CLINICAL STUDY

Hyperthyroid levels of TSH correlate with low bone mineral density: the HUNT 2 study

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Abstract

Objective: To study the relationship between TSH and forearm bone mineral density (BMD) in a general female population.

Design: Cross-sectional, population-based study.

Methods: In a substudy of the Nord-Trøndelag Health Study 1995–1997 (HUNT 2), 5778 women without and 944 with self-reported thyroid disease aged ≥ 40 years had their serum TSH and distal and ultra-distal forearm BMD measured. In range-based categories of TSH, excluding women with previous thyroid disease, a general linear model was used to calculate adjusted mean BMD, and a logistic regression model to compute adjusted odds ratio (OR) for osteopenia and osteoporosis. Corresponding models were used to compare BMD in women with self-reported hypothyroidism or hyperthyroidism to euthyroid women.

Results: In women without self-reported thyroid disease, those with TSH < 0.5 mU/l had 10.7 mg/cm^2 (95% confidence interval (CI) 0.2–21.1) lower distal and 9.1 mg/cm^2 (95% CI -0.7–18.9) lower ultra-distal BMD than women in the reference category (TSH 0.50–1.49 mU/l). No differences were found between the categories with TSH ≥ 0.50 mU/l. Compared to self-reported euthyroid women, self-reported hyperthyroid women had increased odds for osteoporosis both distally (OR 1.35, 95% CI 1.00–1.82) and ultra-distally (OR 1.48, 95% CI 1.10–1.99).

Conclusion: Women with the lowest TSH (< 0.5 mU/l) had lower forearm BMD than the reference category. No differences were observed between the TSH categories ≥ 0.50 mU/l. The prevalence of osteoporosis was higher in women who reported hyperthyroidism than in women without self-reported thyroid disease.

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Introduction

Thyroid hormones affect bone metabolism. There is an ongoing debate whether TSH or the thyroid hormones *per se* are responsible for these effects (1). In hyperthyroidism, there is an increased bone remodeling, with the net effect of bone resorption (2, 3). In accordance with this, several studies have shown overt hyperthyroidism to be a risk factor for osteoporosis (4–8). In a much cited study from 1979, the distal forearm bone mineral content was 17.5% lower in patients with hyperthyroidism than in healthy controls (6). Other studies have also shown an increased fracture risk in patients with hyperthyroidism (9–13).

Recently, two studies reported increasing bone mineral density (BMD) with increasing TSH within the reference range (14, 15). Furthermore, recent studies have also shown hypothyroidism to be a risk factor for fractures (13, 16, 17). This challenges the traditional view that only hyperthyroidism is of importance in bone metabolism, and raises the hypothesis that peak BMD might be found in the upper part of the reference range, with decreased BMD and increased fracture risk below and above this level.

The aim of this study was to assess the relationship between TSH and forearm BMD, and between self-reported former or present hyper- or hypothyroidism and forearm BMD, in a population-based sample of women ≥ 40 years.

Material and methods

Study sample

The Nord-Trøndelag Health Study 1995–97 (HUNT 2) was a comprehensive, population-based health study described in detail elsewhere (18). All participants

answered questionnaires on a range of lifestyle and health related topics, including questions on former or current thyroid illnesses, former or current use of medication for either hypo- or hyperthyroidism, and former treatment with radioactive iodine or thyroid surgery. Standardized measurements of height and weight were conducted, and a non-fasting venous blood sample was drawn from each participant. Altogether, 66 140 (71.2%) of a total population of 92 936 participated.

The total female population ≥40 years in HUNT 2 was 23 959. Among these, three groups were assigned to forearm BMD measurement: Group 1: a 5% random sample of all (1226 women). Group 2: a 30% random sample aged 50–59 years restricted to the urban municipalities (1733 women). Group 3: all women were ≥65 years of age (8787 women). The number of participants who actually underwent BMD measurement was 1029 (85.9%), 1369 (79.0%), and 4692 (53.4%) in group 1, 2, and 3 respectively. Thus, among the 11 746 women who were assigned to BMD measurement, we had BMD data on 7090 (60.4%). Moreover, we excluded 368 women without information on TSH or body mass index (BMI). This left us with 6722 women available for statistical analysis.

