CLINICAL STUDY

The effect of long-term, non-suppressive levothyroxine treatment on quantitative ultrasonometry of bone in women

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Abstract

Objective: To evaluate the impact of long-term, non-suppressive levothyroxine (L-T₄) treatment on quantitative ultrasonometry in women.

Design: This was a case-control study.

Subjects and methods: Altogether 667 women (mean age $\pm$ s.d., 49.5 ± 13.1 years) were studied. Of these, 156 (23%) had non-toxic goitre or hypothyroidism and had been taking L-T₄ (75–100 μ g/day) for at least 5 years (mean $\pm$ s.d., 12.5 ± 7.5 years); the remaining 511 (77%) women were not receiving L-T₄. All women had completed a questionnaire on risk factors for thyroid dysfunction and osteoporosis, and those with diseases or treatments known to effect bone metabolism – other than thyroxine or hormone replacement therapy (HRT) – were excluded. Women underwent quantitative ultrasonometry (QUS) at the heel. Speed of sound (SOS), broadband ultrasound attenuation (BUA) and the stiffness index (SI) were compared, first, in all women taking L-T₄ and controls and, secondly, in women taking L-T₄ and controls pair-matched for age, weight, body mass index (BMI), menopausal status and HRT use.

Results: Even after matching for age, weight, BMI, menopausal and HRT status, women taking L-T₄ had significantly lower values for SOS and SI ($P < 0.05$), but not for BUA. However, absolute T- and Z-scores for SI were not low in either the study or control groups. Lower values were associated, but not significantly so, with years since the menopause and duration of L-T₄ treatment.

Conclusions: Long-term, non-suppressive L-T₄ treatment in women with goitre or hypothyroidism was associated with a slight reduction in QUS values, which was more pronounced in postmenopausal women. This group could be at higher risk for osteoporotic fracture.

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Introduction

Thyroid dysfunction and osteoporosis are common diseases, particularly in postmenopausal women (1–3). Thyroid hormones play an important part in bone remodelling (4). Histomorphometric studies have shown that thyroid hormones stimulate osteoblasts and osteoclasts in cortical and trabecular bone (5). Studies *in vitro* suggest that hyperthyroidism not only increases bone turnover, but increases bone resorption at a rate greater than that of bone formation, leading to bone loss (6–8).

The relation between thyroid function and bone mass has been examined in several cross-sectional and even prospective studies. Some reports, including a meta-analysis by Wüster (9), have suggested that

the bone mineral density (BMD) is reduced in patients taking long-term treatment to suppress thyroid stimulating hormone (TSH) (levothyroxine, L-T₄) compared with controls (10–13). However, other studies have failed to confirm this decremental effect of L-T₄ treatment on BMD (14–17) or on the prevalence of fracture (18, 19). L-T₄ treatment that does not suppress TSH seems to have little effect on bone (20–23). A recent, large prospective study on elderly ambulatory women found no consistent evidence that a low TSH concentration was associated with a low BMD or accelerated bone loss (2).

BMD measurement in all these studies was performed by dual-energy X-ray absorptiometry (DXA) of the spine and the hip or single-photon absorptiometry (SPA) at the distal forearm. Quantitative

ultrasonography (QUS) is a newer method of skeletal evaluation (24–26). Ultrasound variables at the heel correlate highly ($r=0.8$ – 0.9) with BMD and with biomechanical properties at the same site (27–31).

Cross-sectional and prospective studies have shown that QUS is as capable of predicting hip and vertebral fracture as BMD determination, and even provides additional information (32–38). No large QUS study on the effect of non-suppressive L-T₄ treatment has been reported. However, Gomez Acotto *et al.* (39) reported that hyperthyroidism reduced appreciably QUS variables at the heel and that this reduction was as great, or even greater, than that reported for BMD values in these patients. Correction of thyrotoxicosis not only increases BMD, it increases QUS variables (40, 41).

This study aimed to investigate the effects of long-term (>5 years), non-suppressive L-T₄ treatment on QUS of the os calcaneus. It compared QUS values in a large sample of otherwise normal women taking L-T₄ treatment and healthy control women, and aimed to control for possible confounding factors by comparing women taking L-T₄ treatment with controls pair-matched for age, weight, height, body mass index (BMI), age at menarche, age at menopause, menopausal status, pregnancy, and HRT use.

