Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature
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Authors' objectives
To estimate the expected change in serum lipoprotein concentrations after treatment with hydroxine therapy (T4) in patients with mild thyroid failure, i.e. subclinical hypothyroidism.

Searching
The authors searched MEDLINE from 1966 to May 1999 using the textwords 'thyroid disease' and 'cholesterol'. Additional published and unpublished material was located by examining the reference lists of retrieved articles, and contacting their authors.

Study selection
Study designs of evaluations included in the review
RCTs and prospective evaluations (with before-and-after measurements). Inclusion criteria for studies were:

1. The mean pre-treatment basal serum TSH concentration must have been above the upper limit of normal for the assay used in the study, but less than 20 mU/L.

2. Individual patients with serum TSH levels between the upper limit of normal and 10 mU/L must have been included.

3. Relevant lipoprotein data must have been provided for the subset of patients with mild thyroid failure, if other patient types were included in the analysis.

4. The study must have included the mean serum TSH concentration both before and after T4 treatment.

5. The study must have included the mean serum total cholesterol level with a variance estimate both before and after T4 treatment.

Specific interventions included in the review
Levothyroxine therapy using T4 sodium (dosage not stated). The 3 randomised controlled trials (RCTs) compared T4 to placebo.

Participants included in the review
Patients diagnosed with mild thyroid failure (hypothyroidism, hyperthyroidism), hypercholesterolaemia or cardiovascular disease. The mean age of participants ranged from 32 to 71 years, all studies enrolled at least 75% women, and 6 studies enrolled only women. The mean pre-treatment basal serum thyroid stimulating hormone (TSH) concentration for included participants must have been above the upper limit of normal for the assay used in the study, but less than 20 mU/L. Further, patients with serum TSH levels between the upper limit of normal and 10 mU/L must have been included.

Outcomes assessed in the review
Changes in serum lipoprotein concentrations, i.e. total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, and lipoprotein(a).

How were decisions on the relevance of primary studies made?
Three authors reviewed the abstracts for relevance to the review, and any discrepancies were resolved by agreement.

Assessment of study quality
The authors used a 13-item checklist of factors relating to internal and external validity, which covered study design, participant characteristics, treatment characteristics, and loss to follow-up. A score was calculated by assigning one point for each of 13 items assessed, and subscores were calculated for factors related to internal and external validity. Two reviewers evaluated the included studies for internal and external validity.

**Data extraction**
The authors do not state how many of the reviewers performed the data extraction.

Data were extracted for the categories: study identification and year of publication, study design, sample size, mean age within the study, selection criteria for patients, initial TSH (mU/L), final TSH (mU/L), and design score (0 to 13 points).

For each study without a control group, change was calculated as the mean difference between the final and pre-treatment measurements for study participants. For each study with a control group, change was calculated as the difference between the two group mean differences.

**Methods of synthesis**

How were the studies combined?

Weighted mean differences were calculated with 95% confidence intervals (CIs) using both random-effects and fixed-effect models.

Publication bias was assessed using common graphical and computational techniques.

How were differences between studies investigated?

In the fixed-effect analyses, homogeneity was assessed using the chi-squared statistic. The authors also used a weighted analysis of variance to stratify studies according to the individual terms on the study design (validity) checklist.

Weighted linear regression was used to evaluate the relationship between the baseline level of serum cholesterol and the change in serum cholesterol.

**Results of the review**

Thirteen studies were included with 247 participants. Three studies (23%) were RCTs with 81 participants.

**Total cholesterol:**

The mean decrease in the serum total cholesterol concentration (13 studies) was -0.20 mmol/L (-7.9 mg/dL; 95% CI: -0.09, -0.34) using the fixed-effect model, and -0.24 mmol/L (95% CI: -0.06, -0.42) using the random-effects model. The decline in serum total cholesterol was directly proportional to its baseline concentration. The test for heterogeneity suggested that these studies might be too dissimilar to combine.

Studies enrolling hypothyroid participants receiving suboptimal T4 doses (number of studies not stated) reported significantly larger decreases in serum total cholesterol after thyroid-stimulating hormone normalisation than those enrolling previously untreated individuals with mild thyroid failure: -0.44 mmol/L (-17 mg/dL; 95% CI: -0.18, -0.70) versus -0.14 mmol/L (-5.6 mg/dL; 95% CI: -0.01, -0.28); P=0.05.

**LDL cholesterol:**

The change in the serum LDL cholesterol concentration (9 studies) using a fixed-effect model was -0.26 mmol/L (-10 mg/dL; 95% CI: -0.12, -0.41). The results were more heterogeneous than would be expected by chance (P=0.02), but the reduction was similar using a random-effects model, -0.30 mmol/L (95% CI: -0.01, -0.54).

**HDL cholesterol:**
The change in the serum HDL cholesterol concentration (10 studies) was an increase after therapy by 0.08 mmol/L (3.2 mg/dL; 95% CI: 0.04, 0.13) using the fixed-effect model; although statistically significant, the results were driven by one study. These results were also more heterogeneous than would be expected by chance (P<0.001). A similar reduction, which was statistically non significant, was obtained using a random-effects model, 0.02 mmol/L (95% CI: -0.09, 0.12).

Triglycerides:

The mean change in serum triglyceride concentration (12 studies) was -0.01 mmol/L (95% CI: -0.08, 0.06), which was not statistically significant.

The 3 RCTs were compared with the controlled studies, but the two groups were not statistically different. Division of studies into two groups according to the average age of participants, participant pre-treatment TSH level, participant final TSH level, overall study score, gender representation in the study, and use of free T4 testing for diagnosis, still did not separate the studies into statistically different groups.

No study fulfilled all 13 criteria relating to internal and external validity. Three to 8 criteria, with a median of 6 criteria, were met. Only 3 studies were randomised, all with placebo controls; 3 studies did not adequately characterise the selection of participants, and 7 of the studies neither discussed losses to follow-up nor gave sufficient information from which this could be determined.

Authors’ conclusions

The authors state that these results, although based on fewer than 250 patients, suggest that T4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL cholesterol concentrations. The reduction in serum total cholesterol may be larger in individuals with higher pre-treatment cholesterol levels, and in hypothyroid individuals taking suboptimal T4 doses. There do not seem to be significant effects of T4 on serum HDL or triglyceride concentrations.

CRD commentary

This was a good review. The authors stated the research question, and inclusion and exclusion criteria. The literature search was reasonable, although there was no mention of searches for unpublished and grey literature and the searches were restricted to the English language. It is possible that additional relevant studies may have been missed, but the authors tested for, and did not find, publication bias.

The quality of the included studies was formally assessed and discussed in the review. The authors have reported how the articles were selected, and who performed the selection and validity assessment. The authors did not state who performed the data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis using both fixed-effect and random-effects models for comparison, and heterogeneity was assessed.

The authors’ conclusions appear to follow from the results, but as the authors themselves state, these should be viewed with caution because of limitations in the quality of the designs of the included studies.

Implications of the review for practice and research

Practice: The authors state that it is necessary to regularly monitor individuals taking T4 to minimise the potential for iatrogenic effects. Further, the potential for modest reductions in serum total and LDL cholesterol levels, coupled with the potential for reducing subtle symptoms of mild thyroid failure and preventing progression to hypothyroidism, provides a sound basis for considering therapy. Careful re-titration of the T4 dose in patients with hypothyroidism may also have beneficial effects on serum lipids and should not be ignored.

Research: The authors state that a trial of T4 treatment for individuals with both elevated serum TSH and cholesterol...
concentrations seems to be a reasonable strategy.

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