Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Changes of bone mineral density, quantitative ultrasound parameters and markers of bone turnover during treatment of hyperthyroidism

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ABSTRACT

Background: The extent of reversibility of loss of bone mass density (BMD) in hyperthyroid patients after treatment is not clear.

Methods: The bone density measured by dual X-ray absorptiometry (DXA), the parameters of quantitative ultrasound (QUS) and biochemical markers of bone turnover of 22 patients were measured before and after one year of treatment with thiamazole and levothyroxine.

Results: The mean BMD of lumbar spine, femoral neck, Ward triangle and total hip bone density increased by 5.9, 3.8, 3.0 and 6.7%, respectively, after one year of treatment, all significant increases except the increase in Ward triangle bone mass density. There was no significant change in QUS parameters, although the increase in broadband ultrasound attenuation (BUA) of the left and right calcaneus of 5.2 and 4.2%, respectively, suggests reversibility in the long term. Urinary pyridinoline cross-links declined significantly and normalised after treatment. Bone-specific alkaline phosphatase declined after an initial rise, not (yet) reaching normal values after one year of treatment.

Conclusion: The decline in BMD in hyperthyroid patients measured by DXA seems to be reversible after treatment of hyperthyroidism, whereas a change in the QUS parameters, probably also an indicator of bone elasticity and architecture, could not be found.

KEYWORDS

Bone mass, hyperthyroidism, quantitative ultrasound

INTRODUCTION

Hyperthyroidism is associated with osteoporosis. Von Recklinghausen was the first to describe the fractures and the 'worm eaten' appearance of the bones of patients suffering from hyperthyroidism.[1] These days there are therapeutic options such as antithyroid drugs and radioiodine, yet there is still a reduction in bone density in hyperthyroid patients and in patients with subclinical hyperthyroidism by endogenous overproduction or oversuppletion of thyroid hormone.[2] The reason for this is the direct stimulating effect of the thyroid hormone[3] and possibly also the negative regulating effect of thyroid-stimulating hormone (TSH)[4] on bone resorption. Also, increased serum interleukin-6 concentrations in hyperthyroid patients favour osteoclast production and may be an effector of the action of parathyroid hormone on bone.[5]

The extent of reversibility of bone loss after the start of treatment is unclear. Previous studies have yielded variable results. Some studies showed complete normalisation of the bone density.[6-9] Other studies reported no or incomplete recovery of bone density after treatment.[10-16]

Dual X-ray absorptiometry (DXA) is currently the most frequently used instrument for measuring bone mass density (BMD). With little radiation it gives very precise and accurate measurements. There is a strong relationship between fracture risk and BMD measured by DXA.[17]

Quantitative ultrasound (QUS) has also proven to be a good predictor of fracture risk.[18] Instead of measuring bone density directly, it measures the transmission of ultrasound through accessible limb bones or the reflectance of the ultrasound waves from the bone surface. QUS might provide information not only on bone mass but also on bone elasticity and structure.[19-21] Advantages are the lower expense,

portability, and lack of radiation exposure. Yet, the criteria for diagnosing osteoporosis are not well established.
Biochemical markers of bone turnover, such as pyridinoline cross-links and bone-specific alkaline phosphatase, are increased in hyperthyroidism suggesting an increase in osteoclastic and osteoblastic activity. Previous studies show that these markers normalise after treatment.[22-24]
The aim of this study was to determine the influence of treatment of hyperthyroid patients on the bone density measured by DXA, on the parameters of QUS and the effect on the biochemical markers of bone turnover.

SUBJECTS AND METHODS

Subjects

Twenty-two consecutive patients with untreated thyrotoxicosis, caused by Graves' disease, attending our outpatient department were enrolled. Eighteen women and four men participated in the study and gave informed consent. The inclusion criteria were:

- clinical symptoms of hyperthyroidism;
- a suppressed serum thyroid-stimulating hormone (TSH <0.04 mU/l) and an elevated serum free T4 (FT4 >25 pmol/l) and/or free T3 (FT3 >7 pmol/l) and
- confirmation of the Graves hyperthyroidism by Tc99 scan.

Patients with comorbidity (hypo- and hyper-parathyroidism, vitamin D deficiency, Cushing's disease, inflammatory bowel disease, malabsorptive diseases) or on medication (steroids, bisphosphonates, calcium, vitamin D, or hormonal replacement therapy) influencing bone turnover were excluded. Also patients postmenopausal for less than five years were excluded.
All patients were treated with thiamazole and levothyroxine according to the block and replace regime in order to obtain and maintain euthyroid status. Patients were treated with thiamazole 30 mg once a day as monotherapy for six weeks, and consecutively levothyroxine was added six weeks later, depending on results of the TSH levels.

