The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature

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CRD summary
This review assessed the effects of levothyroxine therapy on bone mineral density. The authors concluded that current studies suggest no significant influence of levothyroxine on bone mineral density, but no firm conclusions could be drawn due to the diversity and poor quality of the studies. However, the review itself had some methodological limitations and may not be reliable.

Authors' objectives
To review the effects of thyroid-stimulating hormone (TSH)-suppressive and replacement levothyroxine therapy on bone mineral density (BMD).

Searching
MEDLINE was searched from 1990 to 2001; the search terms were reported. The reference lists of retrieved articles were checked for further studies. Only full-length English-language articles were considered for inclusion in the review.

Study selection

Study designs of evaluations included in the review
There were no specified inclusion criteria for the study design. Cross-sectional studies, cohort studies and intervention trials were included in the review.

Specific interventions included in the review
Studies of levothyroxine therapy of any dose or duration were eligible for inclusion. In the included studies, the treatment dosage ranged from 72 to 259 microg/day and the mean duration of treatment ranged from 0.5 to 20.4 years.

Participants included in the review
There were no inclusion criteria for the participants. The participants were aged from 9 to 98 years, although the majority of included studies were of adults and included women only. There were twice as many studies of postmenopausal than premenopausal women. Four studies included only men. Most of the studies included patients with homogeneous diagnoses although some studies did combine different thyroid diseases.

Outcomes assessed in the review
The studies were required to report BMD as an outcome. BMD could be assessed by any method and measured at any site. Dual-energy X-ray absorptiometry was the most commonly used technique, although single- and dual-photon absorptiometry, quantitative computed tomography, peripheral quantitative computed tomography and quantitative ultrasound were also used. The number of measured sites ranged from 1 to 10. The sites included lumbar spine and peripheral (ultradistal radius, calcaneus) trabecular bone, central (total body, trunk, pelvis) and peripheral (proximal radius, mid radius) cortical bone, and central (Ward’s triangle, trochanter, total hip) and peripheral (distal radius) mixed cortical and trabecular bone.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed by judging the matching of patients and controls (judged as poor, fair or good), sample size and, for longitudinal studies, loss to follow-up in each study. The authors did not state how the papers were assessed for
quality, or how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Effects on BMD at each site were extracted as negative, positive or no effect. The overall effect for each study was classified as: no overall effect, where the outcome of participants receiving levothyroxine and controls did not differ; negative overall effect, where levothyroxine patients had lower BMD at all sites; or partial negative or partial positive effect, where either the results of patients differed at various sites or only subgroups had lower or higher BMD.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
The studies were grouped in tables, both by study design and by the type of levothyroxine therapy given in the study (TSH-suppressive, replacement or both). Differences due to study quality, duration of therapy and dosage were considered within the general narrative synthesis. Separate site-specific narrative syntheses were performed to compare suppressive and replacement treatments. Subgroup results (by age, gender, menopausal state and thyroid disease) were also synthesised separately, as were any results on the reversibility and prevention of levothyroxine effects.

Results of the review
The review included 63 studies assessing a total of 3,279 participants. There were 6 intervention trials (279 participants), 16 cohort studies (933 participants) and 41 cross-sectional studies (2,067 participants).

The mean study quality was rated as moderate. The sample size ranged from 9 to 202; only 5 studies had more than 100 participants. Matching was poor in 27 studies, fair in 26 studies and good in 10 studies. The rate of follow-up was complete in 12 of the 22 longitudinal studies and low in 10 (range: 17% to 70%).

Effect of levothyroxine.

Thirty-one studies showed no overall effect of levothyroxine, 23 studies reported partial negative and/or positive effects, and 9 studies found overall negative effects. When only high-quality studies were considered, 3 studies found no overall effect, 4 studies reported mixed effects and 3 studies showed overall negative effects. Where investigated, most studies found no correlation between BMD and treatment length or levothyroxine dose. Further analyses investigating the effects of different doses at different sites were also reported.

Subgroups.
Several studies reported reduced effects of levothyroxine on BMD in adolescents and younger adults, in men, and in premenopausal women than in postmenopausal women. The impacts of underlying thyroid disease, hormone replacement therapy, pamidronate and calcium on the effects of levothyroxine on BMD were unclear as study findings varied.

Authors' conclusions
Although current studies suggested no significant influence of levothyroxine on BMD, the poor design of many studies and the heterogeneity of the studies meant that an effect of levothyroxine could neither be confirmed nor excluded beyond reasonable doubt.

CRD commentary
The review question was clear although the inclusion criteria were broad. The search for primary studies involved only one database and was limited to studies published in English, therefore some relevant studies might have been missed. It was unclear whether steps were taken to minimise reviewer bias and error during the study selection and data extraction processes. The methodological quality of the included studies was assessed and the impact of including high-quality studies only was checked within the general synthesis. Different study designs were also grouped separately within the synthesis. The authors discussed at length the heterogeneity and poor quality of the included studies, and the potential reasons for differences between study results. The conclusions and recommendations of the review were very cautious, which may be appropriate given the apparent limitations of the primary studies. However, the review itself had some limitations and the conclusions may not, therefore, be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that although it is not clear what clinical implications there are for the general population of patients receiving levothyroxine, they would recommend postmenopausal women be monitored to avoid any potential effect on BMD.

Research: The authors stated that further research would be needed to confirm an effect of levothyroxine on BMD. However, they questioned the clinical relevance of such research and suggested that the prevalence or incidence of bone fracture would be a better outcome measure.

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