Selenium supplementation for Hashimoto's thyroiditis (Review)

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[Intervention Review]

Selenium supplementation for Hashimoto's thyroiditis

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ABSTRACT

Background

Hashimoto's thyroiditis is a common auto-immune disorder. The most common presenting symptoms may include anxiety, negative mood, depression, dry skin, cold intolerance, puffy eyes, muscle cramps and fatigue, deep voice, constipation, slow thinking and poor memory. Clinical manifestations of the disease are defined primarily by low levels of thyroid hormones; therefore it is treated by hormone replacement therapy, which usually consists of levothyroxine (LT_4). Selenium might reduce antibody levels and result in a decreased dosage of LT_4 and may provide other beneficial effects (e.g. on mood and health-related quality of life).

Objectives

To assess the effects of selenium supplementation on Hashimoto's thyroiditis.

Search methods

We searched the following databases up to 2 October 2012: CENTRAL in *The Cochrane Library* (2012, Issue 10), MEDLINE, EMBASE, and Web of Science; we also screened reference lists of included studies and searched several online trial registries for ongoing trials (5 November 2012).

Selection criteria

Randomised controlled clinical trials that assessed the effects of selenium supplementation for adults diagnosed with Hashimoto's thyroiditis.

Data collection and analysis

Study selection, data extraction, assessment of risk of bias, and analyses were carried out by two independent review authors. We assessed the quality of the evidence of included studies using GRADE. We were unable to conduct a meta-analysis because clinical heterogeneity between interventions that were investigated is substantial.

Main results

Four studies at unclear to high risk of bias comprising 463 participants were included. The mean study duration was 7.5 months (range 3 to 18 months). One of our primary outcomes- 'change from baseline in health related quality of life'- and two of our secondary outcomes- 'change from baseline in LT_4 replacement dosage at end of the study' and 'economic costs'- were not assessed in any of the studies. One study at high risk of bias showed statistically significant improvement in subjective well-being with sodium selenite 200 μg plus titrated LT_4 compared with placebo plus titrated LT_4 (relative risk (RR) 4.67, 95% confidence interval (CI) 1.61 to 13.50; P = 0.004; 36 participants; number needed to treat (NNT) = 2 (95% CI 2 to 3)).

Selenomethionine 200 μg reduced the serum levels of anti-thyroid peroxidase antibodies compared with placebo in two studies (mean difference (MD) -917 U/mL, 95% CI -1056 to -778; P < 0.001; 85 participants) and (MD -345 IU/mL, 95% CI -359 to -331; P < 0.001; 169 participants). Pooling of the studies was not feasible due to marked clinical heterogeneity (I^2 = 99%). In a further comparison within the first study where selenomethionine was combined with LT_4 the reduction in TPO antibodies was even more noticeable (MD -1508 U/mL, 95% CI -1671 to -1345; P < 0.001; 86 participants). In a third study, where LT_4 was added to both intervention arms, a reduction in serum levels of anti-thyroid peroxidase antibodies favoured the selenomethionine arm as well (MD -235 IU/mL, 95% CI -374 to -95; P = 0.001; 88 participants). Although the changes from baseline were statistically significant in these three studies, their clinical relevance is unclear. Serum antibodies were not statistically significantly affected in the study comparing sodium selenite 200 μg plus titrated LT_4 with placebo plus titrated LT_4 (MD -25, 95% CI -181 to 131; P = 0.75; 36 participants).

Adverse events were reported in two studies (1 of 85 and 1 of 88 participants, respectively). Selenium supplementation did not appear to have a statistically significant impact on the incidence of adverse events (RR 2.93, 95% CI 0.12 to 70.00; and RR 2.63, 95% CI 0.11 to 62.95).

Authors' conclusions

Results of these four studies show that evidence to support or refute the efficacy of selenium supplementation in people with Hashimoto's thyroiditis is incomplete. The current level of evidence for the efficacy of selenium supplementation in the management of people with Hashimoto's thyroiditis is based on four randomised controlled trials assessed at unclear to high risk of bias; this does not at present allow confident decision making about the use of selenium supplementation for Hashimoto's thyroiditis. This review highlights the need for randomised placebo-controlled trials to evaluate the effects of selenium in people with Hashimoto's thyroiditis and can ultimately provide reliable evidence to help inform clinical decision making.

PLAIN LANGUAGE SUMMARY

Selenium supplementation for Hashimoto's thyroiditis

Hashimoto's thyroiditis is a common disease in which a form of chronic inflammation of the thyroid gland results in reduced function of the gland. It is an auto-immune disorder, which means that a person's own immune system attacks the thyroid gland, so that it no longer makes adequate quantities of thyroid hormones (hypothyroidism). Common clinical manifestations include feeling cold, depressive mood, dry skin, puffy eyes, constipation, weight gain, slowed heart rate, joint and muscle pain and fatigue. Some but not all people with Hashimoto's thyroiditis have an enlarged gland, also called a *goitre*. Hashimoto's thyroiditis is more common in women than in men and tends to run in families. Other auto-immune diseases often occur simultaneously, such as vitiligo, rheumatoid arthritis and diabetes type 1. The disease does not always require treatment, but when it does, it is treated with synthetic thyroid hormone replacement (sometimes desiccated thyroid hormone is used, which is not synthetic). Selenium is an essential trace element that is required in small amounts for correct functioning of the immune system and the thyroid gland.

Four studies at unclear to high risk of bias comprising 463 participants were included. The mean study duration was 7.5 months (range 3 to 18 months). None of the studies addressed our key primary outcome- 'health-related quality of life'. Two of our secondary outcomes- 'change from baseline in levothyroxine (i.e. thyroid hormone) replacement dosage at end of the study' and 'economic costs'- were not assessed either. One study at high risk of bias showed a statistically significant improvement in subjective well-being with sodium selenite 200 μg plus levothyroxine compared with placebo plus levothyroxine (14/18 compared with 3/18, respectively). Selenomethionine 200 μg reduced the serum levels of anti-thyroid peroxidase antibodies in three studies, and although the changes

from baseline were statistically significant, their clinical relevance is unclear. Adverse events were reported in two studies, and selenium supplementation did not lead to more adverse events than were seen with placebo. One adverse event was reported in both studies in the selenomethionine 200 μg plus LT_4 arm versus none in the control arm.

In conclusion, the results of these four studies do not provide enough evidence to support the use of selenium in the treatment of Hashimoto's thyroiditis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Selenium (+LT_4) compared with placebo (+LT_4) for participants with Hashimoto's thyroiditis

Patient or population: participants with Hashimoto's thyroiditis.
Settings: hospital outpatient department.
Intervention: selenium (+ levothyroxine)[a].
Comparison: placebo (+ levothyroxine).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo (+ levothyroxine)	Selenium (+ levothyroxine)				
Change from baseline in health-related quality of life	See comment	See comment	Not estimable	See comment	See comment	Not reported in any study
Change from baseline in assessment of symptoms such as mood, fatigue and muscle weakness Short-Form Health Survey Follow-up: mean 3 months	**167 per 1000**	**778 per 1000** (268 to 1000)	**RR 4.67** (1.61 to 13.5)	36 (1 study)	⊕⊕⊕◯ **low**[b,c,d]	
Proportion of participants reporting an adverse event Follow-up: mean 5 months			**RR 2.71** (0.29 to 25.66)	258 (3 studies[e])	⊕⊕◯◯ **low**[b]	Participants in placebo group counted twice (same participants in both comparisons)

Change from baseline in serum levels of anti-thyroid peroxidase antibodies Decrease from 1508 to 25 IU/L Follow-up: mean 4.5 months	See comment	See comment	Not estimable	252 (4 studies[e])	⊕⊕◯◯ **low**[b]	Data could not be pooled because of substantial clinical heterogeneity of participants, interventions and controls
Change from baseline in LT_4 replacement dosage at end of study	See comment	See comment	Not estimable	See comment	See comment	Not reported in any study
Economic costs	See comment	See comment	Not estimable	See comment	See comment	Not reported in any study

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Karanikas 2008 and Turker 2006 included levothyroxine in both treatment arms. Krysiak 2011 included levothyroxine in one arm combined with selenium.
[b] Randomisation was probably based on prognostic factors, and no mention was made of stratified randomisation.
[c] Wide confidence interval.
[d] RR 4.67.
[e] One study provided two comparisons.

BACKGROUND

Unfamiliar terms are listed in the 'Glossary of terms' (Table 1).

Description of the condition

Hashimoto's thyroiditis (HT) or chronic lymphocytic thyroiditis is a common auto-immune disorder. HT tends to run in families and affects women and men of all ages, although it is most often seen in middle-aged women (Fink 2010; Stathatos 2012). Its prevalence is influenced by ethnicity, environmental factors such as iodine and selenium status, age and gender (Fink 2010; Stathatos 2012). Although data on its prevalence are limited at a global level, HT is estimated to affect 1% to 2% of adult women in the US (Hutfless 2011; Staii 2010) and is the most common cause of hypothyroidism in iodine-sufficient areas of the world. However, subclinical hypothyroidism is more prevalent and occurs in 3% of men and approximately 8% to 10% of women (Chistiakov 2005). Concomitant and other auto-immune diseases such as rheumatoid arthritis, diabetes mellitus type 1, multiple sclerosis and celiac disease are frequently seen in people suffering from HT (Chistiakov 2005; Stathatos 2012).

The most common presenting symptoms may include anxiety, negative mood, depression, dry skin, cold intolerance, puffy eyes, muscle cramps and fatigue, deep voice, constipation, slow thinking and poor memory (Canaris 2000; Carta 2004). The thyroid gland may enlarge and may present in its classical form as goitre; although thyroid enlargement is usually asymptomatic, a few patients have described thyroid pain and tenderness, sometimes requiring surgical intervention (Li 2011). The other major form of HT, not presenting with goitre, is atrophic auto-immune thyroiditis, in which fibrosis is more dominant (Bülow Pedersen 2005). Variant forms of the disorder include silent (painless) thyroiditis and postpartum thyroiditis, both of which are transient but may be followed years later by thyroid failure (Lazarus 1996; Pearce 2003). Hypothyroidism due to HT in pregnant women is frequently associated with increased perinatal morbidity, miscarriage, postpartum thyroiditis and impaired neuropsychological development of the infant (Dosiou 2012; Stathatos 2012).

Although hypothyroidism is the characteristic functional abnormality of HT, the inflammatory process early in the course sometimes involves enough apoptosis to cause thyroid follicular disruption and thyroid hormone release, inducing transient hyperthyroidism (Fatourechi 1971). In rare cases, patients may cycle between hypothyroidism and Graves' disease (Kraiem 1992; Takasu 1990). The usual course of HT involves gradual loss of thyroid function. Patients who have mild (subclinical) hypothyroidism show overt hypothyroidism at a rate of approximately 5% per year (Huber 2002). Overt hypothyroidism, once present, is permanent in nearly all cases, except in some children and postpartum women in whom it is often transient.

Specific serum auto-antibodies such as anti-thyroid peroxidase antibodies (anti-TPOAb) and anti-thyroglobulin antibodies (anti-TgAb) are characteristic of HT; serum thyroxine (T_4) may be normal or low, and thyroid-stimulating hormone (TSH) concentrations may be normal or high (Li 2011). Histopathologic examination merely shows diffuse lymphocytic infiltration and formation of germinal centres, although fibrosis can also be detected (Li 2011; Stuart 2011).

Clinical manifestations of the disease are defined primarily by low levels of thyroid hormones; therefore patients are treated by hormone replacement therapy, which usually consists of levothyroxine (LT_4) (Özen 2011).

Pathogenesis

In HT, thyrocytes are attacked by a variety of cell- and antibody-mediated inflammatory reactions, resulting in low levels of thyroid hormone (Mitchell 2007). Auto-immunity can develop from the interaction of genetic susceptibility and environmental and endogenous factors (Chistiakov 2005; Saranac 2011; Tomer 2002). Several susceptibility genes have been identified, such as *HLA-DR, CD-40, CTLA-4, PTPN-22* and thyroid-specific genes (i.e. thyroglobulin and TSH receptor genes) (Saranac 2011; Stathatos 2012). Auto-antigens, including tissue-specific membrane receptors, enzymes and hormones, are presented by major histocompatibility complex (MHC) class II antigen-presenting cells (APCs) to naive T cells and infiltrate the thyroid gland. Environmental factors such as high iodine intake, selenium deficiency and viral infection can increase the likelihood of this infiltration followed by clonal expansion of both T and B lymphocytes in the draining lymph nodes (Chistiakov 2005; Saranac 2011). Activated CD4+ T-helper cells promote the release of interferon-gamma (INF-γ) by CD8+ cytotoxic T cells; this activates macrophages that capture the damaged thyroid cells, resulting in cytokine-mediated cell death. In addition, auto-antibodies (anti-TSH receptor antibodies, anti-thyroglobulin and anti-TPOAb) produced by B cells cause antibody-mediated cell death (Mitchell 2007). The end result consists of a gradual depletion of thyrocytes and replacement by mononuclear cell infiltration and diffuse fibrosis (Mitchell 2007).

Description of the intervention

Selenium is an essential trace element that is required in small amounts for correct functioning of the immune system. The recommended daily intake for adults is 55 μg/day (Hu 2012). It is obtained from natural selenium rich sources such as brazil nuts, organ meat, muscle meat, cereals, shellfish and fish (Rayman 2008). The selenium content of food depends on local soil conditions, which can vary depending on geographical and geological factors (Rayman 2008). The serum selenium concentration is believed to be in the 70 to 130 ng/mL range (Bleys 2008). Selenomethionine and sodium selenite are the two most common oral forms of

selenium supplementation that are available in variable dosages (100 and 200 μg/day) and are usually taken for HT (Toulis 2010; Turker 2006).