The 5024 women who were without BMD measurement or were excluded, due to lack of information on TSH or BMI, were on average 7.3 years older than the 6722 women with data. After adjusting for age, the 5024 omitted women had higher BMI, smoked or had smoked more, had lower levels of recreational physical activity, and longer time had elapsed since menopause (data not shown).

Among the 6722 women with eligible data on central variables, 944 (14.0%) reported former or present thyroid disease or treatment; 6.8% reported hypothyroidism, 3.2% hyperthyroidism, 4.3% goiter, 1.7% radioiodine treatment, 3.0% thyroid operations, 1.1% other thyroid diseases, 0.3% treatment with carbimazole, and 7.8% treatment with thyroxine (T_4). Subjects who had answered 'no' to the questions 'have you ever had hypothyroidism/hyperthyroidism/any other disease of the thyroid gland?' were recoded as previously hypothyroid if they reported previous T_4 use, and hyperthyroid if reporting previous radioiodine- or carbimazole therapy. Those reporting both prior hypo- and hyperthyroidism, or treatment consistent with both hypo- and hyperthyroidism, were classified as former hyperthyroid. This meant that, after reclassification, 424 women were classified as self-reporters of hypothyroidism and 252 of hyperthyroidism.

For the main analyses in the present study, we included the 5778 women without self-reported thyroid disease. In additional analyses, the 424 women with self-reported hypothyroidism and 252 with self-reported hyperthyroidism were also included, with the intention to study the effect of previous hypo- and hyperthyroidism on BMD. Since a TSH level within the reference range is usually rapidly obtained in the treatment of both hypo- and hyperthyroidism, and since we adjusted for current TSH, the analyses of these subgroups would mainly estimate the effect of previous disease.

Blood samples

A non-fasting venous blood sample was drawn from all participants, regardless of the time of the day. The sera were stored at −20 °C. Serum TSH was analyzed at the Hormone Laboratory, Aker University Hospital, Oslo, Norway, using a DELFIA hTSH Ultra (sensitivity 0.03 mU/l and total analytic variation <5%). Based on the HUNT 2 data, the TSH reference range in the present study was 0.5–3.5 mU/l (19). Free T_4 (fT_4) was measured with DELFIA fT_4 (total analytical variation <7%; reference range 8–20 pmol/l) and total triiodothyronine (T_3) with AutoDELFIA (total analytical variation <5%; reference range 1.2–2.7 nmol/l). Measurement of fT_4 was only done if TSH was <0.2 or >4.0 mU/l, and of T_3 if TSH was <0.2 mU/l.

Bone densitometry

BMD was measured at the distal and ultra-distal part of the non-dominant forearm by three single-energy X-ray bone densitometers (Osteometer DTX 100, Osteometer, AS Copenhagen, Denmark). Starting from a point where the distance between the radius and the ulna was 8 mm, the distal site was defined as 24 mm in the proximal direction of the ulna and radius, while the ultra-distal site was defined as the area of radius distal to this, excluding the endplate. Daily calibrations of the densitometers were performed with a phantom. All examinations were carried out in the continuous presence of specially trained technicians. In case of a previous fracture in the area of interest, the dominant arm was measured (3.7% of the cases). If fractures were reported in both arms, the non-dominant arm was used (0.2%).

Owing to problems with automated determination of the beginning of the radius endplate or the 8 mm radius/ulna distance, all the results were recalculated after manual determination of the beginning of the endplate, according to the protocol of the Tromsø Study (20).

Osteopenia and osteoporosis can be defined by calculating a s.d. score based on the distribution of BMD values. This score is termed *T*-score, and is defined as the individually observed BMD value minus the mean BMD for women aged 20–40 years and divided by the s.d. for women 20–40 years. In the present study, *T*-scores of distal and ultra-distal BMD were calculated in a random 5% selection of women 20–40 years who participated in HUNT 2. A *T*-score of −1 to −2.49 is classified as osteopenia, and a *T*-score ≤ −2.5 as osteoporosis.