Subjects and methods

Subjects

Women attending for routine check-up at the Department of Obstetrics, Gynaecology and Endocrinology at the Philipps University (Marburg, Germany) were recruited to the study. Before entry to the study, all women had completed a detailed questionnaire on important risk factors for thyroid dysfunction and osteoporosis. None had sustained osteoporotic fractures (spine, hip, or forearm) or had a history of thyrotoxicosis, including radioiodine therapy or thyroidectomy. Only women who had been taking L-T₄ long term (>5 years) at a dosage of 75–100 µg/day to treat non-toxic goitre or primary hypothyroidism or healthy controls with no history of thyroid diseases and normal thyroid hormonal pattern were eligible for inclusion. Women with diseases known to affect bone metabolism or those being treated with drugs other than HRT (0.625 mg conjugated oestrogens and progesterone or 2 mg 17β-oestradiol and progesterone) which might have an effect on the skeleton (such as glucocorticoid, anticonvulsant or bisphosphonate drugs or calcitonin, fluoride, calcitriol or tamoxifen) were excluded from the study. Women were considered postmenopausal if their last menstrual bleeding occurred at least 1 year previously. Women who had undergone hysterectomy were considered postmenopausal if their follicle stimulating hormone concentration was >35 IU/l and their oestradiol concentration was <10 pg/ml.

Study design

In the first stage of the study, women taking L-T₄ were compared with those who were not on this treatment. Then, to reduce any bias introduced by confounding variables, treated women were compared with an equal number of controls, matched for age (± 2 years), weight (± 10 kg), BMI (± 2.5 kg/m²), menopausal status, and HRT status (matched pairs). We examined the effect of menopausal status by separate analysis of premenopausal and postmenopausal women taking L-T₄ treatment. Lastly, we examined the influence of the duration of L-T₄ treatment on ultrasound variables.

Hormone assays

Blood samples were drawn (i.v.) after an overnight fast. Serum samples for the determination of TSH were frozen at -90°C until analysis. All other analyses were performed immediately.

Serum TSH was measured by a highly sensitive third generation radioimmunoassay/immunometric technique according to the manufacturer's instructions (Medipan Diagnostica GmbH, Selchow, Germany). Intra-assay and interassay coefficients of variation were 6.5% and 7.8% respectively. The detection limit for both assays was 0.03 mIU/l. Serum FSH was measured by a highly sensitive IRMA assay according to the manufacturer's instructions (Biochem Immunosystems Co, Freiburg, Germany). Intra-assay and interassay coefficients of variation were 6.1% and 6.5% respectively. The detection limit was 0.5 IU/l. Serum oestradiol was measured by a sensitive radioimmunoassay according to the manufacturer's protocol (Biochem Immunosystems Co.). Intraassay and interassay coefficients of variation were 3.8% and 5.8% respectively. The detection limit was 5 pg/ml.

Quantitative ultrasonometry

An Achilles device (Lunar Corporation, Madison, WI, USA) was used. The Achilles system consists of two unfocused transducers (2.5 cm diameter), mounted approximately 9.5 cm apart. One transducer acts as the transmitter and the other as the receiver. Acoustic coupling is accomplished by submerging the transducers and the subject's heel in about 100 cm³ water maintained at 35 °C; the water is changed for each subject. A quality control procedure using a standard phantom was performed each day before the measurements *in vivo*.

Two ultrasound variables were measured at the heel – broadband ultrasound attenuation (BUA), expressed as dB/MHz, and speed of sound (SOS), expressed as m/s. A third variable, the stiffness index (SI) (expressed as a percentage of the mean value in young adults), was used to minimise measurement errors caused by variable heel width and water temperature. This index

should not be confused with the biomechanical term 'stiffness'. The SI is a linear combination of normalised BUA and SOS as follows:

$$SI = 0.67 \times (BUA) + 0.28 \times (SOS) - 420.$$

Short-term precision of the Achilles device was assessed *in vivo* three times in 1 day in 31 healthy volunteers working at the hospital. Short-term precision, expressed as the coefficient of variation, was 1.2% for BUA, 0.2% for SOS and 1.3% for the SI. Quality control was performed every day before measurement began; a standardised phantom was used for this. Long-term precision reported in several other studies using this instrument is about 2% (30, 33–36).

Ethical approval

The study was approved by the ethical committee of the University of Marburg and was carried out according to the requirements of the declaration of Helsinki. Each patient signed a consent form beforehand.

Statistical analysis

Data analyses were performed using SPSS for Windows 7.5. Variables were checked for skewness and kurtosis, and were not normally distributed except for age, weight, and the ultrasound variables. We therefore performed non-parametric statistical tests (U-test) for the former variables and a two-tailed *t*-test for the latter.

Results

Subjects

Altogether 667 women participated in the study. Their ages ranged from 31–81 years (mean $\pm$ s.d., 49.5 ± 13.1 years). Of these 511 (77%) of the women had never used L-T₄. The L-T₄ group comprised 156 (23%) women. The mean duration of L-T₄ use was 12.5 ± 7.5 years, and the length of treatment ranged from 5–45 years.

