Changes in bone mass during prolonged subclinical hyperthyroidism due to \( l \)-thyroxine treatment: a meta-analysis

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\( l \)-Thyroxine (\( l \)-T\(_4 \)) in the treatment of thyroid disease resulting in reduced serum thyrotropin (TSH) has been associated with reduced bone mass and thus the potential risk of premature development of osteoporosis. However, several recent studies have failed to show such a detrimental effect. These disagreements are probably due to only a small number of patients taking part in each study, decreasing the chance of finding significant differences and increasing the risk of missing a real difference (type 1 and 2 errors, respectively). We therefore performed a meta-analysis on the available papers (\( N = 13 \)), in which bone mass was measured in the distal forearm, femoral neck or lumbar spine in a cross-sectional manner in women with suppressed serum TSH due to \( l \)-T\(_4 \) treatment and in a control group. The women were divided according to their pre- and postmenopausal state, because preserved estrogen production plays a protective role against irreversible bone loss. Based on the number of measurements performed on the different sites of the skeleton, a theoretical bone composed of 30.4% distal forearm, 28.8% femoral neck and 40.8% lumbar spine could be constructed in premenopausal women (441 measurements). A premenopausal woman at an average age of 39.6 years and treated with 164 \( \mu \)g \( l \)-T\(_4 \)/day for 8.5 years, leading to suppressed serum TSH, had 2.67% less bone mass than controls (NS), corresponding to an excess annual bone loss of 0.31% after 8.5 years of treatment (NS). The risk of not detecting an excess bone loss of at least 1% per year (type 2 error) was \( p < 0.15 \). Similarly, a postmenopausal woman with a bone consisting of 11.3% distal forearm, 42.0% femoral neck and 46.7% lumbar spine (317 measurements) at an average age of 61.2 years and treated with 171 \( \mu \)g \( l \)-T\(_4 \)/day for 9.9 years had 9.02% less bone mass than controls (2\( p < 0.007 \)), corresponding to a significant excess of annual loss of 0.91% after 9.9 years of treatment. Eighteen papers with a mean of 18 patients showing no difference between postmenopausal patients and controls would have to be published or found before this difference could turn into a non-significant finding (the file drawer problem). In conclusion, the meta-analysis on the available cross-sectional studies did not find any significant reduction in bone mass during prolonged \( l \)-T\(_4 \) treatment resulting in reduced serum TSH in premenopausal women. The risk of the present meta-analysis missing a clinically relevant annual loss of at least 1% in premenopausal women was less than 15%. In contrast, \( l \)-T\(_4 \) treatment in postmenopausal women in a dosage leading to reduced serum TSH resulted in a significant excess of annual bone loss of 0.91%/year after 9.9 years in comparison to control women.

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The introduction of sensitive serum TSH assays in the mid-1980s enabled a distinction to be made between reduced serum TSH concentrations in hyperthyroid patients and normal values in euthyroid subjects. It also revealed that a large group of patients with primary hypothyroidism substituted with \( l \)-T\(_4 \) had reduced serum TSH concentrations. This state of euthyroidism with reduced serum TSH concentration but normal \( T_4 \) and \( T_3 \) values has been designated subclinical hyperthyroidism.

Thyroxine used in a deliberate overdose to suppress serum TSH is commonly used both in the postoperative treatment of thyroid cancer as well as in the treatment of non-toxic goiter.

In the late 1980s several studies reported significantly reduced bone mass measured with bone scanners in patients on prolonged \( l \)-T\(_4 \) treatment presenting with reduced serum TSH (1–8). Several editorials have emphasized the potential risk of premature development of osteoporosis and warned about this risk if the \( l \)-T\(_4 \) substitution therapy was exaggerated (9, 10).

However, during the last few years several well-conducted studies have failed to demonstrate any detrimental effect on the bone mass in \( l \)-T\(_4 \)-treated patients (11–16). All studies are, however, characterized by the inclusion of a small number of patients, thus decreasing the chance of finding significant differences and increasing the risk of missing a real difference (type 1 and 2 errors, respectively).

The power of the conclusion can be increased if the
publications are combined in a meta-analysis. It was therefore the aim of the present study to investigate whether patients treated with \( \text{L-T}_4 \) in doses large enough to suppress serum TSH concentrations had reduced bone mass compared to healthy normal subjects, as evaluated by a meta-analysis.