Methods

Serum thyroid hormones, TSH, calcium (normal value 2.15 to 2.55 mmol/l) and phosphate (normal value 0.8 to 1.5 mmol/l) were measured at baseline and after three, six and 12 months. TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third-generation TSH, Diagnostic Products Corporation, Los Angeles USA, normal value 0.4 to 4.0 mU/l). The FT4 and FT3 concentrations were measured with a solid-phase immunometric assay (IMMULITE Free T4 and Free T3, normal values 10 to 24 pmol/l and 2.7 to 7.0 pmol/l, respectively).
All patients underwent a ^{99m}Technetium scan with 110 MBq Technetium and were scanned with a gamma camera with an energy level of 110 keV. All patients showed a pattern comparable with autoimmune hyperthyroidism.
The biochemical markers of bone turnover, bone-specific alkaline phosphatase (Metra kit, Quidel, USA) and urinary pyridinoline cross-links (sCTx Elecsys Roche), were measured at baseline and after three, six, nine and 12 months. Because of the sex- and age-related variability of bone turnover parameters, results were expressed as Z scores, subtracting the mean value of an age-, ethnicity-, and sex-matched reference population from the patient's value and dividing the difference by the standard deviation (SD) of the reference population. A normal Z score was considered to be between -2 and 2.
Autoantibodies to the TSH receptor (RRA Brahms, normal value <35 kU/l) and anti-TPO antibodies (Immulite 2000 Siemens, normal value <14 E/l) were determined at baseline.
DXA measurement and quantitative ultrasound were performed at baseline and after 12 months. DXA measurement (Hologic QDR 2000, Bedford MA, USA) was performed at the lumbar spine (L1 to L4) and left femur (femoral neck, Ward triangle, and total hip). BMD was expressed in g/cm^2. The Z score was calculated by subtracting the mean BMD of an age-, ethnicity-, and sex-matched reference population from the patient's BMD and dividing the difference by the SD of the reference population.
Quantitative ultrasound was performed with a Hologic ultrasound (Sahara, Hologic Inc, Bedford MA, USA) at os calcis on the left and right side with two subsequent measurements each. Afterwards the mean value of each side was calculated. The QUS device measured the broadband ultrasound attenuation (BUA, dB/MHz) and speed of sound (SOS, m/s).
DXA measurements were performed by independent analists, who were not involved with the study. The Ethics Committee of Máxima Medical Centre gave permission for the study.

Statistical evaluation

Results were expressed as the mean and SD. Data before and after treatment were analysed by paired Students T-test, after assessing the normal distribution of the data by Stem-and-Leaf plot. If this was not normally distributed, the Wilcoxon ranking test was applied. A p value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 40 years, range 24 to 62 years; 82% of the patients were female. The mean body mass index (kg/m^2) was 23.6 with a range of 18.0 to 30.6 kg/m^2.

Seven patients were postmenopausal with a mean age of 57 years.

Table 1 shows the levels of serum thyroid hormones and biochemical markers at baseline, three, six and 12 months. Thyroid hormones decreased and TSH levels rose during treatment and generally reached a normal range. In two of the patients, the levels of FT4 had not yet reached the normal value, despite 12 months of treatment. Mean serum calcium and phosphate decreased but were within normal ranges throughout the study. Serum calcium decreased significantly from 2.36 mmol/l (SD 0.09) to 2.26 mmol/l (SD 0.09), a decrement of 0.10 mmol/l (SD 0.09) after 12 months of treatment.

Anti-TPO antibodies were found in 64% of the patients. Autoantibodies to the TSH receptor were also positive in 64% of the patients.

In *figure 1* the mean values of the Z score of bone-specific alkaline phosphatase and urinary pyridinoline cross-links during one year of treatment of hyperthyroidism are shown. Mean serum bone-specific alkaline phosphatase was above normal level at baseline (Z score 2.5 ± 2.5). After an initial rise to a Z score of 7.3 after three months, bone-specific alkaline phosphatase declined, but did not reach the normal range (Z score 2.9 ± 3.2). Urinary pyridinoline cross-links were above normal values at baseline (Z score 6.0 ± 5.0), but declined significantly ($p<0.01$) after treatment and reached normal range (Z score 0.3 ± 1.8).