Adverse effects of the intervention

The upper tolerable intake level of selenium is 400 μg/day (Rayman 2008). Therefore, oral doses of selenium of less than 400 μg/day will not result in serious adverse effects over the short term (Monsen 2000). However, several adverse effects have been recorded with higher doses, resulting in chronic toxicity or selenosis (e.g. gastrointestinal upset, hair loss, white blotchy nails, garlic breath odour, fatigue, irritability, mild nerve damage) (Goldhaber 2003; Rayman 2008). It has also been reported that selenium may increase the likelihood of type 2 diabetes (Stranges 2007). The suggested mechanism is that selenium may suppress the production of insulin-like growth factor-1 (i.e. influencing glucose homeostasis). Moreover, selenium in high levels may promote the release of glucagon, resulting in hyperglycaemia (Stranges 2007). Likewise, high selenium blood levels may contribute to dyslipidaemia. The potential mechanism is not fully understood, but it has been proposed that elevated levels of selenium might result in high levels of selenoproteins that regulate cholesterol biosynthesis (Stranges 2010).

How the intervention might work

Recent advances in thyroid cell physiology have illustrated the key role that selenium plays in thyroid gland function (Köhrle 2005). Several enzymes in the thyroid gland are selenoproteins, meaning that selenium is incorporated in their molecular structure (Brown 2001; Köhrle 2005). One of the most vital of these enzymes, glutathione peroxidase (GPx), is involved in protecting the gland against oxidative damage. Hydrogen peroxide (H_2O_2), a free radical capable of inflicting oxidative damage, is required as substrate by thyroid peroxidase (TPO) for the iodination and coupling of tyrosyl residues in thyroglobulin to produce thyroid hormone. The active form of thyroid hormone, triiodothyronine (T_3), is produced by de-iodination of the prohormone T_4 by type I and type II iodothyronine de-iodinases (IDIs) in a two-substrate 'ping-pong' mechanism of reaction, along with degradation of H_2O_2 to water by GPx. IDIs, such as GPx, are also selenoproteins. If a selenium deficiency exists, these two enzymes cannot function properly, and the end result is ineffective production of T_3 and inefficient protection against free radicals, inducing cell damage and auto-immune destruction of the gland (Brown 2001; Köhrle 2005; Toulis 2010). In these conditions, selenium supplementation may be of benefit to patients with HT (Toulis 2010).

Why it is important to do this review

Several studies have suggested that selenium supplementation in patients with HT reduces antibodies levels (Gärtner 2002), results in a decreased dosage of LT_4 and may provide other beneficial effects (e.g. on mood and health-related quality of life (HRQoL)) (Ott 2011). On the basis of the last date of searches in 2007, one systematic review (Toulis 2010) concluded that high-level evidence of the benefits of selenium supplementation for periods longer than three months is limited. The review authors also highlighted a lack of "meaningful clinical outcomes" selected and reported in the included trials; therefore at that time, routine selenium supplementation could not be recommended for HT. This previous review is discussed further in the section, 'Agreements and disagreements with other studies or reviews'.

OBJECTIVES

To assess the effects of selenium supplementation for Hashimoto's thyroiditis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials.

Types of participants

Adults (18 years of age and older) diagnosed with Hashimoto's thyroiditis.

Diagnostic criteria

As diagnosed by a physician and supported by serum levels of anti-TPOAb and anti-TgAb above the normal level of the laboratory's normal range.

Types of interventions

Intervention

- Selenium 100 µg or 200 µg supplementation (sodium selenite or selenomethionine) alone or combined with titrated LT_4 to maintain basal TSH within normal range.

Control

- No control or no control plus titrated LT_4 to maintain basal TSH within the normal range.
- Placebo tablets or placebo tablets plus titrated LT_4 to maintain basal TSH within the normal range.

Types of outcome measures

Primary outcomes

- Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study.
- Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study.
- Proportion of participants reporting an adverse event throughout the study period.

Secondary outcomes

- Change from baseline in serum levels of anti-thyroid peroxidase antibodies at end of study.
- Change from baseline in LT_4 replacement dosage at end of study.
- Economic costs.

Timing of outcome measurement

We considered outcomes measured up to three months (short term), from three to six months (medium term) and after six months (long term).

Summary of findings table

We established a 'Summary of findings for the main comparison' table using the following outcomes listed according to priority:

- Change from baseline in HRQoL.
- Change from baseline in assessment of symptoms such as mood, fatigue and muscle weakness.
- Proportion of participants reporting an adverse event.
- Change from baseline in serum levels of anti-thyroid peroxidase antibodies.
- Change from baseline in LT_4 replacement dosage.
- Economic costs.

Search methods for identification of studies

Electronic searches

We used the following sources from inception to 2 October 2012 for identification of trials:

- *The Cochrane Library.*
- MEDLINE.
- EMBASE.
- Web of Science.

We (EvZ) also searched databases of ongoing trials (ClinicalTrials.gov (www.clinicaltrials.gov/)), the Current Controlled Trials metaRegister (www.controlled-trials.com/) and the EU Clinical Trials register (www.clinicaltrialsregister.eu/) on 5 November 2012. We have provided information including trial identifiers for recognised studies in the 'Characteristics of ongoing studies' table and the appendix 'Matrix of study endpoints (protocol/trial documents)'. For every included study, we tried to find its protocol in databases of ongoing trials, in publications of study designs or in both.

For detailed search strategies, please see Appendix 1 (searches were not more than six months old at the time the final review draft was checked into the Cochrane Information and Management System for editorial approval). We used PubMed's 'My NCBI' (National Centre for Biotechnology Information) email alert service to identify newly published studies using a basic search strategy (see Appendix 1).

For future updates, if additional key words of relevance are detected during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms. We have included studies published in any language.

Searching other resources

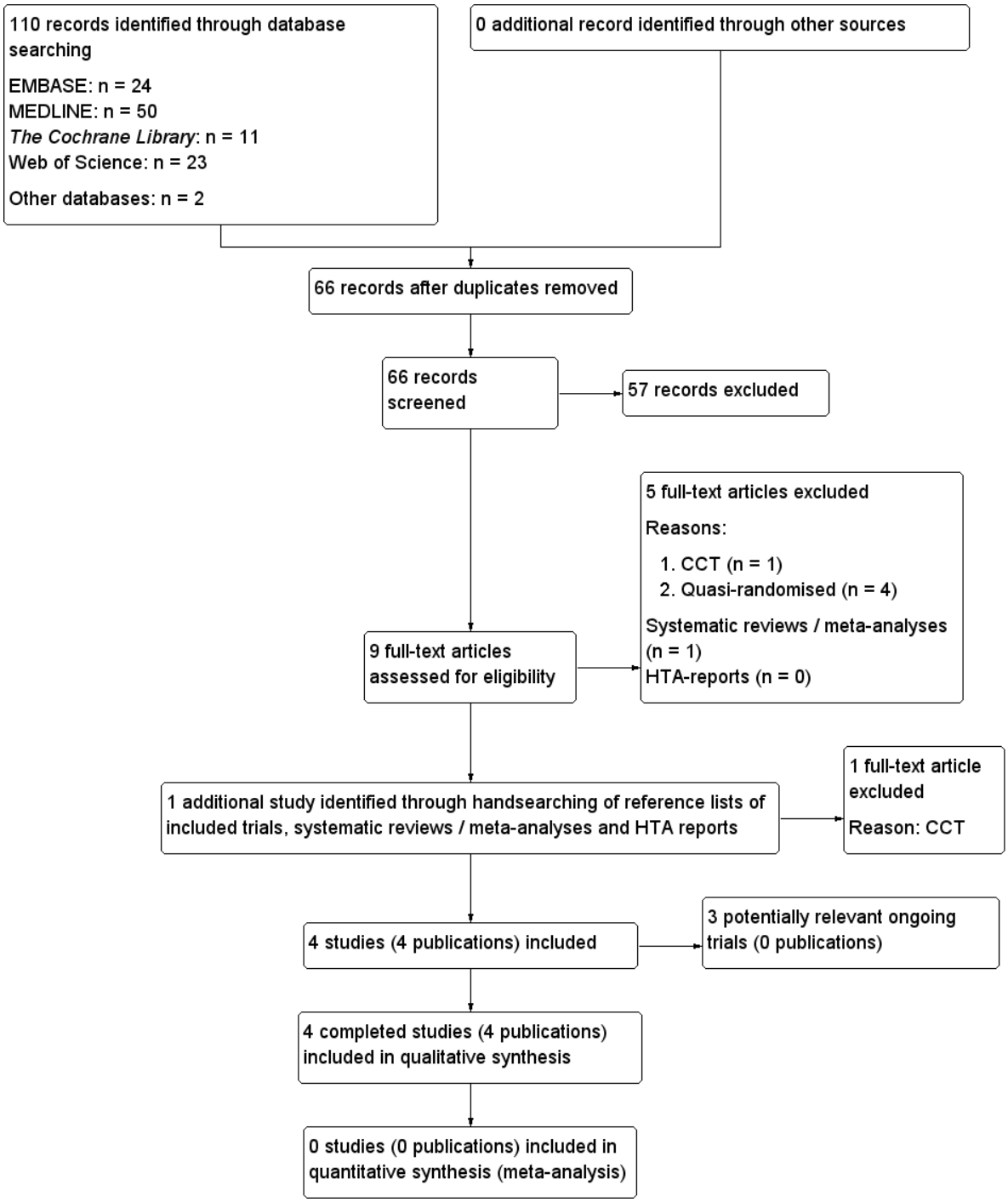
We (EvZ) tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews, meta-analyses and health technology assessment reports.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two review authors (AYA, EvZ) independently scanned the abstract, title or both sections of every record retrieved. We investigated all potentially relevant articles as full text. Where differences in opinion existed, they were resolved by a third party. We present an adapted PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow chart of study selection (Figure 1) (Liberati 2009).

Figure 1. Study flow diagram.



Data extraction and management

For studies that fulfilled inclusion criteria, three review authors (AYA, EvZ, ZF) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies, Table 2; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9) with any disagreements resolved by discussion.

We sent an email request to the contact persons of included studies for further questions regarding the trials. The results of this survey are published in Appendix 10. Thereafter, we sought relevant missing information on the trial from the primary author(s) of the article.

Dealing with duplicate publications and companion papers

In the case of duplicate publications and companion papers of a primary study, we sought to maximise yield of information by simultaneous evaluation of all available data.

Assessment of risk of bias in included studies

Three review authors (AYA, EvZ, ZF) assessed each trial independently. We resolved possible disagreements by consensus.

We assessed risk of bias using The Cochrane Collaboration's tool (Higgins 2011; Higgins 2011a). We used the following bias criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment.
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias) - see Appendix 5.
- Other bias.

We judged risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included a 'Risk of bias' graph figure (Figure 2) and a 'Risk of bias' summary figure (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