Materials and methods

Papers were searched in Medline under the search codes bone mass, bone mineral content and hyper-/hypothyroidism. Additionally, a manual search was performed by screening references from literature and abstracts published at international endocrinological meetings in the years 1985–1992. If needed, the authors were asked to provide additional data. Studies could be included in the meta-analysis if they contained a relevant control group. Only two studies followed bone mass longitudinally, whereas 15 were cross-sectional. Therefore, only cross-sectional data were included in the present analysis.

Data on premenopausal and postmenopausal women were pooled independently, because these two situations seem to be fundamentally different. In premenopausal women, preserved estrogen production plays a protective role against irreversible bone loss, a protection not present in postmenopausal women.

The majority of studies measured bone mass on different sites, typically the distal forearm, the femoral neck and the lumbar spine. Focus was aimed on these three sites in order to obtain as large a patient sample as possible. For each study the differences in the reductions in bone mass were calculated for either pre- or postmenopausal women and for distal forearm, femoral neck or lumbar spine. Bone mass in the distal forearm was measured by single photon absorptiometry, whereas bone mass in the femoral neck and lumbar spine was measured by dual photon absorptiometry, dual-energy X-ray absorptiometry or by quantitative computed tomography. The standard deviation from the patient group was used instead of the pooled standard deviation from the \( t \)-test employed in each study. This was chosen because an uneven number of persons was included in the control groups, which far exceeded the number of persons in the patient groups. This results in a more cautious estimate (17).

The statistics in each of the six subgroups were tested for homogeneity, and it was not possible to detect inhomogeneity. Consequently, it was possible to combine the different statistics in each of the six subgroups in a meta-analysis (18).

The average effect of the size of each subgroup was calculated (mean and 95% confidence level). If the result was insignificant, a theoretical type 2 error was calculated and expressed as the risk of not detecting a real decrease in bone mass of 1% per year. Finally, a theoretical bone consisting of distal forearm, femoral neck and lumbar spine was constructed, and the average age and \( \text{L-T}_4 \) treatment period were calculated in pooled data from pre- and postmenopausal women, respectively.

Results

Fifteen studies fulfilled the inclusion criteria, but in one case the statistics were inappropriate and the authors did not respond to our letter. In three cases the authors provided us with additional data/statistics. One study was excluded because 87% of the patients were treated with \( T_3 \) (3). Thus, 13 studies were included (1, 2, 4–8, 11–16).

Table 1 contains the characteristics of the six subgroups as well as the theoretical average patient for each group with respect to age, \( \text{L-T}_4 \) dose, duration

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
<th>Age</th>
<th>( \text{L-T}_4 ) dose</th>
<th>Reduced TSH (%)</th>
<th>Treatment* time (years)</th>
<th>Cancer* (%)</th>
<th>Hypothyroidism* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radius</td>
<td>134</td>
<td>396</td>
<td>37.9</td>
<td>162</td>
<td>95</td>
<td>7.49</td>
<td>66</td>
</tr>
<tr>
<td>Femur</td>
<td>127</td>
<td>331</td>
<td>39.8</td>
<td>184</td>
<td>83</td>
<td>9.67</td>
<td>39</td>
</tr>
<tr>
<td>Spine</td>
<td>180</td>
<td>633</td>
<td>40.4</td>
<td>153</td>
<td>89</td>
<td>8.45</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>441</td>
<td>1360</td>
<td>39.6</td>
<td>164</td>
<td>90</td>
<td>8.51</td>
<td>55</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radius</td>
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<td>520</td>
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<td>182</td>
<td>100</td>
<td>7.81</td>
<td>72</td>
</tr>
<tr>
<td>Femur</td>
<td>133</td>
<td>494</td>
<td>61.6</td>
<td>164</td>
<td>94</td>
<td>11.19</td>
<td>46</td>
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<tr>
<td>Spine</td>
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<td>767</td>
<td>61.4</td>
<td>169</td>
<td>95</td>
<td>9.31</td>
<td>52</td>
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<tr>
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<td>1781</td>
<td>61.2</td>
<td>171</td>
<td>95</td>
<td>9.93</td>
<td>52</td>
</tr>
</tbody>
</table>

*Percentage of patients with reduced serum TSH.
*Percentage of patients with thyroid cancer.
*Percentage of patients with primary hypothyroidism/non-toxic goiter.
of treatment, percentage of patients with reduced serum TSH (below lower reference range) and percentage distribution between thyroid cancer patients and primary hypothyroidism/non-toxic goiter. Approximately 50% of the patients studied had thyroid cancer. In total, 441 measurements were performed in premenopausal women who were treated for an average of 8.51 years with an average dose of 1-T$_4$ of 164 µg/day, whereas 317 measurements were performed in postmenopausal women treated for an average of 9.93 years with an average dose of 1-T$_4$ of 171 µg/day.