The results of the DXA measurements are shown in *table 2* and *figure 2*. At baseline the mean Z scores of the bone density of femoral neck, total hip, inter and trochanter major were <0. After treatment all mean Z scores were >0. The BMD of lumbar spine, femoral neck, ward triangle and total hip all increased after 12 months of treatment. The mean lumbar spine BMD increased from an initial value of 1.01 g/cm² to 1.07 g/cm², an increase of 5.9% after one year of treatment. Femoral neck, Ward triangle and total hip bone density increased by 3.8, 3.0 and 6.7%, respectively, after one year of treatment. Only the increase of the Ward triangle BMD was not significant.

Figure 1. *Mean Z score of the bone turnover parameters bone-specific alkaline phosphatase and pyridinoline cross-links during one year of treatment with thiamazole and levothyroxine*

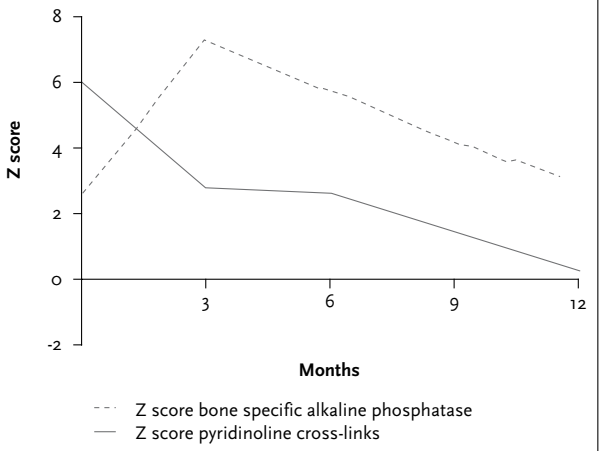
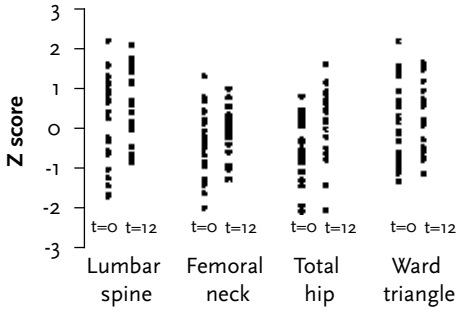


Figure 2. *Z scores of the bone mass density of the individual patients measured by DXA at lumbar spine, femoral neck, total hip and Ward triangle before and after 12 months of treatment with thiamazole and levothyroxine*



t=0 = z score before treatment; t=12 = z score after 12 months of treatment.

Table 1. *Serum thyroid hormone levels and biochemical markers calcium and phosphate (mean ± SD)*

Serum level (normal value)	Baseline	3 months	6 months	12 months	P value (difference 12 months-baseline)
TSH (0.4-4.0 mU/l)	0.0032 ± 0.01	0.38 ± 0.88	2.05 ± 2.94	3,.1 ± 3.76	-
FT4 (10-24 pmol/l)	54.2 ± 17.9	22.5 ± 10.3	20.36 ± 12.49	18,8 ± 5.17	-
FT3 (2.7-7.0 pmol/l)	15.2 ± 6.5	6.23 ± 4.26	5.45 ± 3.52	4.29 ± 1.33	-
Calcium (2.15-2.55 mmol/l)	2.36 ± 0.09	2.30 ± 0.07	2.27 ± 0.07	2.26 ± 0.09	0.000
Phosphate (0.8-1.5 mmol/l)	1.26 ± 0.28	1.13 ± 0.22	1.18 ± 0.18	1.15 ± 0.14	0.085

TSH = thyroid-stimulating hormone; FT = free thyroid.
Measured at baseline and after three, six and 12 months during treatment of hyperthyroidism with thiamazole and levothyroxine according block and replace regime.

Table 2. *Mean values ± SD of DXA measurements BMD (g/cm²) and Z score*

	Baseline BMD (g/cm²)	12 months BMD (g/cm²)	P value BMD	Baseline Z score	12 months Z score	P value Z score
Lumbar spine	1.01 ± 1.4	1.07 ± 0.11	0.003	0.12 ± 1.10	0.63 ± 0.89	0.001
Femoral neck	0.80 ± 0.10	0.83 ± 0.08	0.028	-0.25 ± 0.84	0.04 ± 0.62	0.004
Total hip	0.89 ± 0.10	0.95 ± 0.10	0.000	-0.34 ± 0.82	0.17 ± 0.89	0.000
Ward triangle	0.67 ± 0.15	0.69 ± 0.12	0.552	0.19 ± 0.98	0.29 ± 0.86	0.42

The mean BUA measured by a QUS device at the left and right calcaneus increased by 5.2 and 4.2% after 12 months, but this increase was not significant (*table 3*). The SOS barely increased after 12 months; left and right 0.07 and 0.03%, respectively. There was no significant change.