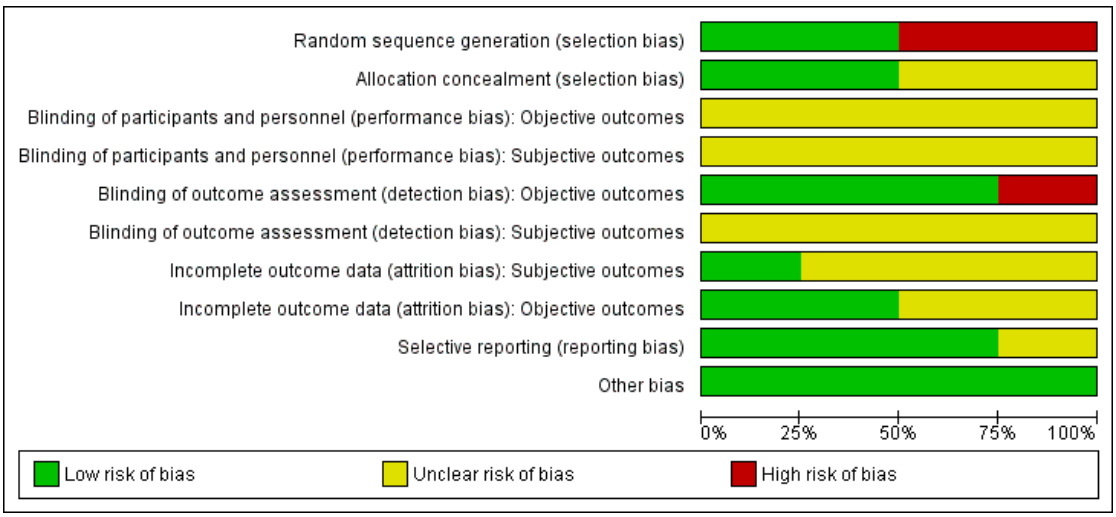
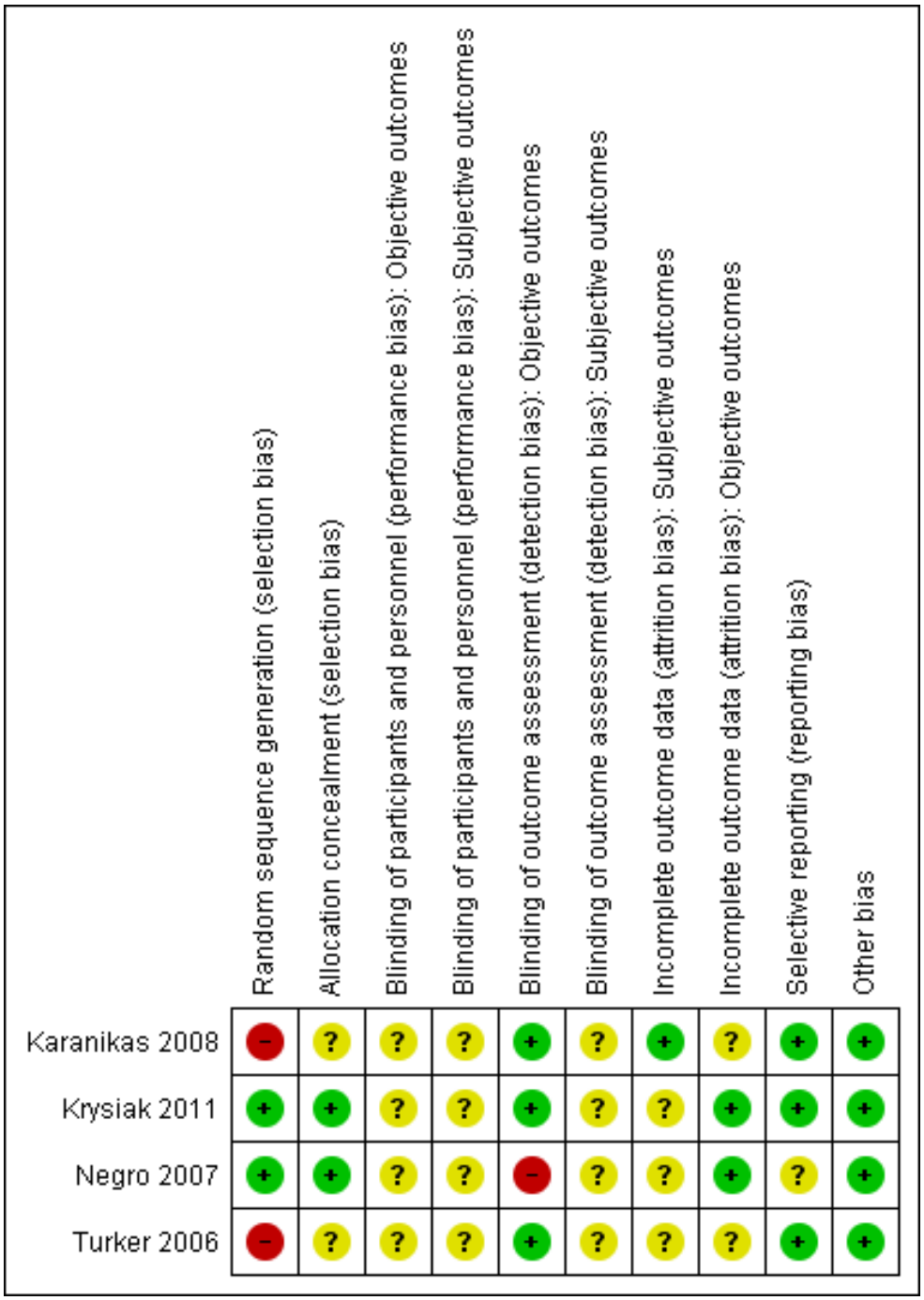


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We assessed the impact of individual bias domains on study results at endpoint and study levels.

For blinding of participants and personnel (performance bias), detection bias (blinding of outcome assessors) and attrition bias (incomplete outcome data), we evaluated risk of bias separately for subjective and objective outcomes.

We defined the following endpoints as subjective outcomes:

- Change from baseline in HRQoL.
- Change from baseline in assessment of mood and fatigue.
- Proportion of participants reporting an adverse event.

We defined the following outcomes as objective outcomes:

- Change from baseline in serum levels of anti-thyroid peroxidase antibodies.
- Change from baseline in LT_4 replacement dosage.
- Change from baseline in muscle weakness.
- Economic costs.

Measures of treatment effect

We presented continuous outcomes on the original scale as reported in each individual study. Dichotomous outcomes were presented as risk ratios (RRs) and if significant were converted to the number needed to treat for an additional beneficial outcome (NNTB).

All outcomes data were reported with their associated 95% confidence intervals (CIs) and were analysed using a random-effects model in RevMan (RevMan 2011) and the Mantel Haenzel test for dichotomous outcome data and invariance analysis for continuous outcome data, unless stated otherwise.

Unit of analysis issues

Cluster-randomised trials

For future updates, if cluster randomised trials (i.e. groups of individuals randomly assigned to intervention or control) are identified from searches, these will be checked for unit of analysis errors based on the advice provided in Section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If studies are analysed that do not account for clustering, standard errors will be inflated for the effect of clustering and CIs and P values re-calculated. If this is not possible, study results will be presented only as point estimates without P values or CIs.

Cross-over trials

Unit of analysis issues can arise in studies in which participants have been randomly assigned to multiple treatments in multiple periods, or where an inadequate wash-out period has been reported. We assessed the carry-over and period effects in one study descriptively and analysed these data based on the advice provided in Section 16.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Studies with multiple treatment groups

Studies that are reported with multiple treatment groups have the potential for participant data to contribute to multiple comparisons. We assessed the comparisons for clinical importance and included only those that address the primary outcomes. In cases where all comparisons are of equal clinical value, we split the 'shared' group equally into the number of comparisons made, as discussed in Section 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

If data were missing from trials that were less than 10 years old, we tried wherever possible to contact the investigators or sponsors of these studies. We tried to re-analyse data according to the intention-to-treat (ITT) principle whenever possible. For dichotomous outcomes, if authors had conducted a per-protocol analysis, we carried out an ITT analysis by imputation setting the missing data to reflect treatment failure, checking the degree of imbalance of the drop-out between arms to determine the potential impact of bias (Section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). For continuous outcomes, a per-protocol analysis was carried out in place of an ITT analysis. In circumstances where partial data were presented in the primary research, we have calculated the change from baseline and associated standard deviation with an assumed correlation coefficient between baseline and follow-up of 0.75, consistent with the nature of biomarker outcomes. In each case the calculation was repeated with an assumed weaker correlation of 0.5.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of studies, the similarity between types of participants and the interventions. We planned to report heterogeneity as important if it was substantial (I^2 between 50% and 90%, Higgins 2011); if the I^2 statistic was greater than 90%, the meta-analysis would not have been carried out. However, if heterogeneity could be explained by clinical reasoning and a coherent argument could be made for combining the studies, we planned to enter these into a meta-analysis. In cases where the heterogeneity could not be adequately explained, we planned not to pool the data.

Assessment of reporting biases

In future updates, assessments of reporting bias will follow the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These assessments will be performed for primary and secondary outcomes for meta-analysis when a minimum number of studies are included to allow a reasonable estimate of the effect of intervention (nominally nine studies). Funnel plots will be presented only when some evidence of asymmetry is seen in the plots. Possible sources of asymmetry will be explored through an additional sensitivity analysis.

Data synthesis

In future updates, if adequate studies are identified from the searches, these data will be analysed in RevMan (RevMan 2011) and reported in accordance with the advice in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A random-effects meta-analysis will be carried out in studies that investigate similar interventions and report data that exhibited not more than moderate heterogeneity.

Subgroup analysis and investigation of heterogeneity

If an adequate number of studies had been reported, we planned to carry out subgroup analyses of the following primary outcomes:

- Age.
- Selenium status at baseline.
- Type of selenium (selenomethionine or sodium selenite).
- Selenium dose (100 or 200 µg/day).
- Different baseline anti-TPOAb.
- Gender.

Sensitivity analysis

In future updates, if adequate numbers of studies are identified, we will perform sensitivity analyses to explore the influence of the following factors on effect sizes:

- Restricting the analysis to published studies.
- Restricting the analysis while taking into account risk of bias, as specified earlier.
- Restricting the analysis to very long or large studies to establish how much they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry vs other) and country.

RESULTS

Description of studies

For a detailed description of studies, see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

Results of the search

The initial search identified 110 records; from these, nine full text papers were identified for further examination. We excluded the other studies on the basis of their titles or abstracts because they did not meet the inclusion criteria, they were not relevant to the question under study or they presented a duplicate report (see Figure 1 for the amended PRISMA [preferred reporting items for systematic reviews and meta-analyses] flow chart). After the full text of the selected publications was screened, four studies (four publications) were deemed to meet the inclusion criteria. All studies were published in English. We contacted all authors of included studies and received a reply from two (Karanikas 2008; Krysiak 2011). We sought additional information from the authors of seven studies (Duntas 2003; Gärtner 2002; Gärtner 2003; Karanikas 2008; Krysiak 2011; Nacamulli 2010; Turker 2006). Six authors responded to these requests and provided further data (see Appendix 10).
After the search had been completed, an additional study (Krysiak 2012) was found, which is located in Characteristics of studies awaiting classification. This study has not been added to Figure 1 but will be considered in the next update of this review.

Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see Characteristics of included studies and appendices). A succinct overview follows.

Comparisons

The four studies described different comparisons (see Appendix 2):

- In Karanikas 2008 the treatment arm received levothyroxine (LT_4) combined with 200 μg sodium selenite, while the control arm received LT_4 with a placebo.
- The study of Krysiak 2011 included four arms; one treatment arm with LT_4, one with selenomethionine 200 μg, one with LT_4 and selenomethionine 200 μg and one placebo arm.
- In Negro 2007 selenomethionine 200 μg was compared with placebo.
- Participants in the treatment arm in the study of Turker 2006 received LT_4 combined with selenomethionine 200 μg, while the control arm received LT_4 plus placebo.

Overview of study populations

A total of 463 participants were included in the four trials; 279 participants were randomised to *intervention* and 184 to *control* groups.
An unclear number of participants finished the study in the *intervention* and *control* groups because of the fact that only means were reported in two studies, and it was unclear whether all participants were entered into the analysis.
Individual sample size ranged from 36 to 170. For further details, see Table 2.

Study design

Studies were randomised controlled trials. All four trials adopted a parallel-group superiority design, and all studies used a placebo control (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006).
Two trials were multi-centred (Negro 2007;Turker 2006), both with two centres.
In terms of blinding, one study was double-blinded for participants and personnel (Krysiak 2011), no studies were single-blinded for participants and in one study, blinding was not defined (Negro 2007). Outcome assessors were blinded in one study (Krysiak 2011). Investigators in two studies stated that the study was blinded, but no further details were given about the specific measures used to blind personnel and participants from knowledge of which intervention a participant was receiving (Karanikas 2008;Turker 2006).
Studies were performed between the years 2006 and 2011.
The duration of interventions ranged from three to 18 months, with a mean study period of 7.5 months.
No study included a follow-up period.
None of the studies had a run-in period.
None of the studies was terminated before regular end.

Settings

All studies were conducted in an outpatient setting in a hospital.

Participants

The participating population consisted of the following: women with auto-immune thyroiditis (Karanikas 2008;Turker 2006), euthyroid women who had recently been diagnosed with Hashimoto's thyroiditis (Krysiak 2011) and pregnant women with positive anti-TPO antibodies (Negro 2007).
Four trials included participants from economically developed countries.
Ethnic groups were distributed as follows: Caucasian (Karanikas 2008; Negro 2007); the other two studies did not provide details on ethnicity.
The duration of auto-immune thyroiditis was not reported in any trial.
Only women were included in all studies (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006).
The mean age of participants in the trials ranged from 28 to 47 years.
One trial reported co-morbidities of participants (Turker 2006), one trial co-interventions in participants (Negro 2007) and no trials co-medications used by participants.
Criteria for entry into the individual studies are outlined in the Characteristics of included studies.

Diagnosis

Participants were diagnosed with auto-immune thyroiditis in all four studies (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006).
None of the studies confirmed the diagnosis of auto-immune thyroiditis against standard diagnostic criteria. All four studies did not refer to standard diagnostic criteria but instead relied on third party diagnosis of auto-immune thyroiditis before study enrolment.

Interventions

One study reported treatment before the start of the trial (Karanikas 2008) consisting of LT_4.
None of the studies had a titration period.
Intervention was applied by the oral route once a day.
The daily dosage of sodium selenite or selenomethionine was 200 μg.
All studies used a matching placebo as the control intervention (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006).
The duration of treatment ranged from three to 18 months, with a mean treatment duration of 7.5 months.

Outcomes

All studies explicitly stated a primary endpoint in the publication (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006); none of the studies provided secondary endpoints.
Reporting of endpoints
One study assessed subjective well-being (Karanikas 2008).
Anti-TPO antibodies were measured from baseline in all studies (Karanikas 2008; Krysiak 2011; Negro 2007; Turker 2006).
Two studies reported on adverse events (Krysiak 2011; Turker 2006).
No studies investigated HRQoL, change from baseline in LT_4 replacement dosage at end of study or cost of treatment.
For a summary of all outcomes assessed in each study, see Appendix 7.
Three studies provided a definition of endpoint measurement (Karanikas 2008; Negro 2007; Turker 2006) for the following outcomes: subjective well-being, anti-TPO antibody measurement and LT_4 replacement.

