Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis


Authors' objectives
To assess detrimental effects on bone mass of long-term treatment with thyroid hormones (TH).

Searching
MEDLINE and Current Contents were searched for papers or abstracts published from January 1982 to December 1994, using the keywords 'thyroid hormones', 'L-T4' and 'bone density'. Additional published and unpublished material was located by searching the annual tables of contents of the most referenced periodicals, by examining references from the relevant literature, and by contacting the companies marketing TH in France.

Study selection
Study designs of evaluations included in the review
Studies were only included if they met the following three criteria: studies were on the effect of TH therapy on bone mass, studies were of controlled cross-sectional design, and numerical data were available for both patients and controls (number of patients, mean BMD with standard deviation or z-score). Exclusions: studies concerning endogenous hyperthyroidism, a few small and short-term longitudinal studies, and studies with large numbers of patients receiving oestrogen replacement therapy or with post-operative hypoparathyroidism, unless separate data were available.

Specific interventions included in the review
Long-term treatment with TH, including suppressive (mean duration of therapy from 7.0 to 9.6 years) and replacement (mean duration of therapy from 7.3 to 14.1 years) thyroid therapy.

Participants included in the review
Patients who received TH therapy including men, premenopausal women and postmenopausal women. The mean age across studies ranged from 28 to 64.8 years.

Outcomes assessed in the review
Bone mass was measured differently among individual studies; methods were based on bone mineral content, bone mineral density (BMD), z-score, percentage of control value, and hydroxyapatite equivalent.

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

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
The results of each study were converted into a treatment effect size (standardised difference) with its confidence interval.

Methods of synthesis
How were the studies combined?
A fixed-effect model was used to combine the standardised effect size from individual studies. The results of individual studies were weighted according to the inverse of their variance.
How were differences between studies investigated?
A Q-test for homogeneity was performed. The funnel plot was symmetrical. Studies were analysed separately as either suppressive or replacement thyroid therapy. Suppressive thyroid therapy was defined as: thyroid-stimulating hormone level below the normal range for the assay used in at least 70% of the patients from the given group; or a suppressed response to the thyrotropin-releasing hormone test in at least 70% of patients; or when none of these data were available, a mean daily dose of T4 greater than 200 microg.

Results of the review
Thirty-three studies (95 men, 584 premenopausal women and 682 postmenopausal women) were included: 27 studies were considered, at least in part, to administer suppressive therapy (95 men, 385 premenopausal women and 420 postmenopausal women); 13 studies were considered, at least in part, to deal with the effect of replacement therapy (199 premenopausal and 262 postmenopausal women).

Standardised effect size of suppressive therapy for men: 0.082 (p=0.62) on lumbar spine.

Standardised effect size of suppressive therapy for premenopausal women: 0.231 (p=0.007) on lumbar spine, 0.02 (p=0.87) on femoral neck, 0.052 (p=0.74) on greater trochanter, 0.134 (p=0.39) on Ward's triangle, 0.029 (p=0.84) on distal radius, and -0.178 (p=0.18) on proximal radius.

Standardised effect size of suppressive therapy for postmenopausal women: -0.348 (p<0.0001) on lumbar spine, -0.276 on femoral neck, -0.484 (p=0.0003) on greater trochanter, -0.386 (p=0.012) on Ward's triangle, -0.328 (p=0.018) on distal radius, and -0.448 (p=0.002) on proximal radius.

Standardised effect size of replacement therapy for premenopausal women: -0.295 (p=0.018) for lumbar spine, -0.545 (p<0.0001) on femoral neck, -0.941 on greater trochanter, -0.481 (p=0.009) on Ward's triangle, -0.327 (p=0.083) on distal radius, and -0.498 (p=0.004) on proximal radius.

Standardised effect size of replacement therapy for postmenopausal women: -0.125 (p=0.29) for lumbar spine, -0.106 (p=0.39) on femoral neck, -0.105 on greater trochanter, -0.209 (p=0.11) on Ward's triangle, -0.407 on distal radius, and -0.641 on proximal radius.

Authors' conclusions
For lumbar spine and hip, suppressive TH therapy was associated with significant bone loss in postmenopausal women, but not in premenopausal women, whereas conversely, replacement therapy was associated with bone loss in premenopausal women (spine and hip), but not in postmenopausal women. The detrimental effect of TH appeared more marked on cortical bone than on trabecular bone. Only a large long-term prospective placebo-controlled trial of TH therapy evaluating BMD, and ideally fracture rate, would provide further insight into these issues.

CRD commentary
The method for assessing and grouping studies was not reported. In addition, there is a lack of information on the outcomes measured in individual studies. Whilst the funnel plot using all study groups was symmetrical, potential publication bias cannot be ruled out for specific subgroups.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.