Study versus control women

Table 1 shows the baseline characteristics of women taking L-T₄ ($n = 156$) and control women ($n = 511$). Women taking L-T₄ had significantly lower values for SOS and SI than control women ($P < 0.001$ and $P < 0.01$ respectively). These included lower T- and Z-scores ($P < 0.01$ and $P < 0.05$ respectively). The L-T₄ treated women also had lower but not suppressed serum TSH concentration ($P < 0.001$); higher mean age ($P < 0.01$), weight ($P < 0.001$), BMI ($P < 0.001$), and number of pregnancies ($P < 0.001$); and fewer of them used HRT ($P < 0.001$) compared with control women. There were no significant differences between

Table 1 Characteristics and QUS values (means $\pm$ s.d.) in women treated with L-T₄ and control women.

	L-T ₄ users ($n = 156$)	Controls ($n = 511$)
Age (years)	$52.4 \pm 10.4^{**}$	48.6 ± 13.7
Weight (kg)	$71.3 \pm 13.9^{***}$	67.3 ± 13.1
Height (cm)	164.9 ± 6.7	164.8 ± 6.2
BMI (kg/m ²)	$26.2 \pm 4.9^{***}$	24.8 ± 4.8
TSH (IU/l)	$0.56 \pm 0.66^{***}$	0.87 ± 0.57
HRT users (%)	53.5 ^{***}	72.5
Age at menarche (years)	13.4 ± 1.6	13.3 ± 1.5
Age at menopause (years)	46.6 ± 6.9	46.6 ± 7.3
BUA (dB/MHz)	112.0 ± 9.8	113.3 ± 10.2
SOS (m/s)	$1537 \pm 27^{***}$	1549 ± 31
SI (%)	$85.1 \pm 12.5^{**}$	89.1 ± 13.8
T-score for SI	$-1.2 \pm 1.0^{**}$	-0.8 ± 1.1
Z-score for SI	$0.2 \pm 1.0^*$	0.4 ± 1.1

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ compared with controls.

the groups for height, age at menarche, age at menopause, or BUA. Due to the relatively high number of HRT users in both groups, the T- and Z-scores for SI were not reduced in either group.

Study women versus matched controls

Table 2 shows the results in 143 study women and their 143 controls matched for age, weight, BMI, menopausal and HRT status. There were also no significant differences in height, age at menarche, age at menopause, number of pregnancies between the groups. The mean serum TSH concentration was lower but not suppressed in L-T₄ users compared with matched controls (0.5 ± 0.6 versus 0.9 ± 0.6 IU/l; $P < 0.001$). With regard to the ultrasound variables, the SOS (1537 ± 27 m/s) and SI ($84.8 \pm 12\%$), as well as the T- (-1.2 ± 1) and Z-scores (0.2 ± 1) for SI, were significantly lower ($P < 0.05$) in the L-T₄ treated women than in the controls, who showed an SOS value of 1545 ± 27 m/s, an SI of $88 \pm 12\%$, a T-score of -0.9 ± 1 , and a Z-score of 0.6 ± 1 . BUA was similar in treated and control women (112 ± 9 versus 113 ± 9 dB/MHz respectively).

Values in relation to menopausal status

Figure 1 shows the Z-score for SI in relation to the menopausal status in L-T₄ users and their controls matched for age, weight, BMI and HRT status. Premenopausal and postmenopausal women currently using L-T₄ for more than 5 years showed a slightly (but not statistically significant) lower Z-score than matched controls. There was also no significant lower T-score in current L-T₄ users compared with matched controls (data not shown). In the case of the postmenopausal L-T₄ users ($n = 83$), the average T-score for SI was -1.3 , while that for control women ($n = 83$) was -1 .

Table 2 Subject characteristics and QUS values (means $\pm$ s.d.) in women treated with L-T₄ and in control women matched for age, weight, BMI, menopausal and HRT status (matched-pairs).

	L-T ₄ users (n = 143)	Controls (n = 143)
Age (years)	52.4 $\pm$ 9.8	52.8 $\pm$ 9.5
Weight (kg)	69.8 $\pm$ 11.6	68.9 $\pm$ 11.2
Height (cm)	165.1 $\pm$ 6.2	164.3 $\pm$ 5.6
BMI (kg/m ²)	25.6 $\pm$ 4.1	25.5 $\pm$ 4.1
TSH (IU/l)	0.54 $\pm$ 0.64***	0.88 $\pm$ 0.61
Postmenopausal (%)	53.3	53.3
HRT users (%)	59.1	59.1
Age at menarche (years)	13.5 $\pm$ 1.6	13.2 $\pm$ 1.3
Age at menopause (years)	46.7 $\pm$ 6.9	46.3 $\pm$ 7.0
Number of pregnancies	1.9 $\pm$ 1.3	1.9 $\pm$ 1.1
BUA (dB/MHz)	111.7 $\pm$ 9.4	113.4 $\pm$ 9.0
SOS (m/s)	1537 $\pm$ 27*	1545 $\pm$ 27
SI (%)	84.8 $\pm$ 12.3*	88.0 $\pm$ 11.9
T-score for SI	-1.2 $\pm$ 0.9*	-0.9 $\pm$ 0.9
Z-score for SI	0.2 $\pm$ 1.0**	0.6 $\pm$ 1.0

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ compared with controls.