Excluded studies

Six studies were excluded after careful evaluation of the full text of the publication (Balázs 2008; Contempré 1992; Duntas 2003; Gärtner 2002; Gärtner 2003; Nacamulli 2010) (see Figure 1).
The main reason for exclusion was that these appeared to be controlled clinical trials. Four studies were reported to be randomised, but after e-mail contact with the investigators, these were classified as quasi-randomised. For further details, see Characteristics of excluded studies.

Risk of bias in included studies

For details on risk of bias of included studies, see Characteristics of included studies.
For an overview of review authors' judgments about each risk of bias item for individual studies and across all studies, see Figure 2 and Figure 3.
We investigated performance bias, detection bias and attrition bias separately for objective and subjective outcome measures.
We defined 'objective outcome' measures as follows: change from baseline in serum levels of anti-thyroid peroxidase antibodies, change from baseline in LT_4 replacement dosage, change from baseline in muscle weakness and economic costs.
We defined 'subjective outcome' measures as follows: change from baseline in HRQoL, change from baseline in assessment of mood and fatigue and proportions of participants reporting an adverse event.

Allocation

Sequence generation

In two studies (Krysiak 2011; Negro 2007), the method used to generate the allocation sequence was described in sufficient detail; therefore, this domain was judged as low risk of bias for these studies. However, in the two remaining studies (Karanikas 2008; Turker 2006), sequence generation was based on prognostic factors such as serum level of anti-TPO antibodies and age, and there was no indication that stratified randomisation had been used; accordingly, the domain was judged as at high risk of bias.

Allocation concealment

Reports of two studies (Krysiak 2011; Negro 2007) provided sufficient detail and reassurance that participants and investigators enrolling those participants could not foresee the upcoming assignment. For the other two studies (Karanikas 2008; Turker 2006), the method used to conceal the allocation sequence was not reported; thus, they received a judgment of unclear risk of bias for this domain.

Blinding

Three studies explicitly stated that blinding of participants and personnel was undertaken but did not provide sufficient information about blinding procedures (Karanikas 2008; Krysiak 2011; Turker 2006); the remaining study did not report any blinding (Negro 2007).
Most of the objective outcomes were based on blood tests; however, this is unlikely to have introduced bias into the outcome assessment. We judged this for three studies as having low risk of bias (Karanikas 2008; Krysiak 2011; Turker 2006). One study included thyroid ultrasound as well as an outcome; this can be potentially confounded by prior knowledge of treatment intervention (Negro 2007). Therefore we judged the domain for detection bias here as high risk of bias. Only one study assessed a subjective outcome (Karanikas 2008), but the method used to blind the assessment of subjective outcomes by participants was not described; therefore we judged this as having unclear risk of bias.

Incomplete outcome data

Only one study described a subjective outcome (Karanikas 2008); the other studies included only objective outcomes (Krysiak 2011; Negro 2007; Turker 2006).
Numbers of study withdrawals were described in two studies that had losses to follow-up (Krysiak 2011; Negro 2007).
Analysis was reported as ITT in one study for the subjective outcome but not for the objective outcomes (Karanikas 2008). No ITT analysis was undertaken in the trials by Krysiak 2011 and Negro 2007.
Two studies did not report losses to follow-up and reported only means of the outcomes without numbers of participants (Karanikas 2008; Turker 2006).

Selective reporting

The protocol for three of the studies was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported; therefore we judged this domain in these studies as having low risk of bias (Karanikas 2008; Krysiak 2011; Turker 2006). However, the free thyroxine (FT_4) values were incompletely reported in Negro 2007, and we judged this as having unclear risk of bias (see also Appendix 5).

Other potential sources of bias

All four studies appeared to be free of other forms of bias, and we judged this domain as having low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Selenium (+LT4) compared to placebo (+LT4) for participants with Hashimoto's thyroiditis

Baseline characteristics

For details of baseline characteristics, see Appendix 3 and Appendix 4.

(1) Sodium selenite 200 μg plus titrated LT_4 versus placebo plus titrated LT_4

One study judged as having high risk of bias provided data for this comparison (Karanikas 2008).

Primary outcomes

Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study

This outcome was not assessed.

Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study

Subjective well-being (assessed with short form health survey) was improved in 14/18 participants receiving sodium selenite compared with 3/18 in the placebo group (RR 4.67, 95% CI 1.61 to 13.50; P = 0.004; number needed to treat (NNT) = 2 (95% CI 2 to 3).

Proportions of participants reporting an adverse event throughout the study period

This outcome was not assessed.

Secondary outcomes

Change from baseline in serum levels of anti-thyroid peroxidase (TPO) antibodies at end of study

The anti-TPO antibodies changed from 524 ± 452 IU/mL at baseline to 505 ± 464 IU/mL for the sodium selenite group and from 521 ± 349 IU/mL to 527 ± 354 IU/mL for the placebo group. The mean difference (MD) was estimated to be -25 (95% CI -181 to 131; P = 0.75; 36 participants).

Change from baseline in LT_4 replacement dosage at end of study

This outcome was not assessed.

Economic costs

This outcome was not assessed.

(2) Selenomethionine 200 μg versus placebo

Two studies compared the efficacy of selenomethionine versus placebo (Krysiak 2011; Negro 2007).

Primary outcomes

Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study

This outcome was not assessed.

Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study

This outcome was not assessed.

Proportions of participants reporting an adverse event throughout the study period

No adverse events were reported in either group (Krysiak 2011). This outcome was no assessed in the other study (Negro 2007).

Secondary outcomes

Change from baseline in serum levels of anti-TPO antibodies at end of study

There was a clearly discernible end of study reduction in anti-TPO antibody values, as compared to baseline, for participants in the selenomethionine group in both studies. The MDs were estimated as -917 IU/mL (Krysiak 2011) and -345 IU/mL (Negro 2007), both P < 0.001. Pooling of the studies was not feasible due to marked clinical heterogeneity, which was attributable to variability in the characteristics of the women included in the studies i.e. recently diagnosed euthyroid women not undergoing treatment with high baseline TPO antibodies (Krysiak 2011), versus pregnant women diagnosed with Hashimoto's and low baseline TPO antibodies (Negro 2007). These results are presented in a forest plot, partitioned into two subgroups (I^2 = 99%; P < 0.0001, see Analysis 1.1).This analysis demonstrates a clear reduction in

serum levels of anti-TPO antibodies between selenomethionine (200 μg) and placebo (see Analysis 1.1).

Change from baseline in LT_4 replacement dosage at end of study

This outcome was not assessed.

Economic costs

This outcome was not assessed.

(3) Selenomethionine 200 μg plus titrated LT_4 versus placebo

The study evaluating comparison (2) also compared the efficacy of selenomethionine plus titrated LT_4 versus placebo (Krysiak 2011).

Primary outcomes

Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study

This outcome was not assessed.

Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study

This outcome was not assessed.

Proportions of participants reporting an adverse event throughout the study period

In the active treatment group, 1/43 reported an adverse event versus 0/42 in the placebo group (RR 2.93, 95% CI 0.12 to 70.00).

Secondary outcomes

Change from baseline in serum levels of anti-TPO antibodies at end of study

Anti-TPO antibodies changed from 1810 ± 452 U/mL at baseline to 463 ± 104 U/mL at end of study in the group treated with selenomethionine plus titrated LT_4 and from 1723 ± 410 IU/L to 1884 ± 346 U/mL in the placebo group. The MD was estimated to be -1508 U/mL (95% CI -1672 to -1345); P < 0.001; 86 participants). This demonstrated a clear reduction in serum levels of anti-TPO antibodies between selenomethionine (200 μg) plus titrated LT_4 and placebo.

Change from baseline in LT_4 replacement dosage at end of study

This outcome was not assessed.

Economic costs

This outcome was not assessed.

(4) L-selenomethionine 200 μg plus titrated LT_4 versus placebo plus titrated LT_4

This comparison was examined by one study at high risk of bias (Turker 2006).

Primary outcomes

Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study

This outcome was not assessed.

Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study

This outcome was not assessed.

Proportions of participants reporting an adverse event throughout the study period

In the selenomethionine group, 1/48 reported an adverse event (gastric discomfort) versus 0/40 in the placebo group (RR 2.63, 95% CI 0.11 to 62.95).

Secondary outcomes

Change from baseline in serum levels of anti-TPO antibodies at end of study

Anti-TPO antibody levels decreased from 804 ± 484 IU/L to 572 ± 517 IU/mL in the selenomethionine group and from 770 ± 406 IU/mL to 773 ± 373 IU/mL in the placebo group. The MD was estimated to be -235 IU/mL (95% CI -374 to -95; P = 0.001; 88 participants); this demonstrated a reduction in serum levels of anti-TPO antibodies between L-selenomethionine (200 μg) plus titrated LT_4 and placebo plus titrated LT_4.

Change from baseline in LT_4 replacement dosage at end of study

This outcome was not assessed.

Economic costs

This outcome was not assessed.

Subgroup analyses

We did not perform subgroup analyses because the number of studies was insufficient to allow estimation of effects in various subgroups.

Sensitivity analyses

To assess the impact of estimating the change from baseline correlation as 0.75, we changed this to 0.5 and noted no changes in study findings.

Assessment of reporting biases

Only one study was identified for each comparison; therefore, we were not able to assess reporting bias.

DISCUSSION

Summary of main results

Four studies at unclear to high risk of bias comprising 463 participants were included. None of the studies addressed our principal primary outcome of 'health-related quality of life' (HRQoL). Two of our secondary outcomes ('change from baseline in LT_4 replacement dosage at end of study' and 'economic costs') were not assessed either. One study at high risk of bias showed a statistically significant improvement in subjective well-being with sodium selenite 200 μg plus titrated levothyroxine (LT_4) compared with placebo plus titrated LT_4 (Karanikas 2008). Selenomethionine 200 μg supplementation was associated with a reduction in the serum levels of anti-TPO antibodies in three studies (Krysiak 2011; Negro 2007; Turker 2006), and although the changes from baseline were significant, they were not considered to be clinically important. One study (Karanikas 2008), which assessed sodium selenite 200 μg plus titrated LT_4, did not confirm this reduction in serum anti-thyroid antibodies. Adverse events were reported in two studies, and selenium supplementation did not lead to a statistically significant increase in the number of adverse events when compared with placebo.
For further details, see the 'Summary of findings for the main comparison'.

Three ongoing studies were identified that may eventually help to fill in some of the gaps in evidence for the efficacy of selenium as a supplement in people with Hashimoto's thyroiditis.

Overall completeness and applicability of evidence

The four studies at unclear to high risk of bias provided very limited data. No clinically relevant conclusions can be drawn on the basis of these four included studies. Hashimoto's thyroiditis has many very debilitating symptoms; therefore, outcomes such as change in HRQoL and improvement in symptoms such as mood, fatigue and muscle weakness are crucial meaningful markers of clinical status. Results of these studies provide incomplete evidence to support or refute the efficacy of selenium in people with Hashimoto's thyroiditis.

Quality of the evidence

Limitations in study design and implementation

Although study design in two of the included studies appeared to have been at best adequate, we judged the sequence generation of the other two studies as having high risk of bias. We were unsuccessful in our attempts to contact the investigators of these last two studies to clarify the methods used to generate the sequence and to conceal the allocation and to obtain details of blinding and losses to follow-up (see Risk of bias in included studies section and Appendix 10 of this review). Furthermore, our key outcomes such as HRQoL and effects on mood, well-being and fatigue were not addressed in any of the studies, with the exception of well-being in one study, which was assessed as having high risk of bias. One of our remaining outcomes reflected changes in anti-TPO antibodies, which, as long as they remain positive, can be considered to a large extent to be not clinically meaningful.

Indirectness of the evidence

Participants in the included study in general constituted a clinically representative sample matching the inclusion criteria; therefore, we had no significant concerns about the appropriateness of participants identified in the review.
Placebo-controlled trials are still required to evaluate whether selenium supplementation has any potential beneficial effect on Hashimoto's thyroiditis. The results of these studies provide insufficient evidence to allow any firm conclusions to be drawn to support or refute selenium as additional therapy.
Patient-relevant outcomes are a pre-requisite for informing evidence-based clinical decision making, but the importance of patient-reported outcomes (PROs), specifically those used in evaluating the impact of the intervention on quality of life, appears to have been underestimated by investigators in all of the included studies.

Inconsistency of the results

In view of the clinical heterogeneity noted between the studies, and, more specifically, the comparisons evaluated, it was not possible to pool study data; and thus no inferences could be drawn about any possible inconsistency in the results.

Imprecision of the results

The primary outcome for this review was assessment of HRQoL, which was not measured in any of the included studies. The results of our secondary outcomes provided varying estimates of anti-TPO antibody level reduction in each comparison. These effect estimates were generated from single studies that reported large reductions bound by tight confidence intervals. All estimates showed clear reductions, but it should be noted that these were generated from single studies and were subject to increased risk of bias.

Publication bias

Although our attempts to identify additional studies yielded three ongoing studies, the possibility of further unpublished research on this topic cannot be excluded. In future updates, and if additional trials are identified for inclusion, we will assess publication bias as specified in the Assessment of reporting biases section of this review.

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review minimised the potential for additional bias.