Tables 2 and 3 give the differences in mean bone mass and so for the patient groups extracted from the individual studies. In premenopausal women the excess loss of bone mass compared to healthy premenopausal women for the distal forearm, femoral neck or lumbar spine was a mean of 0.46%, 0.27% and 0.15% per year after 7.49, 9.67 and 8.45 years of 1-T$_4$ treatment, respectively (all non-significant).

For all premenopausal women, a theoretical bone composed of 30.4% distal forearm, 28.8% femoral neck and 40.8% lumbar spine could be constructed (N = 441 measurements). A premenopausal woman at an average age of 39.6 years and treated with 1-T$_4$ for 8.51 years, leading to suppressed serum TSH, would then have an excess loss of bone mass of 2.67% (2p < 0.22). This corresponds to an excess annual loss of 0.31% after 8.51 years of 1-T$_4$ treatment as compared to healthy premenopausal women, which is not significantly different. The risk of not detecting an excess bone loss of 1% per year (as typically seen in healthy postmenopausal women) was p < 0.15.

In postmenopausal women the loss of bone mass for the distal forearm, femoral neck and lumbar spine was a mean of 1.39% (2p < 0.19), 0.77% (2p < 0.07) and 0.92% (2p < 0.15) per year more than control women after 7.81, 11.19 and 9.31 years of 1-T$_4$ treatment, respectively.

For all postmenopausal women a theoretical bone consisting of 11.3% distal forearm, 42.0% femoral neck and 46.7% lumbar spine was constructed (N = 317 measurements). A postmenopausal woman at an average age of 61.2 years and treated with 1-T$_4$ for 9.93 years, leading to suppressed serum TSH, would then have an excess loss of bone mass of 9.02%
(2p < 0.007). This corresponds to an excess annual loss of 0.91% after 9.93 years of l-T4 treatment as compared to healthy postmenopausal women.

A file drawer estimate was calculated, i.e. how many papers should be published or found, all showing zero difference of bone mass between 17.6 patients and a control sample, before the demonstrated significant difference would turn into a non-significant result. The number was 18 (17).

Discussion

It is generally accepted that no or only a very small loss of bone mass takes place in premenopausal women (19). However, when perimenopause is reached a gradual acceleration in the loss of bone mass takes place, reaching about 1–2.5% per year in late perimenopause (19, 20) and 3–5% per year in the early postmenopausal years (19, 21). Later in the postmenopause the loss of bone seems more modest, typically 1–2.5% per year (21, 22). Preserved estrogen production is anticipated as being the main reason for the lack or only minimal loss of bone mass in premenopausal women. It was anticipated, therefore, that a slight increase in bone turnover induced by a slight overtreatment with l-T4 (identified as resulting in reduced serum TSH) would have greater impact on the postmenopausal than on the premenopausal bone mass. We therefore pooled pre- and postmenopausal women independently in the present analysis.

The combination in a meta-analysis of available data from cross-sectional studies demonstrated that the bone mass, as measured over the distal forearm, femoral neck and lumbar spine in premenopausal women treated with l-T4 for 8.51 years resulting in reduced serum TSH, was not different from that of controls. Thus, reduced serum TSH as a sign of subclinical hyperthyroidism seemed not to be detrimental to bone mass. Roughly, the bone mass was reduced equally at all three sites of measurement, with a mean of 2.67% (non-significant) when looking at the theoretical bone composed of distal forearm, femoral neck and lumbar spine. This corresponded to a non-significant annual loss of bone of 0.31% after 8.51 years of l-T4 treatment. Even if l-T4 treatment induced an excess bone loss of 0.31% per year, such an effect seems to be of minor clinical relevance. Ten years of treatment would then induce a bone loss of approximately 3%, an amount lost in the first perimenopausal year (19, 20). The risk of missing a clinically relevant difference in the excess
bone loss of at least 1% per year was less than 15% (type 2 error), indicating that it seems fair to conclude that premenopausal women have, if any, only a minimal excess bone loss with no or little clinical relevance.