Statistical analyses

In the analyses of women without self-reported thyroid disease, we used a general linear model (GLM) to calculate mean BMD in five categories of TSH (<0.50, 0.50–1.49, 1.50–2.49, 2.50–3.50, and >3.50 mU/l), and to estimate the crude and adjusted mean difference with 95% confidence interval (95% CI) between the categories, using TSH 0.50–1.49 mU/l as the reference category. The TSH categorization and choice of reference group were based on the laboratory's reference range and previous HUNT 2 studies (19). In order to test whether an effect of TSH was confined to subgroups, similar analyses were conducted after stratifying TSH into ten categories (<0.1, 0.1–0.49, 0.5–0.99, 1.0–1.49, 1.5–1.99, 2.0–2.49, 2.5–2.99, 3.0–3.5, 3.51–9.99, and ≥10.0 mU/l), and with TSH 1.0–1.49 mU/l as the reference group. We also performed a test for trend, in which these ten TSH categories were entered as an ordinal variable in the regression model.

In a supplementary analysis, we compared women with TSH above the 97.5 percentile (TSH ≥ 6.0 mU/l) with all women who were within the reference range (considered as one group).

In a logistic regression model with either a) osteopenia or osteoporosis, or b) osteoporosis alone, as the dependent variable, we estimated adjusted odds ratios (OR) with 95% CI within different levels of TSH compared to the reference category of TSH 0.50–1.49 mU/l.

In additional analyses similar to those described above, we compared women with self-reported hypothyroidism or hyperthyroidism to euthyroid women. In a GLM, we calculated the differences in mean BMD between the groups, and in logistic regression analysis we estimated the OR for a) osteopenia or osteoporosis and b) osteoporosis alone.

All associations were adjusted for the potential confounding effect of age, BMI, recreational physical activity, smoking status, estrogen replacement therapy, and menstrual status. In the analyses of self-reported hypo- and hyperthyroid women, we also included current TSH as a potential confounder in the regression model.

For the purpose of the adjusted analyses described above, menstrual status was categorized into women still menstruating and three postmenopausal groups. Information on menstrual status and menopause was missing in 20.1%, and these women were defined as menstruating if their age was <51 years and as menopausal if they were aged ≥51 years (21). The variable 'recreational physical activity' was based on two questions on physical activity intensity and duration and categorized as no, little, moderate, and much physical activity. Information on the use of estrogen classified the women as current, former, or never users, and smokers were classified as current, former, or never smokers. For the variables recreational physical activity, estrogen use and smoking status, there were a proportion of women without information (Table 1). They were included as separate missing groups in the analyses. We had complete variable information on 2505 women.

Effect modification by both age and BMI on the association between TSH and BMD were tested including interaction terms in the models.

All statistical tests were two-sided, and all analyses were conducted using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The Norwegian Social Science Data Services and the Regional Committee for Medical Research approved the study.

Results

The characteristics of the 5778 women without self-reported thyroid disease are shown in Table 1. Osteoporosis and osteopenia were found in 30.1 and 43.8% of the women at the distal site respectively, while corresponding figures at the ultra-distal site were 26.7 and 53.7% respectively. The BMI and age increased with increasing TSH (with the exception that the TSH <0.50 mU/l group was older than the 0.50–1.49 and 1.50–2.49 mU/l groups), whereas the

Table 1 Basic characteristics of the study population of women aged ≥40 years without self-reported thyroid disease.