Agreements and disagreements with other studies or reviews

We identified another systematic review that attempted "to summarize available data and provide an evidence-based recommendation regarding selenium supplementation in the treatment of Hashimoto's thyroiditis" (Toulis 2010). This review included a meta-analysis of data extracted solely from trials that were 'blinded, randomized, placebo-controlled in design'. Although this review relied on the consensus process negotiated between investigators and was therefore deemed reasonably transparent, we are in disagreement over the robustness of its methodological approach. Lack of clarity in the process and ultimately its limited reproducibility were illustrated by incomplete reporting of some of the important steps taken in study assessment and handling of missing trial details and data. It appears that no attempts were made to contact any of the investigators in the included studies for clarification of methods used to generate the sequence, allocation concealment or blinding or to retrieve missing data. Furthermore, and quite significantly, no risk of bias assessments of the included studies were undertaken. Of the four studies (Duntas 2003; Gärtner 2002; Karanikas 2008; Turker 2006) included in the meta-analysis of this review (Toulis 2010), two were excluded in our review because through email contact, the trial investigators confirmed that these were quasi-randomised (Duntas 2003; Gärtner 2002). In the other two studies, it was unclear whether participants had been randomly assigned according to strata, or whether the studies were also quasi-randomised (Karanikas 2008; Turker 2006), and we were unsuccessful in our attempts to contact study investigators. The other systematic review included two additional studies (Gärtner 2003; Mazokopakis 2007), which were excluded from our review. We excluded Gärtner 2003 on the basis that email communication revealed that this study appeared to be quasi-randomised, and although the study design was not an exclusion criterion for the systematic review of Toulis 2010, this study was excluded from the meta-analysis. Mazokopakis 2007 was not considered eligible for our review as it was clear from the abstract that it was not a randomised controlled trial. Negro 2007 was excluded on the basis of inclusion criteria, which stated that no pregnant women would be included; however, the second phase of this study included women after delivery and could have been included.

Although the authors in Toulis 2010 sought to provide evidence-based recommendations for selenium supplementation, they failed to indicate how the quality of the evidence was rated, or how the strength of subsequent recommendations was graded.

A recently published non-systematic review was a valuable resource for increasing our knowledge and giving us a better understanding of the relationship between selenium and thyroid metabolism, the functions of selenium and its role in the different thyroid diseases. It did not include a systematic search of the literature, nor did it provide a critical appraisal of the studies cited as references in support of selenium supplementation for the management of Hashimoto's thyroiditis (Drutel 2013).

Our assessments of the overall quality of the evidence and conclusions on the efficacy of selenium supplementation for Hashimoto's thyroiditis were largely in agreement with the recently updated topic summary in DynaMed, a clinical reference derived from systematic literature surveillance with explicit critical appraisal criteria (DynaMed 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review demonstrate that at present, objective evidence is insufficient to support clinical decision making regarding

the use of selenium supplementation for the treatment of patients with Hashimoto's thyroiditis.

Implications for research

This review highlights the need for randomised placebo-controlled trials to evaluate the effects of selenium in people with Hashimoto's thyroiditis, which can ultimately provide reliable evidence to support clinical decision making.

Any future randomised controlled trials must be well designed, well conducted and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Reporting should conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/); this will promote appraisal and interpretation of results and accurate judgement of risk of bias and of the overall quality of the evidence.

Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995).

For further research recommendations based on the EPICOT (evidence, population, intervention, comparison, outcomes, and time) format (Brown 2006), see Table 3.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Karanikas 2008

Methods	**Parallel randomised controlled clinical trial.** **Randomisation ratio**: 1:1. **Superiority design.**
Participants	**Inclusion criteria**: • LT_4 substitution. • Positivity for anti-TPOAb. • Negativity for anti-thyrotropin (TSH) receptor antibodies. • Thyroid ultrasound imaging suggestive of chronic thyroiditis (typical hypoechogenicity). • Otherwise healthy participants. **Exclusion criteria**: • Clinical history of hyperthyroidism. • Drugs known to induce thyroid dysfunction (cytokines, lithium, amiodarone). • Pregnancy in the last 12 months before enrolment. • No history of rheumatoid diseases. • No further treatment such as over-the-counter vitamins or trace elements or corticoid or anti-inflammatory therapy. **Diagnostic criteria**: • Positivity for anti-TPOAb. • Thyroid ultrasound imaging suggestive of chronic thyroiditis (typical hypoechogenicity).
Interventions	**Number of study centres**: 1, **Treatment before study**: LT_4 substitution. **Titration period**: not reported. **Intervention**: LT_4 + 200 μg sodium selenite once a day during 3 months. **Control**: LT_4 + placebo once a day during 3 months.
Outcomes	**Outcomes reported in abstract of publication**: • FT_4, TSH, anti-TPOAb. • Plasma Se. • Intracellular cytokine evaluation in CD4+ and CD8+ T cells of peripheral blood mononuclear cells. • Subjective well-being of participants.
Study details	**Run-in period**: not reported. **Study terminated before regular end**: no.
Publication details	**Language of publication**: English. **Commercial / non-commercial / other funding**: not reported. **Publication status:** full article.

Stated aim for study	**Quote from publication** (page 8): "The aim of our study was to evaluate the immunological benefit of Se administration in unselected AIT patients and thus address the question whether Se administration should generally be recommended for AIT patients"
Notes	Abbreviations: AIT: auto-immune thyroiditis; CD4+/8+: cluster of differentiation 4/8; FT_4: free thyroxine; LT_4: levothyroxine; Se: selenium; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibodies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	**Quote** (page 8): "Enrolled patients were randomized into two groups according to their initial TPOAb titer, age, and supposed duration of the disease" **Comment**: randomisation seems to be based on prognostic factors, with no mention of stratified randomisation **After email contact**: no further details; see Appendix 10
Allocation concealment (selection bias)	Unclear risk	**Comment**: the method used to conceal the allocation sequence, that is, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported **Comment**: information was insufficient to permit a clear judgement
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote** (page 9): "..blinded.." **Comment**: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote** (page 9): "..blinded.." **Comment**: the report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Karanikas 2008 (*Continued*)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote** (page 9): "..blinded.." **Comment**: the report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received; however, as all objective outcomes were based on blood tests, this is unlikely to have introduced bias into the outcome assessment; we judged this as having low risk of bias
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote** (page 9): "..blinded.." **Comment**: the method used to blind the assessment of subjective outcomes by participants was not described; information was insufficient to permit a clear judgement
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Comment**: intention-to-treat analysis **Comment**: we judged this as having low risk of bias
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment**: as only means were reported, it was unclear whether all participants were entered into the analysis **Comment**: information in the report was insufficient to permit a clear judgement
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appear to have been reported **Comment**: we judged this as having low risk of bias
Other bias	Low risk	**Comment**: the study appears to be free from other sources of bias

Krysiak 2011

Methods	**Parallel randomised controlled clinical trial.** **Randomisation ratio**: 1:1:1:1. **Superiority design.**
Participants	**Inclusion criteria**: • Females between 18 and 60 years. • Positive anti-TPOAb > 100 U/mL. • Reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography. • Euthyroid function (TSH < 4.0 mU/L, normal values for FT_4 and FT_3).

	• Medically stable. • In the judgement of the investigators, otherwise acceptable for entry on the basis of the findings of medical history, physical examination and routine laboratory tests. • Only individuals with newly diagnosed and previously untreated Hashimoto's thyroiditis were included. **Exclusion criteria**: • Any acute and chronic inflammatory processes. • Other auto-immune disorders. • Positive serum antibodies against TSH receptor. • Current treatment with thyroid hormones. • Concomitant treatment with drugs that may affect inflammatory processes in the vascular wall. • Concomitant treatment with other drugs known to affect thyroid hormones or to interact with levothyroxine and selenomethionine. • BMI > 40 kg/m^2. • Turner or Down syndrome. • Any form of coronary artery disease. • Moderate or severe arterial hypertension (ESC/ESH grade 2 or 3). • Symptomatic congestive heart failure. • Diabetes, impaired glucose tolerance or impaired fasting glucose. • Impaired renal or hepatic function. • Pregnancy or lactation. • Poor patient compliance. **Diagnostic criteria**: • Positive antibodies (> 100 U/mL) against thyroid peroxidase (TPOAb). • Reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography. • Euthyroid function (TSH < 4.0 mU/L, normal values for FT_4 and FT_3).
Interventions	**Number of study centres**: 1. **Treatment before study**: no treatment. **Titration period**: not reported. **Intervention 1**: levothyroxine sodium 0.5 μg/kg once a day for participants with TSH levels below 1.0 mIU/mL, 0.75 μg/kg once a day for individuals with TSH levels between 1.0 and 2.0 mIU/mL, and 1 μg/kg for participants with a TSH above 2.0 mIU/mL during 6 months **Intervention 2**: selenomethionine once a day 200 μg during 6 months. **Intervention 3**: combination of interventions 1 and 2 once daily during 6 months **Control**: placebo during 6 months.
Outcomes	**Outcomes reported in abstract of publication**: The primary endpoint was to evaluate monocyte- and lymphocyte-suppressing as well as systemic anti-inflammatory effects of levothyroxine, selenomethionine or their combination using a panel of inflammatory markers: tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, monocyte chemotactic protein (MCP)-1, IL-2, interferon-γ and high-sensitivity C-reactive protein (hsCRP)
Study details	**Run-in period**: not reported. **Study terminated before regular end**: no.

Publication details	**Language of publication**: English. **Non-commercial funding: quote** (page 2214): "This work was supported by the scientific Grant 2 P05F 03629 of the Committee of Scientific Research" **Publication status:** full article.
Stated aim for study	**Quote from publication**: "Our objective was to compare the effect of levothyroxine and selenomethionine on monocyte and lymphocyte cytokine release and systemic inflammation in patients with Hashimoto's thyroiditis"
Notes	**Abbreviations**: BMI: body mass index; ESC/ESH: European Society of Cardiology/ European Society of Hypertension; FT_3: free triiodothyronine; FT_4: free thyroxine; LT: levothyroxine; TPOAb: thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote** (page 2207): "The included patients were randomised in a double-blind manner to receive…" **Comment**: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups **After email contact**: a computer random number generator was used **Comment**: probably done
Allocation concealment (selection bias)	Low risk	**Comment**: the method used to conceal the allocation sequence, that is, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported **Comment**: information was insufficient to permit a clear judgement **After email contact**: **quote**: ".. two other persons to help us with allocation procedure and drug distribution (based on the results of allocation). During all visits, both investigators were unaware of a record number and an identity card number, receiving patient documentation not containing these data." **Comment**: reasonable attempts have been made to conceal the allocation; see Appendix 10

Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote** (page 2207): "…in a double blind manner.." **Comment**: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received to permit a clear judgement **After email contact**: **quote**: "The names of drugs had not been placed on the packages or on the drugs. However, levothyroxine, selenomethionine and placebo were stored on different shelves but the same for each drug. Although the participants were not informed about this, theoretically, they may see from which shelves they received their drugs" **Comment**: risk of bias remains unclear; see Appendix 10
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes were reported
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote** (page 2207): "A person performing laboratory assays was unaware of patient's personal data, clinical status, treatment group, and study sequence." **Comment**: the report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received; however, as all the objective outcomes were based on blood tests, this is unlikely to have introduced bias into the outcome assessment; we judged this as having low risk of bias **After email contact**: **quote**: "The person helping us to perform laboratory assays (a technician) worked in another building and received samples which had previously been coded to protect patient identity." **Comment**: outcomes were investigator assessed; unlikely blinding could be broken; see Appendix 10
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes

Krysiak 2011 (*Continued*)

Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote** (page 2208): "Only data of individuals who completed the study were included in the final analyses" and (page 2209) "Only the data of 165 subjects who completed the study were included in the final analyses" **Comment**: reasons reported **Comment**: although this was a per-protocol analysis, the low and balanced number of drop-outs was unlikely to introduce bias
Selective reporting (reporting bias)	Low risk	**Comment**: the protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appear to have been reported **Comment**: we judged this as having low risk of bias
Other bias	Low risk	**Comment**: the study appears to be free from other sources of bias

Negro 2007

Methods	**Parallel randomised controlled clinical trial.** **Randomisation ratio**: 1:1. **Superiority design.**
Participants	**Inclusion criteria**: • Euthyroid, anti-TPOAb - positive pregnant women. **Exclusion criteria**: • Thyroid dysfunction. • Treated with drugs that interfere with thyroid function. **Diagnostic criteria**: • Anti-TPOAb titers of more than 100 kIU/L were considered positive. • Thyroid ultrasound.
Interventions	**Number of study centres**: 2. **Treatment before study**: no treatment. **Titration period**: not reported. **Intervention**: selenomethionine 200 μg once a day from 12 weeks' gestation until 12 months after delivery **Control**: placebo once a day from 12 weeks' gestation until 12 months after delivery

Negro 2007 (*Continued*)

Outcomes	**Outcomes reported in abstract of publication**: Prevalence of post-partum thyroid disease and hypothyroidism: • Se status. • Thyroid ultrasound. • TSH and FT_4. • Anti-TPOAb.
Study details	**Run-in period**: not reported. **Study terminated before regular end**: no.
Publication details	**Language of publication**: English. **Commercial / non-commercial / other funding**: no. **Publication status:** full article.
Stated aim for study	**Quote from publication** (page 1263): "We examined whether Se supplementation, during and after pregnancy, influences the thyroidal auto-immune pattern and function"
Notes	**Abbreviations**: FT_4: free thyroxine; Se: selenium; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibodies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote** (page 1264): "TPOAb(+) pregnant women with were randomly divided into two groups". "A computer program was used to randomly assign the TPOAb(+) patients to either group S1 or group S0" **Comment**: this was probably done
Allocation concealment (selection bias)	Low risk	**Quote** (page 1264): "A sealed opaque envelope was assigned to each patient; only the doctor who treated the patient, and who did not participate in any subsequent phase of the study, knew to which group the patient was assigned" **Comment**: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment; this was probably done
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Comment**: no report on any blinding **Comment**: we judged this as having unclear risk of bias

