The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma

CRD summary
The authors concluded that postmenopausal women taking thyrotropin-suppressive therapy may be at greatest risk of osteoporosis, but studies generally found no increased risk in premenopausal women and men. Poor reporting of review methods, an inadequate quality assessment of the included studies, and the reliance upon studies with small sample sizes make commenting on the reliability of the conclusions difficult.

Authors' objectives
To evaluate the effects of thyrotropin (TSH)-suppressive thyroxine therapy on bone metabolism in patients with well-differentiated thyroid carcinoma (DTC).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched to January 2006 for reports written in English; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Identified studies were subsequently excluded for the following reasons: patients did not have sufficiently suppressed serum TSH concentrations; serum TSH was not reported; subgroup analyses based on gender and menopausal status were not conducted; lack of indication if other risk factors for osteoporosis were investigated; and lack of a control group. The included studies were prospective studies or cross-sectional studies.

Specific interventions included in the review
Studies of TSH-suppressive thyroxine therapy were eligible for inclusion. Studies that did not report the duration of treatment were excluded. The majority of included studies compared the intervention with an unspecified control group. Where reported, the mean or median duration of treatment generally ranged from 6 to 12 years.

Participants included in the review
Studies of patients with DTC were eligible for inclusion. Most of the included studies excluded patients with diseases and patients taking glucocorticoids or other drugs that might affect bone mineral density (BMD). The included studies were in premenopausal women, postmenopausal women and men. In some studies, participants in the control groups were matched for age, gender and menopausal status.

Outcomes assessed in the review
Studies that assessed BMD were eligible for inclusion. The included studies assessed BMD at various sites, including the lumbar spine, femoral neck, trochanter, Ward's triangle and distal radius.

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
The authors scored each study semiquantitatively using the following criteria: reporting of hormonal status of females; whether participants were oestrogen replete or oestrogen deplete; reporting of additional risk factors for osteoporosis; use of a control group; and duration of follow-up longer or shorter than 5 years. However, lack of a control group was an exclusion criterion. The authors did not state how the validity assessment was performed.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, where possible, the BMD at end point was presented for each treatment group (generally as BMD z-scores) along with the level of statistical significance of the treatment difference.

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 according to study design and the characteristics of the participants (premenopausal women, postmenopausal women and men); the results were discussed separately for these subgroups.

Results of the review
The authors stated that 21 studies were included, and that these included 6 prospective studies and 17 cross-sectional studies with and without control groups. The data extraction tables list 6 reference numbers for longitudinal studies and 18 unique reference numbers for cross-sectional studies; however, 2 studies are listed as both longitudinal and cross-sectional. There appeared to be no obvious explanation for these discrepancies.

The sample size ranged from 5 to 52.

Twelve cross-sectional studies (n=304) and 4 prospective studies (n=67) evaluated effects in premenopausal women. Fourteen cross-sectional studies (n=326) and 4 prospective studies (n=132) evaluated effects in postmenopausal women. Eight cross-sectional studies (n=147) and 1 prospective study (n=9) evaluated effects in men.

All studies.
Four of 6 prospective studies reported that TSH-suppressive thyroxine therapy was associated with a significant decrease in BMD from baseline. Four of 17 cross-sectional studies reported a significant difference between patients with DTC and controls.

Premenopausal women (16 studies).
Two of the 12 cross-sectional studies reported a significant decrease in BMD in patients with DTC compared with controls. The other 10 cross-sectional studies reported no significant differences between patients with DTC and controls. Two of the 4 prospective studies reported a significant decrease in BMD in patients with DTC compared with controls.

Postmenopausal women (16 studies).
Four of the 14 cross-sectional studies reported a significant decrease in BMD in patients with DTC compared with controls. The other 10 cross-sectional studies reported no significant differences between patients with DTC and controls. Two of the 4 prospective studies reported a significant decrease in BMD in patients with DTC compared with controls; in one of these studies (a randomised controlled trial) the BMD was unchanged in patients randomised to calcitonin or calcium, but was significantly lower in patients taking placebo.

Men (9 studies).
One of the 8 cross-sectional studies reported that BMD was significantly lower in patients with DTC or Graves disease compared with controls. The only prospective study reported a significant decrease in BMD compared with baseline at the distal radius, but not the femoral neck, in patients with DTC.

Authors' conclusions
Findings suggest that postmenopausal women taking TSH-suppressive thyroxine therapy are at greatest risk of reduced BMD. Studies generally found no increased risk of reduced BMD in premenopausal women and men.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and outcomes; exclusion rather than inclusion criteria were defined for study design. Several relevant sources were searched but no apparent attempts were made to minimise publication or language bias. The assessment of study validity was limited, thus the results from these studies and any synthesis may not be reliable. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias.

In view of the diversity of the studies, a narrative synthesis with studies grouped by participants and study design was appropriate. Although the sample size of most studies might have been too small to detect a statistically significant effect on BMD, this point was not highlighted. Lack of reporting of review methods, lack of an adequate quality assessment of the included studies, and a reliance upon studies with small sample sizes make commenting on the reliability of the conclusions difficult.

Implications of the review for practice and research
Practice: The authors stated that postmenopausal women with DTC who are receiving TSH-suppressive thyroxine therapy should be screened when treatment starts, regularly monitored, and treated with bone-protective agent if required.

Research: The authors did not state any implications for further research.

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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.