findings, it is likely that failure to account for differences in the fT_4 concentration in women with low or undetectable serum TSH levels explains the inconclusive findings of previous studies.

We suggest that inclusion of fT_4 level when evaluating a possible relationship between subclinical hyperthyroidism and BMD or between low or undetectable serum TSH levels and BMD would better appreciate the HPT axis setpoint. Both the HPT axis setpoint and BMD are continuous parameters and extremes of their normal reference ranges represent variations of normal that may result in long-term metabolic risk. Such consideration is consistent with the concept that there is a physiological trade-off between the HPT axis setpoint and BMD. We favour the interpretation that the combination of thyroid hormones and TSH should be considered responsible for the effect on BMD because i) studies cannot discriminate between the two because of their physiological inverse relationship and ii) no studies have been designed to address this point specifically in a discriminatory way.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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