Negro 2007 (*Continued*)

Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	**Comment**: no reporting on any blinding; outcome assessment was not blinded **Comment**: although the objective outcomes were blood test results and thyroid ultrasound findings, a potentially high risk of bias cannot be excluded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Comment**: 8/85 in the S1 group and 10/84 in the S0 group dropped out; reasons stated; per-protocol analysis **Comment**: although the analysis was per-protocol, the low number of well balanced drop-outs across both groups posed a low risk of bias
Selective reporting (reporting bias)	Unclear risk	**Comment**: the protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appear to have been reported; however, the FT_4 values were incompletely reported **Comment**: the potential risk of bias was unclear
Other bias	Low risk	**Comment**: the study appears to be free from other sources of bias

Turker 2006

Methods	**Parallel randomised controlled clinical trial.** **Randomisation ratio**: 1:1. **Superiority design.**
Participants	**Inclusion criteria**: • Females with known AIT and elevated serum anti-TPOAb (> 100 IU/mL) and/or anti-TgAb (> 188 IU/mL). **Exclusion criteria**:

	• Using treatment with corticosteroids, vitamins, trace elements or antidepressive/ antipsychotic drugs. **Diagnostic criteria**: Elevated serum anti-TPOAb (> 100 IU/mL) and/or anti-TgAb (> 188 IU/mL)
Interventions	**Number of study centres**: 2. **Treatment before study**: not reported. **Titration period**: not reported. **Intervention**: LT_4 + 200 μg + L-selenomethionine once a day during 3 months. **Control**: LT_4 + placebo once a day during 3 months.
Outcomes	**Outcomes reported in abstract of publication**: • Serum TSH. • FT_3, FT_4. • Anti-TPOAb and anti-TgAb levels.
Study details	**Run-in period**: not reported. **Study terminated before regular end**: no.
Publication details	**Language of publication**: English. **Commercial / non-commercial / other funding**: no. **Publication status:** full article.
Stated aim for study	**Quote from publication** (page 152): "1: To test the effect of 200 mg L-selenomethionine/day therapy in a larger group to determine the parameters that may affect success rates. 2: To observe the dose-response curves by shifting doses (200-100 mg/day) after saturation of tissues with a high dose (200 mg/day) of Se for 3 months, which may exclude any doubt about the Se status of the tissue stores, instead of subjective measurements of the serum Se levels. 3: Finally, to follow the long-term effects of therapy"
Notes	After 3 months, the Se group (S2) was split into 2 groups. Group S22 went on taking L-selenomethionine 200 μg/day, while others (group S21) lowered the dose to 100 μg/day. Then after another 3 months, 12 participants in group S22 (group S222) went on taking L-selenomethionine 200 μg/day, while 12 participants in group S21 (S212) increased the dose to 200 μg/day In the absence of a wash-out period, we considered only data from the first 3 months Abbreviations: AIT: auto-immune thyroiditis; FT_3: free triiodothyronine; FT_4: free thyroxine; LT_4: levothyroxine; Se: selenium; TgAb: thyroglobulin antibodies; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibodies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote** (page 152): "Patients were randomized into two groups according to their initial serum TPOAb and TSH concentrations and ages to exclude any difference in serum TPOAb and TSH levels or age."

		Comment: randomisation seems to be based on prognostic factors, and no mention is made of stratified randomisation
Allocation concealment (selection bias)	Unclear risk	**Comment**: the method used to conceal the allocation sequence, that is, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported **Comment**: information was insufficient to permit a clear judgement
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote** (page 151): "We conducted a blinded, prospective study" **Comment**: the report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received; we judged this as having unclear risk of bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote** (page 151): "We conducted a blinded, prospective study" **Comment**: the report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received; however, all objective outcomes were based on blood tests, and this is unlikely to have introduced bias into the outcome assessment; therefore, we judged this as having low risk of bias
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment**: not applicable; no subjective outcomes
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment**: as only means were reported, it was unclear whether all participants were entered into the analysis **Comment**: information in the report was insufficient to permit a clear judgement

Turker 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	**Comment**: the protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appear to have been reported **Comment**: we judged this as having low risk of bias
Other bias	Low risk	**Comment**: this study appears to be free from other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balázs 2008	The full text reveals that this appeared to be a CCT.
Contempré 1992	The full text reveals that this appeared to be a CCT.
Duntas 2003	Email contact revealed that this appeared to be a quasi-randomised trial; see Appendix 10.
Gärtner 2002	Email contact revealed that this appeared to be a quasi-randomised trial; see Appendix 10.
Gärtner 2003	Email contact revealed that this appeared to be a quasi-randomised trial; see Appendix 10.
Nacamulli 2010	Email contact revealed that this appeared to be a quasi-randomised trial; see Appendix 10.

CCT: controlled clinical trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Krysiak 2012

Methods	**Parallel randomised controlled clinical trial.** **Randomisation ratio**: 1:1:1:1. **Superiority design.**
Participants	**Inclusion criteria**: • Euthyroid women, aged between 18 and 65 years, with recently diagnosed and previously untreated Hashimoto's thyroiditis. • Positive antibodies (> 100 U/mL) against thyroid peroxidase (anti-TPOAb). • Reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography. • Serum TSH less than 4.0 mU/L. • Plasma levels of FT_4 and FT_3 within the reference range.

	Exclusion criteria: • Any acute and chronic inflammatory processes. • Other auto-immune disorders. • Positive serum antibodies against TSH receptor. • Current treatment with thyroid hormones. • Concomitant treatment with drugs that may affect inflammatory processes in the vascular wall. • Concomitant treatment with other drugs known to affect thyroid hormones or to interact with levothyroxine and selenomethionine. • Body mass index (BMI) above 40 kg/m^2. • Turner or Down syndrome. • Any form of coronary artery disease. • Moderate or severe arterial hypertension (ESC/ESH grade 2 or 3). • Symptomatic congestive heart failure. • Diabetes, impaired glucose tolerance or impaired fasting glucose. • Impaired renal or hepatic function. • Pregnancy or lactation. • Inadequate patient compliance. **Diagnostic criteria**: • Anti-TPOAb > 100 U/mL. • Euthyroid function (TSH < 4.0 mU/L, normal values for FT_4 and FT_3.) • Reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography.
Interventions	**Number of study centres**: 1. **Treatment before study**: no treatment. **Titration period**: not reported. **Intervention 1**: levothyroxine sodium 0.5 μg/kg once a day for participants with TSH levels below 1.0 mIU/mL, 0.75 μg/kg once a day for individuals with TSH levels between 1.0 and 2.0 mIU/mL and 1 μg/kg for participants with a TSH above 2.0 mIU/mL during 6 months **Intervention 2**: selenomethionine once a day 200 μg during 6 months. **Intervention 3**: combination of interventions 1 and 2 once daily during 6 months **Control**: placebo during 6 months.
Outcomes	**Outcomes reported in abstract of publication**: The prothrombin time ratio, the activated partial thromboplastin time, and plasma levels/activities of fibrinogen, factor VII, von Willebrand factor, factor X and plasminogen activator inhibitor-1 (PAI-1)
Study details	**Run-in period**: not reported. **Study terminated before regular end**: no.
Publication details	**Language of publication**: English. **Non-commercial funding: quote** (page 980): "This work was supported by the scientific grant No. 2 P05F 036 29 of the Committee of Scientific Research" **Publication status:** full article.
Stated aim of study	**Quote from publication**: "To investigate for the first time whether levothyroxine and selenomethionine, administered alone or in combination, affect coagulation and fibrinolysis in Hashimoto's thyroiditis patients with normal thyroid function tests"

Notes	**Abbreviations**: ESC/ESH: European Society of Cardiology/European Society of Hypertension; FT_3: free triiodothyronine; FT_4: free thyroxine; LT: levothyroxine; Se: selenium; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone

Characteristics of ongoing studies *[ordered by study ID]*

EudraCT2007-001107-38

Trial name or title	**Description of study**: dose-finding study to investigate efficacy and tolerability of 6-month oral treatment with selenium in participants with auto-immune thyroiditis; prospective, controlled parallel-group study with Cefasel versus placebo; double-blind, randomised clinical multicentre study of phase II with four treatment groups
Methods	**Allocation**: randomised. **Endpoint classification**: dose-finding study. **Intervention model**: active- and placebo-controlled, parallel-group. **Masking**: double-blind. **Primary purpose**: **quote**: "The main objective is to evaluate the optimal dose with the best efficacy of a 6-month oral treatment with 100 µg, 200 µg and 300 µg selenium daily compared with placebo concerning the auto-immune process and the function of the thyroid gland in patients with auto-immune thyroiditis"
Participants	**Condition**: auto-immune thyroiditis (Hashimoto's thyroiditis). **Enrollment**: 200. **Inclusion criteria**: • Mature ambulant patient at the age of 18 to 80 years. • Participants who have given their signed declaration of consent and data protection declaration. • Thyroid peroxidase (TPO) antibody titre at least tenfold above the normal range or at least fivefold above the normal range and positive finding on sonography (diffuse reduced echogenicity of the tissue). • Basal TSH < 4.5 mIU/L and FT_4 within normal range. **Exclusion criteria**: • Previous and concomitant therapy not permitted. • Basedow's disease. • Further manifestations of pluriglandular insufficiency syndrome with the exception of vitiligo. • Indication of thyroid functional autonomies. • Manifest hypothyroidism, defined by basal TSH above normal range for the respective method and FT_4 below normal range. • Previous radioiodine therapy or operation on the thyroid. • Suspicion of a malignant tumour of the thyroid gland on sonography. • Indication of malassimilation. • Intolerance against any excipient of Cefasel 100 µg. • Females in the child-bearing years without appropriate contraception. • Pregnancy (present or planned) or lactation. • Present malignant disease (current or within the past 5 years without recurrence). • Severe somatopathic, neurological and/or psychiatric disease. • Patients who do not agree to the transmission of their pseudonymous data within the liability of documentation and notification. • Participation in another clinical trial (parallel or within the previous 6 months).

EudraCT2007-001107-38 (*Continued*)

	• Participation in the same clinical trial. • History of alcohol and/or drug of abuse. • Patients who are unable to understand the nature, scope and possible impact of the study or considered to be non-compliant concerning drug intake or study activities. • Planned move or holidays during the course of the study so that not all study visits can be followed. • Insufficient knowledge of language (German - written and spoken).
Interventions	**Intervention(s)**: 100 µg, 200 µg and 300 µg selenium daily. **Control(s)**: placebo.
Outcomes	**Primary outcome**: Difference in concentrations of anti-TPO antibodies after 6-month therapy with selenium relative to baseline for treatment groups given 100 µg, 200 µg and 300 µg compared with placebo **Secondary outcomes**: • Concentrations of TSH, FT_3 and FT_4 evaluated analogously to the primary endpoint. • The ratio of participants developing during the course of the study with hypothyroidism requiring treatment (TSH > 10 mIU/L, FT_4 in normal range or TSH above and FT_4 below normal range). • Quality of life and sonographic results.
Starting date	**Study start date**: 26-05-2008. **Study completion date**: 18-04-2012.
Contact information	**Responsible party/principal investigator**: Cefak KG, Germany.
Study identifier	EudraCT: 2007-001107-38.
Official title	Dose-finding study to investigate efficacy and tolerability of 6-month oral treatment with selenium in participants with auto-immune thyroiditis: prospective, controlled parallel-group study with Cefasel versus placebo- double-blind, randomised, clinical multicentre study of phase II with four treatment groups
Stated purpose of study	**Quote**: "The main objective is to evaluate the optimal dose with the best efficacy of a 6-month oral treatment with 100 µg, 200 µg and 300 µg selenium daily compared to placebo concerning the auto-immune process and the function of the thyroid gland in patients with auto-immune thyroiditis"
Notes	Website accessed 5-11-2012. Abbreviations: FT_3: free triiodothyronine; FT_4: free thyroxine; TSH: thyroid-stimulating hormone.

ISRCTN26633557

Trial name or title	**Description of study**: selenium supplementation in euthyroid participants with thyroid peroxidase antibodies
Methods	**Allocation**: randomised. **Endpoint classification**: efficacy study. **Intervention model**: placebo-controlled, parallel-group **Masking**: double-blind. **Primary purpose**: not reported.