Variables	n	Mean (S.D.)
Age (years)	5778	66.6 (11.5)
Body mass index (kg/m^2)	5778	27.1 (4.4)

	n	%
Smoking		
Current	1385	24.0
Former	735	12.7
Never	2306	39.9
Unknown	1352	23.4
Menstruation		
Still menstruating	659	11.4
Menopause <5 years ago	379	6.6
Menopause 5–9 years ago	328	5.7
Menopause >9 years ago	3249	56.2
Unknown	1163	20.1
Recreational physical activity		
No	1065	18.4
Little	1930	33.4
Moderate	884	15.3
Much	396	6.9
Unknown	1503	26.0
Estrogen use		
Current	535	9.3
Former	232	4.0
Never	3081	53.3
Unknown	1930	33.4

Table 2 TSH in relation to bone mineral density (BMD) in 5778 women aged ≥ 40 years without self-reported thyroid disease.

		BMD at distal site (mg/cm^2)			BMD at ultra-distal site (mg/cm^2)		
TSH (mU/l)	*n*	Mean	Crude difference	Adjusted[a] difference (95% CI)	Mean	Crude difference	Adjusted[a] difference (95% CI)
< 0.50	136	390.8	−22.1	−10.6 (−21.1, −0.2)	303.6	−19.6	−9.1 (−18.9, 0.7)
0.50–1.49	2188	412.9	0.0	0.0 (reference)	323.2	0.0	0.0 (reference)
1.50–2.49	2110	408.7	−4.2	0.8 (−2.8, 4.4)	319.9	−3.3	1.3 (−2.1, 4.7)
2.50–3.50	802	405.7	−7.2	2.6 (−2.3, 7.5)	315.4	−7.8	0.7 (−3.9, 5.3)
> 3.50	542	400.5	−12.4	2.3 (−3.4, 8.0)	310.1	−13.1	0.7 (−4.7, 6.1)

CI, confidence interval.
[a]Adjusted for age, body mass index, recreational physical activity, smoking status, estrogen use, and menstrual status.

numbers of smokers and ex-smokers decreased. For the other covariables, no obvious patterns emerged. This means that the differences between the unadjusted and adjusted estimates in Tables 2–5 were mainly caused by these three covariables.

In analysis of women without self-reported thyroid disease and with TSH classified into five categories, those with TSH ≤ 0.50 mU/l had 10.7 mg/cm^2 (95% CI, 0.2–21.1) lower adjusted distal BMD and 9.1 mg/cm^2 (95% CI, −0.7–18.9) lower adjusted ultra-distal BMD compared to the reference group of women with TSH 0.5–1.49 mU/l (Table 2). No statistically significant differences in BMD were found between the reference group and the higher TSH categories.

Figure 1 shows the adjusted mean distal and ultra-distal BMD across ten categories of TSH. At the distal site, the TSH < 0.10 mU/l group had statistically significantly lower adjusted BMD than all the other groups ($P < 0.05$). Ultra-distally, the TSH < 0.10 mU/l group had statistically significantly lower BMD compared to all groups ($P < 0.05$), except the 0.10–0.49 mU/l group ($P = 0.151$). Compared to women with TSH 1.0–1.49 mU/l, those with

TSH < 0.10 mU/l had 35.9 mg/cm^2 (95% CI, 16.5–55.3) lower adjusted distal and 21.1 mg/cm^2 (95% CI, 2.9–39.4) lower adjusted ultra-distal BMD. The mean (s.d.) fT$_4$ and T$_3$ in the TSH < 0.10 mU/l group were 20.9 (10.6) pmol/l and 3.0 (1.1) nmol/l respectively, indicating that many of the women in this group had clinically overt hyperthyroidism. At both the distal and ultra-distal site, the 0.10–0.49 mU/l TSH group had slightly lower adjusted BMD than the higher TSH groups, but no statistically significant differences were seen. The test for trend gave a *P* value of 0.07 for the distal and 0.24 for the ultra-distal site.

When we compared women with TSH above the 97.5 percentile with all women within the reference range (considered as one group), the groups had similar adjusted mean BMDs, both at the distal and ultra-distal site (data not shown).