In contrast to the premenopausal situation, reduced serum TSH due to l-T4 treatment in postmenopausal women resulted in a significant reduction in bone mass: a mean of 9.02% after 9.93 years in the theoretical bone composed of distal forearm, femoral neck and lumbar spine. This corresponded to an increased annual loss of bone of 0.91% after 9.93 years of treatment, as compared to healthy postmenopausal women. As the control women have an annual loss of bone of approximately 1–2.5% (21, 22), the relative bone loss in l-T4-treated patients with reduced serum TSH is increased by approximately 40–100%. Focusing at the individual sites of measurement of bone mass, reductions only reached marginal significance (distal forearm: $2p = 0.19$, femoral neck: $2p = 0.07$, lumbar spine: $2p = 0.15$). This was probably because of insufficient sample size, as reflected in the great risk of not detecting a difference of at least 1% excess bone loss per year (a type 2 error), of between 93 and 95% (Table 3, last column).

The changes found seemed to be distributed equally throughout the skeleton, although there are great differences in the content of trabecular and cortical bone and thus bone turnover throughout the body. Trabecular bone constitutes approximately 20% of the skeleton but 80% of the bone turnover rate, whereas cortical bone constitutes approximately 80% of the skeleton and 20% of the bone turnover rate. A negative bone balance might thus have greater impact on trabecular than on cortical bone. At the site of the distal forearm where bone mass typically is measured, 20–40% seems to be trabecular bone (23); with regard to the lumbar spine and femoral neck, 30–60% trabecular bone has been quoted (24). No clear difference in the loss of bone mass between the three measurement sites was seen. It seems fair to conclude that postmenopausal women have a significant and probably clinically relevant excess bone loss during suppressive l-T4 treatment.

However, the significant loss in bone mass in postmenopausal women could be a result of publication bias if only those papers showing significant effects have been published. It is possible to construct a theoretical study with a study population the size of the average size included in the present meta-analysis ($N = 17.6$), in order to find a difference of zero. It is then possible to calculate how many such studies should be included in the present meta-analysis before the net result becomes insignificant. If only a small number of such theoretical studies are needed, the power of the conclusion of the meta-analysis is weak and is subject to publication bias. But if a large number of such theoretical studies are needed, then the conclusion seems to be safe. Therefore, the finding of a significant difference in the postmenopausal women seems valid, because 18 studies in the file drawers seems to be an unrealistically high number.

A potential problem was that in no studies used for the meta-analysis was it obvious that the patients presenting with reduced serum TSH had had a stable reduction for all the years under l-T4 treatment. Furthermore, a small number of patients presented a serum TSH concentration within the normal range at the time of the study (10% of the premenopausal and 5% of the postmenopausal women) (Table 1) and still were included in the studies. These patients, however, were often thyroid cancer patients in whom the general intention with the l-T4 treatment was to suppress serum TSH. Therefore, the authors most probably observed reduced serum TSH concentrations previously, but not on the day of the bone mass measurement. All studies used so-called second-generation TSH methodology, i.e. the TSH assay used had a lower detection limit of around 0.05 mU/l, making the authors able to distinguish between reduced and normal levels of serum TSH. These considerations might indicate that the reductions found in bone mass are minimum values.

On the other hand, 50% of the patients received l-T4 after a total thyroidectomy due to cancer. In these patients it is the general therapeutic intention to obtain high-normal or even elevated serum T4 levels in order to suppress effectively the serum TSH level. This probably means that some patients who are slightly hyperthyroid (i.e. having elevated serum T4) have been enrolled in the studies with the potential risk of aggravating the estimated reduction in bone mass. It is only clear from very few of the 13 studies used in the meta-analysis as to how many patients in fact did have increased serum T4 levels.

A total thyroidectomy due to thyroid cancer most often results in calcitonin deficiency. This might theoretically result in excess bone loss. McDermott et al. (25) did demonstrate a reduced bone mass in the distal radius in a small number of patients with calcitonin deficiency, whereas Ahmann et al. (11) in a larger series of patients were unable to find any difference between l-T4-treated (suppressive dosis) patients with and without presumed calcitonin deficiency as measured on different sites of the skeleton. Among the 13 papers used in the meta-analysis, there was no clear difference in bone loss between cancer and non-cancer patients, and it therefore does not seem likely that calcitonin deficiency plays a major role as compared to the l-T4 treatment.