ISRCTN26633557 (*Continued*)

Participants	**Condition**: euthyroid with thyroid peroxidase antibodies. **Enrollment**: 150. **Inclusion criteria**: • Thyroid peroxidase (TPO) antibodies greater than 100 kU/L. • Thyroid-stimulating hormone (TSH) 0.4 to 4.0 mE/L. • Free thyroxine (FT_4) 10 to 23 pmol/L. • Triiodothyronine (T_3) 1.30 to 2.70 nmol/L. • Female sex. **Exclusion criteria:** • Use of multivitamin tablets containing selenium in the month preceding inclusion. • Drug or alcohol abuse. • No informed consent.
Interventions	**Intervention(s)**: selenium supplementation. **Control(s)**: placebo.
Outcomes	**Primary outcomes:** • Change in anti-TPO antibody concentration. • Difference in TSH level. **Secondary outcomes:** • Development of subclinical or overt hypothyroidism. • Quality-of-life estimation.
Starting date	**Study start date**: 01-08-2005. **Study completion date**: 31-07-2007.
Contact information	**Responsible party/principal investigator**: Dr S.A. Eskes Academic Medical Centre Department of Endocrinology P.O. Box 22660 1105 AZ Amsterdam, The Netherlands s.eskes@sfg.nl
Study identifier	ISRCTN26633557.
Official title	Selenium supplementation in euthyroid patients with thyroid peroxidase antibodies
Stated purpose of study	Not reported.
Notes	Website accessed 5-11-2012

NCT01465867

Trial name or title	**Description of study**: selenium supplementation in pregnancy (Serena).
Methods	**Allocation**: randomised. **Endpoint classification**: interventional study. **Intervention model**: parallel. **Masking**: double-blind. **Primary purpose**: prevention.
Participants	**Condition**: euthyroid women with auto-immune thyroiditis. **Enrollment**: 150. **Inclusion criteria**: • Pregnant women with 4 to 8 ± 2 weeks of gestation. • Women in whom embryo transfer is expected within 60 days. • Euthyroid women (0.4 μIU/mL < TSH < 2.7 μIU/mL), positive for anti-TPOAb and/or anti-TgAb, not assuming LT_4 replacement. • Euthyroid women (0.4 μIU/mL < TSH < 2.7 μIU/mL), positive for anti-TPOAb and/or anti-TgAb under LT_4 replacement (to maintain TSH within the control range). • Women with TSH > 2.7 μIU/mL positive for anti-TPOAb and/or anti-TgAb, not assuming LT_4 replacement (requiring the beginning of LT_4 replacement). • Women with TSH > 2.7 μIU/mL positive for anti-TPOAb and/or anti-TgAb, under LT_4 replacement (requiring an adjustment in LT_4 replacement). **Exclusion criteria**: • Use of antidepressive/psychotic drugs, amiodarone, propranolol, lithium, cytokines. • History of hyperthyroidism positive anti-thyrotropin antibodies. • Known fetal anomaly. • Known infection (pelvic inflammatory disease, human immunodeficiency virus, hepatitis C virus) and mola hydatidosas. • Chronic renal failure. • Uncontrolled hypertension. • Uterine malformation. • History of medical or metabolic complication such as heart disease or diabetes.
Interventions	**Intervention(s)**: • Selenium. • Selenium + L-Thyroxine (LT_4). **Control(s)**: • Sugar pill placebo. • Sugar pill placebo + L-Thyroxine (LT_4).
Outcomes	**Primary outcomes**: • Changes in anti-TPOAb and/or anti-TgAb. **Secondary outcomes**: • Changes in thyroid volume and echogenicity. • Changes in thyroid hormones (TSH, FT_4, FT_3). • Evaluation of maternal risks. • Pre-eclampsia. • Evaluation of Infant risks. • Changes in of quality of life. • Evaluation of health services.

NCT01465867 (*Continued*)

	• Changes in the selenium-dependent anti-oxidant enzyme glutathione peroxidase. • Changes in implantation and pregnancy rates.
Starting date	**Study start date**: not yet recruiting. **Study completion date**: February 2015.
Contact information	**Responsible party/principal investigator**: Andrea M. Isidori, University of Roma La Sapienza Department of Experimental Medicine, Section of Clinical Pathophysiology and Endocrinology, "Sapienza" University of Rome andrea.isidori@uniroma1.it
Study identifier	**NCT NUMBER**: NCT01465867.
Official title	Selenium supplementation treatment in euthyroid pregnant women with auto-immune thyroid disease: effects on obstetrical complications
Stated purpose of study	**Quote**: "to establish the effect of Se supplementation in euthyroid women with AIT (pregnant and in whom embryo transfer is expected within 60 days) on Ab trend, thyroid function and structure, implantation rates, pregnancy rates, pregnancy outcome and numbers of obstetrical, fetal and neonatal complications"
Notes	**Abbreviations**: FT_3: free triiodothyronine; FT_4: free thyroxine; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LT_4: levothyroxine; PID: pelvic inflammatory disease; TgAb: thyroglobulin antibodies; TSH: thyroid-stimulating hormone; TPOAb: thyroid peroxidase antibodies

DATA AND ANALYSES

Comparison 1. Selenomethionine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anti-TPO antibody levels	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 1700 IU/mL levels at baseline	1	85	Mean Difference (IV, Random, 95% CI)	-917.0 [-1029.16, -804.84]
1.2 600 IU/mL at baseline	1	169	Mean Difference (IV, Random, 95% CI)	-345.0 [-358.79, -331.21]

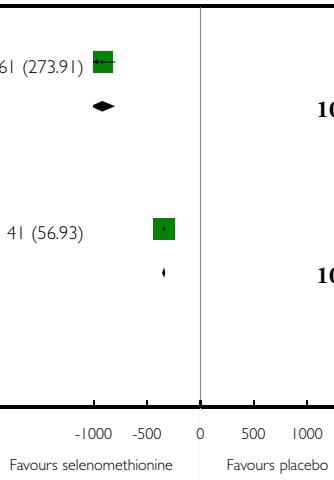
Analysis 1.1. Comparison 1 Selenomethionine versus placebo, Outcome 1 Anti-TPO antibody levels.

Review: Selenium supplementation for Hashimoto's thyroiditis

Comparison: 1 Selenomethionine versus placebo

Outcome: 1 Anti-TPO antibody levels

Study or subgroup	Selenomethionine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 1700 IU/mL levels at baseline							
Krysiak 2011	43	-756 (252.98)	42	161 (273.91)		100.0 %	-917.00 [-1029.16, -804.84]
Subtotal (95% CI)	**43**		**42**			**100.0 %**	**-917.00 [-1029.16, -804.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 16.02 (P < 0.00001)							
2 600 IU/mL at baseline							
Negro 2007	85	-304 (30.46)	84	41 (56.93)		100.0 %	-345.00 [-358.79, -331.21]
Subtotal (95% CI)	**85**		**84**			**100.0 %**	**-345.00 [-358.79, -331.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 49.04 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 98.43, df = 1 (P = 0.0), I^2 =99%							



ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Explanation
Auto-antigen	Usually a normal protein or complex of proteins (sometimes deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)) that is recognised by the immune system of patients suffering from a specific auto-immune disease
Antibody	Produced by immune cells, B cells, to identify and neutralise foreign objects such as bacteria and viruses. The antibody recognises a unique part of the foreign target, called an *antigen*; this might also be an auto-antigen.
Atherosclerosis	A condition in which an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol
Biosynthesis	An enzyme-catalysed process in cells of living organisms by which substrates are converted to more complex products
Cytokines	Small protein molecules, secreted by several types of cells to stimulate other cells
CD4+ T-helper cells	A subgroup of T-cell lymphocytes, a type of white blood cell that plays an important role in the immune system, particularly the adaptive immune system
CD8+ cytotoxic T cells	A subgroup of T-cell lymphocytes that induce the death of cells infected with viruses (and other pathogens) or otherwise damaged or dysfunctional
Dyslipidaemia	High cholesterol or fat levels in the blood.
Goitre	A swelling in the thyroid gland.
GPx4	Phospholipid hydroperoxide glutathione peroxidase, a selenoprotein enzyme
GPx	Glutathione peroxidase, a selenoprotein enzyme that has an antioxidant function
Homeostasis	A state of balanced levels of the molecule in the human body
Hyperglycaemia	High glucose levels in the blood.
IFN-γ	Interferon-gamma; a cytokine or type II interferon that is critical for innate and adaptive immunity against viral and intracellular bacterial infections and for tumour control. Aberrant IFN-γ expression is associated with a number of auto-inflammatory and auto-immune diseases
LDL	Low-density lipoproteins or 'bad' cholesterol.
Macrophage	A type of immune cell that differentiates from monocytes in tissue and phagocytises (engulfs) foreign materials
Pancreatitis	Inflammation of the pancreas.

Table 1. Glossary of terms (*Continued*)

Rheumatoid arthritis	A chronic, systemic inflammatory disorder that may affect many tissues and organs but principally attacks flexible (synovial) joints
Selenoprotein	Selenium incorporated into proteins.
Stroke	A condition of impaired blood supply to the brain resulting in rapid loss of brain function(s)
Thyrocyte	Thyroid gland epithelial cells.
Vitiligo	An auto-immune disorder that affects the skin, causing loss of pigment

Table 2. Overview of study populations

Characteristic	Intervention(s) and comparator(s)	[N] Screened/ eligible	[N] Randomised	[N] Safety	[N] ITT	[N] Finishing study	[%] Randomised finishing study	Follow-up[a]
Karanikas 2008	I: LT_4 + 200 μg sodium selenite	36	18	-	-	-	-	3 months
	C: LT_4 + placebo		18	-	-	-	-	3 months
		total:	36	-	-	-	-	3 months
Krysiak 2011	I1: Levothyroxine sodium	-	42	-	N/A	41	98	6 months
	I2: Selenomethionine 200 μg		43	-	N/A	42	98	6 months
	I3: Levothyroxine sodium + selenomethionine 200 μg		43	-	N/A	42	98	6 months
	C1: Placebo		42	-	N/A	40	95	6 months
		total:	170	165	N/A	165	97	6 months

Table 2. Overview of study populations (*Continued*)

Negro 2007	I: 200 μg selenomethionine	2227	85	-	-	77	91	from 12 weeks' gestation to12 months' post partum
	C: Placebo		84	-	-	74	88	
		total:	169	-	-	151	89	
Turker 2006	I: LT_4 + 200 μg + L-selenomethionine	-	48	-	-	-	-	3 months
	C: LT_4 + placebo		40	-	-	-	-	3 months
		total:	88	-	-	-	-	3 months
Total	**All interventions**		***279***			**-**		
	All controls		***184***			**-**		
	All interventions and controls		***463***			**-**		

[a] Duration of intervention and/or follow-up under randomised conditions until end of study.
- = not reported.
ITT: intention-to-treat; N/A: not applicable.

Table 3. Research recommendations based on a gap in the evidence of the effects of selenium for Hashimoto's thyroiditis

Core elements	Issues to consider	Status of research for this review
Evidence (E)	What is the current state of the evidence?	This systematic review identified one randomised controlled trial (RCT). Incomplete evidence of efficacy and safety of selenium for Hashimoto's thyroiditis
Population (P)	Diagnosis, disease stage, co-morbidity, risk factors, gender, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	Inclusion criteria: • Hashimoto's thyroiditis as diagnosed by a physician and supported by serum levels of anti-TPOAb and anti-TgAb above the normal level of the laboratory's normal ranges. Exclusion criteria:

Table 3. Research recommendations based on a gap in the evidence of the effects of selenium for Hashimoto's thyroiditis (*Continued*)

		• Clinical history of hyperthyroidism. • Any acute and chronic inflammatory processes. • Drugs known to induce thyroid dysfunction (cytokines, lithium, amiodarone). • Concomitant treatment with drugs that may affect inflammatory processes in the vascular wall. • Pregnancy in the last 12 month before enrolment. • No further treatment such as over-the-counter vitamins or trace elements or corticoid or anti-inflammatory therapy.
Intervention (I)	Type, frequency, dose, duration, prognostic factor	Selenium 100 µg or 200 µg supplementation (sodium selenite or selenomethionine) plus titrated LT_4 to maintain basal TSH within normal range for at least 3 months
Comparison (C)	Type, frequency, dose, duration, prognostic factor	• No control plus titrated LT_4 to maintain basal TSH within normal range for at least 3 months. • Placebo tablets plus titrated LT_4 to maintain basal TSH within normal range for at least 3 months.
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence or accomplish? Which methods of measurement should be used?	Primary outcomes • Change from baseline in HRQoL assessed using any validated quality-of-life instrument at end of study. • Change from baseline in symptoms such as mood, fatigue and muscle weakness assessed using any validated instrument at end of study. • Proportions of participants reporting an adverse event throughout the study period. Secondary outcomes • Change from baseline in serum levels of anti-thyroid peroxidase antibodies at end of study. • Change from baseline in LT_4 replacement dosage at end of study. • Economic costs.
Time Stamp (T)	Date of literature search or recommendation	1 November 2012
Study Type	What is the most appropriate study design to address the proposed question?	• RCT (adequately powered/multi-centred). • Methods: concealment of allocation sequence. • Blinding: blinding of participants, trialists and outcomes assessors. • Setting: hospital/university.

APPENDICES

Appendix 1. Search strategies

Search terms and databases
Unless otherwise stated, search terms are free-text terms. Abbreviations: '$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word
The Cochrane Library
#1 MeSH descriptor Thyroiditis, Autoimmune explode all trees #2 ((hashimoto* in All Text near/6 syndrom* in All Text) or (hashimoto* in All Text near/6 thyroidit* in All Text) or (hashimoto* in All Text near/6 diseas* in All Text)) #3 (((thyroidit* in All Text near/6 chronic in All Text) and lymphocytic in All Text) or (thyroidit* in All Text near/6 autoimmun* in All Text)) #4 (#1 or #2 or #3) #5 MeSH descriptor Selenium explode all trees #6 MeSH descriptor Selenomethionine explode all trees #7 (selenium in All Text or selenomethionin* in All Text or (sodium in All Text and selenit* in All Text)) #8 (#5 or #6 or #7) #9 (#4 and #8)
MEDLINE
1 exp Thyroiditis, Autoimmune/ 2 (hashimoto adj6 (syndrom* or thyroidit* or diseas*)).tw,ot. 3 (thyroidit* adj6 (chronic lymphocytic or autoimmun*)).tw,ot. 4 or/1-3 5 exp Selenium/ 6 exp Selenomethionine/ 7 (selenium or selenomethionin* or sodium selenit*).tw,ot. 8 or/5-7 9 4 and 8 10 randomized controlled trial.pt. 11 controlled clinical trial.pt. 12 randomi?ed.ab. 13 placebo.ab. 14 drug therapy.fs. 15 randomly.ab. 16 trial.ab. 17 groups.ab. 18 or/10-17 19 Meta-analysis.pt. 20 exp Technology Assessment, Biomedical/ 21 exp Meta-analysis/ 22 exp Meta-analysis as topic/ 23 hta.tw,ot.