No statistically significant differences in the prevalence of either the combination of osteopenia or osteoporosis nor osteoporosis alone were found between the reference category with TSH 0.50–1.49 mU/l and the other TSH categories in the adjusted analyses. However, a non-significant pattern of more osteoporosis

Table 3 Odds ratio (OR) for either osteopenia or osteoporosis combined or for osteoporosis assessed from bone mineral density (BMD) measures at the distal or ultra-distal forearm, associated with TSH in 5778 women aged ≥ 40 years without self-reported thyroid disease.

	Osteopenia or osteoporosis combined[a]				Osteoporosis[b]			
TSH (mU/l)	Non-cases	Cases	OR[c]	OR[d] (95% CI)	Non-cases	Cases	OR[c]	OR[d] (95% CI)
Distal forearm BMD measures								
< 0.50	27	109	1.65	1.51 (0.90, 2.53)	82	54	1.62	1.35 (0.87, 2.09)
0.50–1.49	633	1555	1.00	1.00 (reference)	1551	637	1.00	1.00 (reference)
1.50–2.49	529	1581	1.21	1.08 (0.91, 1.27)	1503	607	0.98	0.86 (0.74, 1.00)
2.50–3.50	197	605	1.25	0.95 (0.76, 1.19)	554	248	1.10	0.86 (0.70, 1.06)
> 3.50	124	418	1.38	0.88 (0.67, 1.15)	360	182	1.24	0.93 (0.74, 1.17)
Ultra-distal forearm BMD measures								
< 0.50	21	115	1.55	1.35 (0.77, 2.35)	91	45	1.46	1.14 (0.74, 1.77)
0.50–1.49	482	1708	1.00	1.00 (reference)	1628	562	1.00	1.00 (reference)
1.50–2.49	411	1698	1.16	1.02 (0.85, 1.22)	1567	542	0.94	0.90 (0.77, 1.06)
2.50–3.50	131	670	1.44	1.18 (0.91, 1.53)	577	224	1.13	0.94 (0.76, 1.16)
> 3.50	87	455	1.48	0.97 (0.72, 1.30)	374	168	1.31	1.03 (0.82, 1.30)

CI, confidence interval.
[a]Osteopenia or osteoporosis defined as a *T*-score ≤ −1.0 based on BMD measures.
[b]Osteoporosis defined as a *T*-score ≤ −2.5 based on BMD measures.
[c]Crude OR.
[d]OR adjusted for age, body mass index, recreational physical activity, smoking status, estrogen use, and menstrual status.

Table 4 Self-reported hypo- and hyperthyroidism in relation to distal and ultra-distal forearm bone mineral density (BMD) in 6454 women aged ≥40 years.

Thyroid status	n	BMD at distal site (mg/cm²)			BMD at ultra-distal site (mg/cm²)		
		Mean	Crude difference	Adjusted[a] difference (95% CI)	Mean	Crude difference	Adjusted[a] difference (95% CI)
Euthyroid	5778	408.5	0.0	0.0 (reference)	318.9	0.0	0.0 (reference)
Hyperthyroid	252	390.6	−17.9	−4.5 (−12.4, 3.4)	302.9	−16.0	−3.3 (−10.7, 4.1)
Hypothyroid	424	405.6	−2.9	2.8 (−3.5, 9.2)	314.3	−4.6	1.2 (−4.8, 7.1)

CI, confidence interval.
[a]Adjusted for age, body mass index, recreational physical activity, smoking status, estrogen use, menstrual status, and measured level of TSH.

and osteopenia was found in the TSH <0.50 mU/l category (Table 3).

In additional analysis comparing mean BMD in women with self-reported hypo- or hyperthyroidism to those who were euthyroid, there was a tendency towards lower BMD in the hyperthyroid group, but no statistically significant differences (Table 4). When studying the prevalence of osteoporosis, we found that women with self-reported hyperthyroidism had an adjusted OR of 1.48 (95% CI 1.10–1.99) at the ultra-distal and 1.35 (95% CI 1.00–1.82) at the distal site compared to euthyroid women (Table 5). No statistically significant associations were found in the analyses where the combination of osteopenia and osteoporosis was used instead of osteoporosis.