Values in relation to duration of treatment

Figure 2 shows the Z-score of women using L-T₄ for more than 5 years in relation to the duration of treatment. The Z-score shows a small but insignificant decrease that was duration dependent.

Discussion

This study showed that the SI was 5% lower in women taking L-T₄ than in controls. In women taking L-T₄ compared with pair-matched controls, the slightly smaller difference of 4% remained significant. The Z-score for SI in both L-T₄ users and controls was slightly above that expected for age-matched normal women, perhaps because a large number of our sample

had used HRT. Our results also indicated that the duration of L-T₄ use correlated negatively with the reduction in ultrasound variables.

Thyroid hormone has a potent effect on bone turnover and on BMD. Histomorphometric studies have shown reduced activity in the recruitment and maturation of bone cells, leading to decreased osteoblast and osteoclast function in untreated hypothyroid patients (42–44). Thyrotoxicosis, however, accelerates bone turnover; the number of osteoclasts, resorption sites and the ratio of resorptive to formative bone surface all increase leading to bone loss (4, 7, 8, 42).

The effect of L-T₄ treatment on BMD in premenopausal women is uncertain. Several studies showed a reduction in BMD (13, 45, 46), but the meta-analyses by Faber & Galloë (47) and by Wüster (9) found no significant BMD reduction associated with suppressive treatment in premenopausal women. Marcocci *et al.* (48) examined BMD and biochemical markers of bone turnover in 47 premenopausal women treated for more than 5 years where TSH was monitored to minimise the L-T₄ dose. Carefully monitored suppressive therapy was not associated with bone loss in premenopausal women.

Postmenopausal women have a greater susceptibility to bone loss, but not necessarily a great skeletal responsiveness to thyroid hormone (49). The meta-analyses by Faber & Galloë (47) found that the BMD in postmenopausal women using suppressive L-T₄ treatment was 9% lower than that in matched controls. These results have been confirmed by a more recent and much larger meta-analysis by Uzzan *et al.* (3).

Even non-suppressive L-T₄ treatment seems to be associated with a small but significant reduction in BMD at the spine and hip in postmenopausal women. The detrimental effect of L-T₄ treatment seems to be more pronounced on cortical bone than on trabecular bone. Kung & Pun (20) and Paul *et al.* (11) found that BMD at the spine was unaffected, but that BMD

Figure 1 Median Z-score for the SI in relation to menopausal status in women on L-T₄ treatment and control women matched for age, weight, BMI and HRT use.

Figure 2 Z-score for the SI in relation to the duration of L-T₄ treatment.

at the femur was reduced by 5–10% with long-term treatment. De Rosa *et al.* (45) showed a significant postmenopausal reduction in BMD at the spine (–1.3%) and femoral neck (–1.5%) in a 1 year prospective study of women with subnormal but not suppressed serum TSH values and controls. Our results also tended to show that suppressive L-T₄ treatment had a greater effect on postmenopausal than premenopausal women, even after controlling for confounding factors, but in both groups the effect on QUS variables was small.

Hanna *et al.* (50) and Saggese *et al.* (51) reported controversial findings that L-T₄ had no detrimental effect on the BMD at the spine (mean, 9 years treatment) and hip (mean, 13.4 years). In addition, a recent study by Bauer *et al.* (2) examined the relation between BMD and TSH values in 487 women, including 198 women taking T₄, randomly selected from a cohort of 9704 older women participating in the study of osteoporotic fracture (SOF). The TSH value was not associated with a low BMD or accelerated bone loss after adjustment for age, weight, use of oestrogen or previous hyperthyroidism.

In conclusion, these results show that hyperthyroidism can adversely affect bone, which is known to be associated with an increased risk of hip fracture. Studies on the effect of long-term, non-suppressive L-T₄ treatment on bone have provided controversial results. This is the first study in which QUS has been used in a large cohort of healthy women. Like others, our results showed that long-term, non-suppressive L-T₄ treatment led to accelerated bone loss, although absolute values were not in the osteoporotic range. Further studies are needed to investigate whether this bone loss is associated with a higher fracture rate in postmenopausal women.

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