Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism

CRD summary
The review concluded that thyroxine plus triiodothyronine replacement therapy did not improve well-being, cognitive function, or quality of life compared with thyroxine alone (which may be beneficial in improving psychological or physical well-being). The review's sometimes poor or inconsistent reporting, coupled with the questionable quality of several included trials, indicate that the authors' conclusions should be interpreted with caution.

Authors' objectives
To compare the effectiveness of thyroxine alone with thyroxine plus triiodothyronine replacement therapy for patients with hypothyroidism.

Searching
MEDLINE, EMBASE, Science Citation Index Expanded, the Cochrane Library, and China National Knowledge Infrastructure databases were searched, without language restrictions, to 2008. The Chinese Journal of Isotopes, Radiologia Pratica, the Chinese Journal of Endocrinology and Metabolism, and conference literature were also manually searched.

Study selection
Randomised controlled trials (RCTs) comparing thyroxine alone with thyroxine plus triiodothyronine replacement therapy in patients with hypothyroidism were eligible for inclusion. The main outcomes of interest were serum thyroid hormone levels, quality of life, cognitive performance, mood states, physical symptoms, and clinical variables. Adverse events were also reported.

The vast majority of participants in the included trials were women. Most participants had primary hypothyroidism following thyroiditis. A small number of participants also had depression. Mean ages of treatment arms ranged from 43.1 to 49.5 years. Duration of disease (where reported) ranged from 54 to 140 months.

Three reviewers independently selected studies, with disagreements resolved by consensus.

Assessment of study quality
Three reviewers independently evaluated trial quality by assessing allocation concealment, completeness of follow-up, degree of blinding, use of a sample size calculation, group baseline comparability, type of analysis (intention-to-treat or per protocol) and, for cross-over trials, assessment of wash-out phase and testing for a carryover effect. Disagreements were resolved by consensus.

Data extraction
Three reviewers independently extracted data in order to calculate mean differences with 95% confidence intervals (CI). Authors were contacted for missing data when necessary.

Methods of synthesis
Meta-analyses of pooled weighted mean differences (WMD) were performed using a fixed-effect model (or a random-effects model when there was significant heterogeneity). Heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic.

Subgroup analyses were planned to examine the effect of cause of disease (autoimmune or non-autoimmune).

Results of the review
Ten RCTs (n~1200 patients, the exact total was unclear) were included (six of which had a cross-over design). The authors reported that two other trials were identified, but subsequently excluded because standard errors were not reported (and could not be obtained from investigators). Trial quality (overall) was described as being adequate; all
trials reported on losses to follow-up, all were reported as having used adequate methods for randomisation and blinding (further details on these two criteria were not given), but only three trials reported using an intention-to-treat analysis. Only one of the crossover trials had a washout phase.

The authors stated there were statistically significant reductions of serum-free and total thyroxine in patients treated with thyroxine plus triiodothyronine, but the confidence intervals reported could not clearly confirm this.

Thyroxine alone showed significant benefits for psychological or physical well-being for the following outcomes: general health (WMD -0.38; 95% CI -0.71 to -0.05; four RCTs), physical component summary (WMD 0.7, 95% CI 0.53 to 0.87; one RCT), mental component summary (WMD 0.58, 95% CI 0.25 to 0.75; two RCTs); physical functioning (WMD 1.60, 95% CI 1.29 to 1.90; two RCTs); bodily pain (WMD 2.50, 95% CI 2.11 to 2.88; two trials), and role-emotional (WMD 2.08, 95% CI 1.17 to 2.99; two RCTs), and mental health (WMD 1.30, 95% CI 0.97 to 1.64; two RCTs) in items of the Short Form-36 Health Survey.

Thyroxine alone also showed significant benefits for general well-being for the following: the Thyroid Symptom Questionnaire (WMD -1.90, 95% CI -2.48 to -1.32; one RCT); Letter Number Sequencing-working memory test cognitive performance scores (WMD 1.10, 95% CI 0.08 to 2.13; two RCTs), blurred vision (WMD -4.66, 95% CI -5.34 to -4.00; three RCTs) and aches and pain (WMD -0.80, 95% CI -1.34 to -0.26; one RCT).

Thyroxine plus triiodothyronine replacement therapy showed significant benefit in improving cognitive performance (WMD -0.49, 95% CI -0.90 to -0.08, two RCTs).

There were no significant differences in adverse effects.

Further results were reported.

Authors' conclusions
Thyroxine plus triiodothyronine replacement therapy did not improve well-being, cognitive function, or quality of life compared with thyroxine alone. Thyroxine alone may be beneficial in improving psychological or physical well-being.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant trials in any language were undertaken via several methods. Suitable procedures (e.g. independent duplicate processes) were employed to reduce the risks of reviewer error and bias throughout the review.

Trial quality appeared to be adequately assessed, but results were only provided for nine of the ten trial, and the results were used little in interpreting and discussing the review results. No narrative synthesis was provided for the two trials which appeared to meet the inclusion criteria, but were subsequently excluded from the meta-analyses (so not all the evidence was presented). Also, no clear dose information about the interventions was presented, and it was unclear which particular trials contributed to the pooled results (no forest plots were provided). No specific results of heterogeneity tests were presented.

The review's sometimes poor or inconsistent reporting, coupled with the questionable quality of several included trials, indicate that the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that thyroxine alone continues to be the most appropriate therapy for patients with primary hypothyroidism.

Research: The authors stated that further study is required to elucidate why some patients prefer combination therapy, and to clarify the discrepancy between patient preference and the lack of difference between treatment groups on objective measures of outcome. Research is also needed looking at the long-term effects of thyroxine plus triiodothyronine replacement therapy, and examining frequency and types of administration of thyroxine.
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