There were no modifying effects of either BMI or age on the association between TSH and BMD, and corresponding stratifications were not necessary.

Discussion

This large population-based cross-sectional study of women aged ≥40 years showed that TSH <0.50 mU/l was associated with a lower distal forearm BMD than the reference category with TSH 0.50–1.49 mU/l. The lower BMD was most prominent for women with TSH <0.10 mU/l. For women with TSH levels ≥0.5 mU/l, no differences in BMD were seen. The pattern was the same ultra-distally, although fewer comparisons reached statistical significance. Furthermore, compared to euthyroid women, self-reported hyperthyroidism was associated with a statistically significant increased risk for osteoporosis at the ultra-distal site, and a close to statistically significant increased risk at the distal site.

This study is the largest one in a general female population on the relationship between TSH and BMD. The strength of the study is the number of participants and the population-based design. The numbers of participants were unequally distributed by age, but we have no indications that this should bias our results.

TSH levels vary biologically throughout the day, and are also influenced by exogenous factors like exercise and sleep deprivation (22). Our blood samples were drawn at any time during daytime and without considering external factors. This might have added non-differential bias to the study that could have weakened the observed associations.

For all covariates there were women with missing information. Only about 43% had complete data on all covariables. For menstrual status, age made us able to categorize them with relatively low risk for misclassification. For recreational physical activity, smoking status and estrogen use, those with missing information were included as separate categories. This might add

Table 5 Odds ratio (OR) for either osteopenia or osteoporosis combined[a] or for osteoporosis[b] assessed from bone mineral density (BMD) measures at the distal or ultra-distal forearm, associated with self-reported hypo- and hyperthyroidism in 6454 women aged ≥40 years.

Thyroid status	Osteopenia or osteoporosis combined[a]			Osteoporosis[b]	
	n	OR[c]	OR[d] (95% CI)	OR[c]	OR[d] (95% CI)
Distal forearm BMD measures					
Euthyroid	5778	1.00	1.00 (reference)	1.00	1.00 (reference)
Hyperthyroid	252	1.34	0.96 (0.67, 1.38)	1.56	1.35 (1.00, 1.82)
Hypothyroid	424	1.07	0.91 (0.69, 1.20)	1.10	1.02 (0.79, 1.30)
Ultra-distal forearm BMD measures					
Euthyroid	5778	1.00	1.00 (reference)	1.00	1.00 (reference)
Hyperthyroid	252	1.32	0.90 (0.60, 1.35)	1.68	1.48 (1.10, 1.99)
Hypothyroid	424	1.07	0.87 (0.65, 1.18)	1.09	1.01 (0.79, 1.30)

CI, confidence interval.
[a]Osteopenia or osteoporosis defined as a *T*-score ≤ −1.0 based on BMD measures.
[b]Osteoporosis defined as a *T*-score ≤ −2.5 based on BMD measures.
[c]Crude OR.
[d]OR adjusted for age, body mass index, recreational physical activity, smoking status, estrogen use, menstrual status, and measured level of TSH.
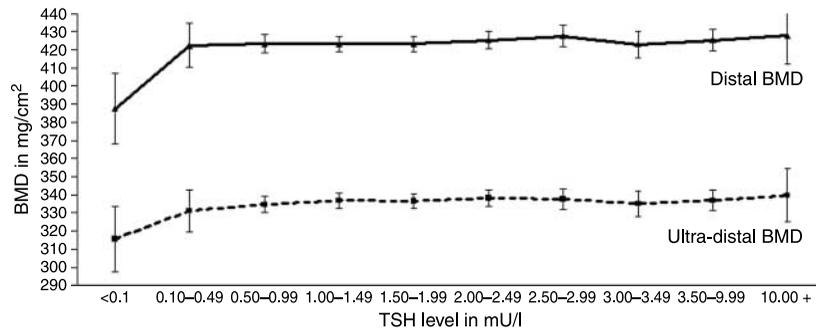
Figure 1 Distal and ultra-distal forearm bone mineral density (BMD) in mg/cm^2 with 95% CI by TSH levels: adjusted for age, body mass index, recreational physical activity, smoking status, estrogen use, and menstrual status.

residual confounding, but sensitivity analyses revealed consistent results.