DISCUSSION

Our study shows that BMD of patients with hyperthyroidism measured by DXA increases during the first year of treatment with thiamazole and levothyroxine. The mean BMD of lumbar spine, femoral neck and total hip all increased significantly by 5.9, 3.8 and 6.7%, respectively.

Previous studies reported varying percentages of increment. Only Toh and colleagues found no significant difference in two years of treatment after a significant decrease in bone mineral content (BMC) in the first year and a recovery in the second year, using a single-photon absorptiometry. Krolner and colleagues found an increase of lumbar spine BMC of 3.7% using dual-photon absorptiometry. Diamond *et al.* reported a significant increase of 6.6% of lumbar spine BMD in one year, measured by DXA. Femoral neck and trochanter did not change significantly (increment 1.2 and 3.2%, respectively). A recent study by Acotto and colleagues showed a large increase of 10.4% of lumbar spine BMD and 8% of femoral neck BMD after one year of treatment and 14 and 12.2%, respectively, after two years of treatment, measured by DXA. Rosen *et al.* suggested a longer lasting effect on bone mineral density by reporting an increase of lumbar spine BMD of 11% after five years of treatment. Karga *et al.* found no significant difference in Z score after three years of treatment in comparison with controls. Langdahl and colleagues also found a normal bone quantity (mineral content and density) in hyperthyroid patients, after treatment for at least four years. After performing a meta-analysis, Vestergaard *et al.* found a decreased bone mineral density and an increased fracture risk in hyperthyroid patients, with normalisation of bone density after one to four years of treatment.

However, whether the damage of the architecture and elasticity (quality) of the bone due to a period of hyperthyroidism is reversible after treatment is not well known. *In vitro* studies suggest that quantitative ultrasound not only provides information on bone density but also on bone architecture and elasticity. Acotto *et al.* reported significantly lower QUS parameters (BUA and SOS) in hyperthyroid patients in comparison with controls.[25] Not many studies have investigated changes in QUS parameters of the calcaneus in treated hyperthyroid patients.
Acotto *et al.* recently reported an increase in mean BUA of 5.4% after one year but then a decrease of 1.6% after two years of treatment. SOS increased by 1.2% after two years. However, ultrasound parameters did not reach normal values after two years of treatment. Our study could not confirm these results: we found no change in mean SOS (increase of 0.07 and 0.03% on left and right calcaneus) during the first year of treatment. Although BUA increased by 5.4 and 4.2% on the left and right side, respectively, these changes were not statistically significant. A new study, including more patients and with a longer follow-up, is needed to confirm the suggested increase of BUA and determine the reversibility in the long term. For practical use the development of quality standards for and cross-calibrations of QUS as well as criteria for diagnosing osteoporosis are necessary.

Several studies reported increased markers of bone turnover in hyperthyroid patients.[15,21-23] Our study shows comparable results: after treatment of hyperthyroidism urinary pyridinoline cross-links, a marker of bone

Table 3. *Mean values of broadband ultrasound attenuation (BUA) and speed of sound (SOS) at baseline and after 12 months of treatment*

	Mean ± SD at baseline		Mean ±SD after 12 months		P value	
	Left	Right	Left	Right	Left	Right
BUA (dB/MHz)	72.6 ± 15.5	72.7 ±15.7	76.4 ± 14.8	75.8 ± 14.1	0.110	0.180
SOS (m/s)	1543.0 ± 32.5	1542.3 ± 30.5	1544.1 ± 31.3	1542.7 ± 32.8	0.728	0.777

resorption, declines rapidly and normalises. Bone-specific alkaline phosphatase, a marker of bone formation, declines after an initial rise during the first three months of treatment, not (yet) reaching normal values after one year of treatment.

CONCLUSION

Our study shows a significant increment in BMD measured by DXA after one year of treatment. The QUS parameters, an indicator not only of bone density but probably also of bone architecture and elasticity, did not change significantly. More studies with long-term follow-up and larger patient populations have to be performed to assess the reversibility of declined QUS parameters as indicator of bone architecture and elasticity in hyperthyroid patients during treatment. The increased markers of bone turnover declined during treatment. This result is consistent with results of previous studies.

ACKNOWLEDGEMENTS

We thank MSD for providing the quantitative ultrasound device, Eveline van der Veer for measurement of markers of bone turnover and Professor A. Hermus for discussing the article with us.

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