One study was excluded because 87% of the patients were treated with T3 (3). This study, however, demonstrated a more substantial reduction in bone mass in the distal radius than that seen in patients treated with l-T4, and raises the question as to whether T3 has a more detrimental effect on bone mass than l-T4. In line with this, Schoutens et al. (26) followed early postmenopausal women and suggested that serum T3
levels were higher among those women with the most negative bone balance. Furthermore, specific T3 receptors have been demonstrated on bone cells, primarily osteoblasts (27). These considerations demonstrate a weak point of the meta-analysis, namely the fact that we were unable to split the data up according to normal or elevated serum T3 levels, because most papers did not give precise values, if any.

Non-toxic goiter is another clinical setting where patients with subclinical hyperthyroidism (reduced serum TSH and normal serum T4 and T3) might be identified. Only two studies of bone mass have been performed in such patients. Mudd et al. (28) found reduced bone mass in the distal forearm in women with non-toxic goiter along with reduced serum TSH, whereas Faber et al. (29) found no difference in distal forearm or lumbar spine, either cross-sectionally or during follow-up for up to 2 years. In line with the present findings on l-T4-treated patients, the negative results by Faber et al. (29) were obtained on premenopausal women, whereas Mudd et al. (28) studied predominantly postmenopausal women.

Cross-sectional studies might be insensitive to small changes in bone mass. There are, however, only very few longitudinal studies on the effect of l-T4 on bone mass. Stall et al. (5) studied 10 postmenopausal women with reduced serum TSH (25% having elevated serum T4) and found no changes in bone mass on the distal forearm or femoral neck but found a significant reduction of 1.7% per year in the lumbar spine. Pioli et al. (30) studied premenopausal women with thyroid cancer on l-T4 suppressive therapy. Annual loss of bone in the lumbar spine was significantly enhanced by 2.4%. However, approximately 50% of these women had serum T4 levels above the normal range, thus being biochemically overt hyperthyroid and not just subclinical hyperthyroid.

All studies of the effect of l-T4 on the skeleton concentrate on bone mass as measured by osteodensitometry. This gives figures on bone mass but not bone strength, and therefore the connection to fractures later in life is not direct. The bone remodeling process is characterized by a constantly ongoing resorption and formation taking place in lacunae both in trabecular and cortical bone. In the case of a negative bone balance, the thickness of the trabeculae in trabecular bone is reduced, which increases the risk of perforations, with the consequence of broken architecture of the bone and thus a loss of strength. This is not visualized by a bone mass measurement (31). Therefore, studies of morbidity in l-T4-treated patients are of great importance. Only a few such studies are available: Leese et al. (32) recently reported no increased risk of fractures during a 1-year follow-up of women over the age of 45 years with reduced serum TSH due to l-T4 treatment. No type 2 error calculations were presented. In contrast, Bauer et al. (33) in a preliminary report found an increased risk of hip fracture in women over 60 years old with a previous history of hyperthyroidism as well as current use of l-T4 (no indications of serum TSH values), whereas Petersen et al. (34) did not find any increased morbidity in women on l-T4 with normal serum TSH levels. Again, no type 2 error calculations were presented.

In conclusion, available data in premenopausal women seems to indicate that prolonged subclinical hyperthyroidism due to l-T4 treatment is not associated with a clinically relevant reduction in bone mass. In contrast, postmenopausal women with subclinical hyperthyroidism due to l-T4 treatment seem to have reduced bone mass. We therefore advise continuous caution with regard to the detrimental effects of a slight overtreatment with l-T4 (resulting in reduced serum TSH) on the skeleton, especially in postmenopausal women, and maybe also in women being in a negative bone balance due to other reasons. The clinical impact of the present meta-analysis seems to be that serum TSH during l-T4 suppression in postmenopausal women should be kept in an intermediate range between normal and hyperthyroid values, and not totally suppressed. Alternatively, one might consider treatment with estrogen/gestagen in order to slow down the negative bone balance.

**Addendum.** After submitting the present study, one study on the subject has been published (35) demonstrating no significant excess bone loss due to long-term suppressive l-T4 treatment (47 pre- and 17 postmenopausal women (32% and 18%, respectively) had elevated serum T4), 49 with thyroid cancer and 15 with goiter) as measured on different sites of the skeleton.

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