Among women ≥65 years, only 53.4% had bone densitometry measurements. In the five urban municipalities, bone densitometry was performed at the same time as the rest of the screening examinations, while in the rural municipalities this examination was performed 6–8 weeks after the screening. This, in addition to longer distances to the measurement stations in the rural municipalities, mainly explains lower participation rate among those ≥65 years. There is, however, no reason to believe that there should be different relations between TSH and BMD by municipality.

Categorization of women as former hypo- or hyperthyroid, partly according to answers on use of medication or treatment, may have lead to misclassifications. T_4 is sometimes used to treat goiter and radio-iodine in the treatment of thyroid cancer. Even so, the use of such treatments in these settings is quite rare, and it is not likely that this would have distorted our results.

For measurement of BMD, the hip and the lumbar spine are the commonly preferred sites. In the present study, we have based our classification of osteoporosis and osteopenia on *T*-scores calculated from forearm BMD measurements. For middle-aged women, measurements in the forearm are likely to overestimate the prevalence of osteoporosis, compared to measurements at the hip and spine (23). Thus, a *T*-score threshold of ≤ −2.5 to define osteoporosis has been recommended only when hip measurements are used (24). Nevertheless, it is not likely that this misclassification is differential between the TSH categories.

Hyperthyroidism affects cortical more than trabecular bone, and forearm measurements are recognized and well suited for studying the effect of thyroid hormones on bones (3). In accordance with this, we also found a stronger association between TSH and BMD at the distal (mainly cortical bone) than ultra-distal site (mainly trabecular bone).

The detrimental effect of hyperthyroidism on the skeleton has been known since 1891 (25). Traditionally, this has been considered a direct effect of the thyroid hormones. Recent research has challenged this view, indicating an independent bone protective role for TSH (1). TSH receptors have been found on both osteoclast and osteoblast precursor cells (26).

Treatment with TSH has been shown to have an anti-resorptive effect, as measured on blood and urine bone markers, and to have a beneficial effect on BMD in animals (27–29). Tumour necrosis factor-α has been suggested to mediate the effect of TSH on bone (30). In 2008, a cross-sectional Dutch population study in patients with former thyroid carcinomas found TSH to be independently inversely correlated to markers of both bone resorption and formation (31).

Whether subclinical hyperthyroidism has the same impact as overt hyperthyroidism is controversial. Inherent problems are that different hormone levels have been used in definitions, and that both exogenously and endogenously subclinical hyperthyroidism have been studied (32). Since we only had data on fT_4 and T_3 in subpopulations, we could not analyze the data according to formal criteria for the subclinical conditions. Instead we studied the TSH 0.10–0.49 mU/l subgroup separately. Our results suggest that women with a slightly subnormal TSH have a BMD between those with lower and higher TSH (Fig. 1). However, the differences did not reach statistical significance, which may be due to lack of statistical power after subdivisions.

Many recent studies have addressed the relationship between TSH and BMD. Two cross-sectional studies focused especially on different TSH strata within the reference range. A hospital-based study from South Korea found an increasing hip and lumbar BMD with increasing TSH from the subclinical level to the high normal TSH level (14). Comparing quintiles within the normal range, the highest quintile (2.8–5.0 mU/l) had significantly higher BMD than the lowest quintile (0.5–1.1 mU/l). Based on the National Health and Nutrition Examination Survey III (NHANES III) data, Martha S Morris studied the association between normal range TSH-strata and hip BMD in postmenopausal women (15). Dividing the participants dichotomously based on mean TSH, she found that the low TSH group (0.39–1.79 mU/l) had higher risk for osteopenia and osteoporosis than the high TSH (1.8–4.6 mU/l) group. Furthermore, a regression analysis confirmed a positive relation between BMD and TSH quintiles within the normal range.

Another South Korean study found that both subclinical hypo- and hyperthyroidism were associated with reduced femoral neck BMD, as compared to

euthyroid women (33). In a recent population-based study from Tromsø in Norway, the higher 2.5% female TSH group (>4.56 mU/l group) had statistically significantly higher femoral neck BMD than euthyroid women (34). In the Tromsø study, within the normal TSH range, no relationship between TSH and BMD was seen. In recent years, population-based studies have also shown a relationship between hypothyroidism and increased fracture risk (13, 16, 17).

In the present study, no statistically significant differences in BMD were found if TSH was within or above the reference range. We consider this our single most important finding. Neither could we reproduce the effect on BMD among women with TSH above the 97.5 percentile that was reported from the Tromsø study (34). Instead, our study showed a threshold BMD in the low-normal TSH range, above which the BMD remained stable. This suggests that differences in BMD based on TSH, with the exception for low TSH, are of minor clinical importance.

As described above, our results concerning TSH within the normal range is contradictory to the findings of two recent epidemiologic studies, but in agreement with the findings of the Tromsø study (14, 15, 34). One reason might be that our study (and most of the results from the Tromsø study) was based on forearm BMD measurements, whereas the other studies used hip and lumbar spine measurements. Other differences between the studies were different populations, different subject inclusion and exclusion criteria, and different covariables.

One possible explanation for the previously reported association between hypothyroidism and fractures, if this proves to be a reproducible finding, might be increased extra-skeletal morbidity in hypothyroidism, for example falls. Another explanation could be that hypothyroidism has a detrimental influence on bone quality without corresponding effect on demineralization, like what is found in excess of glucocorticosteroids.

There is controversy on whether the patients treated for hyperthyroidism fully regain their BMD loss. Some longitudinal studies have shown only partial recovery in BMD (6, 35, 36). In accordance with this, in a large case–control study, former hyperthyroidism was associated with an increased fracture risk for 5 years following the hyperthyroidism diagnosis (17). On the contrary, two Danish studies from 1996 found no difference in BMD between previously treated hyperthyroid patients and controls (37, 38). The latter studies were performed after at least 4 and 6 years of euthyroidism respectively. The results from the present study fit the hypothesis that former hyperthyroidism is a risk factor for low BMD. However, our data on self-reported hyperthyroidism could not differentiate between present or previous hyperthyroidism or estimate the duration of euthyroidism after treatment. We did try to adjust for these factors by adding current TSH as a covariable. Additionally, as explained above,

defining hyperthyroidism on the basis of treatment consistent with hyperthyroidism may have lead to some misclassification. Therefore, based on the present study, conclusions on the relationship between former hyperthyroidism and BMD should be drawn with caution.

According to Marshall *et al.* one S.D. reduction in distal radius BMD is associated with an increased risk for forearm and vertebral fractures of 1.7 and hip fracture of 1.8 (39). Based on the distal forearm results of the present study, this means that those with TSH <0.50 mU/l, compared to the 0.50–1.49 mU/l group, would have about 8% higher fracture risk. For those with TSH <0.1 mU/l, compared to the TSH 1.0–1.49 mU/l group, the fracture risk would be about 31% higher.

In conclusion, no association was found between TSH within and above the reference range and forearm BMD. Subnormal TSH was associated with a decreased BMD, especially prominent in the TSH <0.10 mU/l group. Self-reported hyperthyroid women had an increased prevalence of osteoporosis.

Declaration of interest

We declare that we do not have any conflict of interest.

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Author contribution statement

Contributors: A Svare conceived the idea, designed the study, did the analyses, and wrote the paper. T I L Nilsen participated in the statistical analyses and interpretation of the results, and contributed in writing the paper. T Bjøro designed the study, interpreted the results, and contributed in writing the paper. S Forsmo and B Schei interpreted the results and contributed in writing the paper. A Langhammer designed the study, was responsible for bone densitometry, quality assurance of BMD and questionnaire data, interpreted the results, and contributed in writing the paper.

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