(*Continued*)

24 (health technology adj6 assessment$).tw,ot.
25 (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
26 (search* adj10 (medical databas*or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content*)).tw,ot.
27 (systematic adj3 review*).tw,ot.
28 or/19-27
29 18 or 28
30 (comment or editorial or historical-article).pt.
31 29 not 30
32 9 and 31
33 limit 32 to humans

EMBASE

1 exp autoimmune thyroiditis/
2 (hashimoto* adj6 (syndrom* or thyroidit* or diseas*)).tw,ot.
3 (thyroidit* adj6 (chronic lymphocytic or autoimmun*)).tw,ot.
4 or/1-3
5 exp selenium/
6 exp selenomethionine/
7 (selenium or selenomethionin* or sodium selenit*).tw,ot.
8 or/5-7
9 4 and 8
10 exp Randomized Controlled Trial/
11 exp Controlled Clinical Trial/
12 exp Clinical Trial/
13 exp Comparative Study/
14 exp Drug comparison/
15 exp Randomization/
16 exp Crossover procedure/
17 exp Double blind procedure/
18 exp Single blind procedure/
19 exp Placebo/
20 exp Prospective Study/
21 ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
22 (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
23 ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
24 (cross over or crossover).ab,ti.
25 or/10-24
26 exp meta analysis/
27 (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
28 (search$ adj10 (medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
29 exp Literature/
30 exp Biomedical Technology Assessment/
31 hta.tw,ot.
32 (health technology adj6 assessment$).tw,ot.
33 or/26-32
34 25 or 33

(*Continued*)

35 (comment or editorial or historical-article).pt. 36 34 not 35 37 9 and 36
'My NCBI' alert service
("hashimoto disease"[MeSH Terms] OR ("hashimoto"[All Fields] AND "disease"[All Fields]) OR "hashimoto disease"[All Fields] OR ("hashimoto"[All Fields] AND "thyroiditis"[All Fields]) OR "hashimoto thyroiditis"[All Fields]) AND Randomized Controlled Trial[ptyp]
Web of Science (d atabases = SCI-EXPANDED, SSCI, A&HCI; timespan = all years)
1 Topic=(autoimmune thyroidit*) OR Topic=(hashimoto* thyroidit*) OR Topic=(hashimoto* syndrom*) OR Topic=(hashimoto* diseas*) OR Topic=(chronic lymphocytic thyroidit*) # 2 Topic=(selenium) OR Topic=(selenomethionin*) OR Topic=(solium selenit*) # 3 #1 AND #2 # 4 Topic=(randomized controlled trial*) OR Topic=(controlled clinical trial*) OR Topic=(random*) OR Topic=(placebo*) # 5 Topic=(meta-analys*) OR Topic=(hta) OR Topic=(systematic review*) OR Topic=(health technology assessment*) # 6 #4 OR #5 # 7 #3 AND #6

Appendix 2. Description of interventions

Characteristic	Intervention(s) [route, frequency, total dose/day]	Comparator(s) [route, frequency, total dose/day]
Karanikas 2008	Levothyroxine (LT_4) + 200 μg sodium selenite (oral, once a day during 3 months)	Levothyroxine (LT_4) + placebo (oral, once a day during 3 months)
Krysiak 2011	Levothyroxine sodium (oral, 0.5 μg/kg once a day for participants with thyroid-stimulating hormone levels below 1.0 mIU/mL, 0.75 μg/kg once a day for individuals with thyroid-stimulating hormone levels between 1.0 and 2.0 mIU/mL and 1 μg/kg for participants with a thyroid-stimulating hormone level above 2.0 mIU/mL during 6 months)	Placebo (oral, once a day during 6 months)
	Selenomethionine (oral, 200 μg once daily during 6 months).	
	Levothyroxine sodium plus selenomethionine (oral, dosage as described above, once a day during 6 months)	

(*Continued*)

Negro 2007	200 μg selenomethionine (oral, once a day from 12 weeks' gestation to 12 months' post partum)	Placebo (oral, once a day from 12 weeks' gestation to 12 months' post partum)
Turker 2006	Levothyroxine (LT_4) + 200 μg L-selenomethionine (oral, once a day during 3 months).	Levothyroxine (LT_4) + placebo (oral, once a day during 3 months)

Appendix 3. Baseline characteristics (I)

Characteristic	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up) [mean (SD) /range months, or as reported]	Participating population	Study period [year to year]	Country	Setting	Ethnic groups [%]	Duration of disease [mean/ range years (SD), or as reported]
Karanikas 2008	I: LT_4 + sodium selenite C1: LT_4 + placebo	3 months	Women with autoimmune thyroiditis	-	Austria	Outpatient department medical university	Caucasian (100)	-
Krysiak 2011	I1: levothyroxine sodium I2: selenomethionine I3: levothyroxine sodium + selenomethionine C: placebo	6 months	Euthyroid women with recently diagnosed and previously untreated Hashimoto's thyroiditis	-	Poland	Outpatient department hospital	-	-
Negro 2007	I: selenomethionine	from 12 weeks' gestation until	Pregnant anti-	-	Italy	Outpatient department	Caucasian (100)	-

(*Continued*)

	C: placebo	12 months' post partum	TPOAb-positive women			hospital		
Turker 2006	I: LT_4 + selenomethionine	3 months	Women with autoimmune thyroiditis	-	Turkey	Out-patient department hospital	-	-
	C: LT_4 + placebo							

Footnotes
"-" denotes not reported
C: control; I: intervention; LT_4: levothyroxine; SD: standard deviation; TPOAb: thyroid peroxidase antibodies

Appendix 4. Baseline characteristics (II)

Characteristic Study ID	Intervention(s) and control(s)	Sex [female %]	Age [mean (SD)/range years, or as reported]	Co-medications / Co-interventions	Co-morbidities
Karanikas 2008	I1: LT_4 + sodium selenite	100	-	-	-
	C1: LT_4 + placebo		-	-	
	all:		47 (19 to 85)	-	
Krysiak 2011	I1: levothyroxine sodium	100	39 (4)	-	-
	I2: selenomethionine		40 (4)		
	I3: levothyroxine sodium + selenomethionine		37 (3)		
	C1: placebo		38 (3)		
	C2: healthy controls		36 (4)		

(*Continued*)

Negro 2007	I1: selenomethionine	100	28 (6)	-	-
	C1: placebo		28 (5)		
	all:		28 (5) (18 to 36)	LT_4 treatment was initiated during pregnancy if participants had TSH values above the normal range and/or FT_4 values below the normal range. After delivery, LT_4 administration was stopped, and substitutive treatment, in cases of hypothyroidism, was initiated for participants with TSH values > 10 mIU/L. Patients whose substitutive treatment was initiated during the post-partum period stopped receiving LT_4 at the end of the post-partum period to determine whether the condition of hypothyroidism was permanent. During pregnancy, LT_4 administration was titrated to keep FT_4 values in the middle to higher tercile and TSH less than 2.5 mIU/L; after pregnancy, LT_4 was titrated to keep TSH and FT_4 within the normal range.	-
Turker 2006	I1: LT_4 + selenomethionine	100	41 (13)	-	1 vitiligo 1 discoid lupus 6 vitamin B_{12} at the lower limit of normal

(*Continued*)

	C1: LT_4 + placebo	100	39 (14)		4 vitamin B_{12} at the lower limit of normal
	all:	100	40 (13) (15 to 77)		-

Footnotes
"-" denotes not reported
FT_4: free thyroxine; LT_4: levothyroxine; SD: standard deviation; TSH: thyroid-stimulating hormone

Appendix 5. Matrix of study endpoints (publications)

Characteristic study ID	Endpoint	Time of measurement[a]	Clear that outcome was measured and analysed[b] [trial report states that outcome was analysed but reports only that result was not significant]	Clear that outcome was measured and analysed[c] [trial report states that outcome was analysed but no results are reported]	Clear that outcome was measured[d] [clear that outcome was measured but not necessarily analysed (judgement says likely to have been analysed but not reported because of non-significant results)]	Unclear whether the outcome was measured[e] [not mentioned; clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results]
Karanikas 2008	FT_4, TSH,*anti-TPOAb (P)*	0, 3 mo	N/A	N/A	N/A	N/A
	Intracellular cytokine evaluation in CD4+ and CD8+ T-cells of peripheral blood mononuclear cells (P)	0, 3 mo	N/A	N/A	N/A	N/A
	Plasma Se (P)	0, 3 mo	N/A	N/A	N/A	N/A
	Subjective well-being of participants (P)	0, 3 mo	N/A	N/A	N/A	N/A

(*Continued*)

Krysiak 2011	**Adverse effects** (O)	-, 6 mo	N/A	N/A	N/A	N/A
	Monocyte and lymphocyte suppression (P)	0, 3, 6 mo	N/A	N/A	N/A	N/A
	Systemic anti-inflammatory effects (P)	0, 3, 6 mo	N/A	N/A	N/A	N/A
	Anti-TPOAb (O)	0, 3, 6 mo	N/A	N/A	N/A	N/A
Negro 2007	FT_4, TSH (P)	0, 20 and 30 wk gestation, at delivery, 1, 2, 5, 9, 12 mo after delivery	N/A	N/A	N/A	x[f]
	Se status (P)	0, 20 and 30 wk gestation, at delivery, 6, 12 mo after delivery	N/A	N/A	N/A	N/A
	Anti-TPOAb (P)	0, 20 and 30 wk gestation, at delivery, 1, 2, 5, 9, 12 mo after delivery	N/A	N/A	N/A	N/A
	Thyroid ultrasound (P)	0, at delivery, 12 mo after delivery	N/A	N/A	N/A	N/A
Turker 2006	TgAb, TSH, FT_4, FT_3 (P)	0, 3 mo	N/A	N/A	N/A	N/A
	Anti-TPOAb (P)	0, 3 mo	N/A	N/A	N/A	N/A

Footnotes

[a] Underlined times of measurement denote data as reported in the results section of the publication (other times represent planned but not reported points in time)

(P) primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes that were not specified as 'primary' or 'secondary' outcomes in the publication

Endpoint in bold = review of primary outcome, endpoint in italic = review of secondary outcomes.

'High risk of bias' categories for outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting in reports of randomised trials (Kirkham 2010).

[b] Classification 'A' (Table 2, Kirkham 2010).

[c] Classification 'D' (Table 2, Kirkham 2010).

[d] Classification 'E' (Table 2, Kirkham 2010).

(*Continued*)

[e] Classification 'G' (Table 2, Kirkham 2010).
[f] FT_4 incompletely reported.
CD4+/CD8+: cluster of differentiation 4/8; FT_3: free triiodothyronine; FT_4: free thyroxine; mo: months; N/A: not applicable; Se: selenium; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone

Appendix 6. Matrix of study endpoints (protocol/trial documents)

Characteristic Study ID trial identifier	Endpoint[a]	Time of measurement
Turker 2006 (Clinicaltrials.gov: NCT00271427)	*Statistically important change in serum anti-TPOAb titers (P)*	-
	Observe the long-term effects to 9th mo (S)	-

Footnotes
[a] Endpoint in italic = review secondary outcome
[b] (P) Primary or (S) secondary endpoints refer to verbatim statements in the publication; (O) other endpoints relate to outcomes that were not specified as 'primary' or 'secondary' outcomes in the report
mo: months

Appendix 7. Definition of endpoint measurement

Characteristic Study ID	Health-related quality of life	Symptoms	Adverse events	Antibodies	Levothyroxine replacement dosage	Economic costs
Karanikas 2008	N/A	Subjective well-being (short-form health survey)	N/A	Using Immulite 2000 Anti-TPO (EURO = DPC, Gwynedd, United Kingdom).	N/A	N/A
Krysiak 2011	N/A	N/A	N/D	Serum anti-TPOAb and thyroglobulin antibodies (anti-TgAb) levels were determined by radioligand assay	N/A	N/A

(*Continued*)

				using reagents obtained from BRAHMS (Berlin, Germany).		
Negro 2007	N/A	N/A	N/A	Anti-TPOAb titers were determined using an RIA kit (Brahms Diagnostica, Berlin, Germany). The reference range was 0 to 100 kIU/L. Anti-TPOAb titers greater than 100 kIU/L were considered positive	LT_4 treatment was initiated during pregnancy if participants had TSH values above the normal range and/or FT_4 values below the normal range. After delivery, LT_4 administration was stopped, and substitutive treatment, in cases of hypothyroidism, was initiated for participants with TSH values > 10 mIU/L. Patients whose substitutive treatment was initiated during the post-partum period stopped receiving LT_4 at the end of the post-partum period to determine whether the condition of hypothyroidism was permanent. During pregnancy, LT_4administration was titrated to	N/A

(*Continued*)

					keep FT_4 values in the middle-higher tercile and TSH less than 2.5 mIU/L; after pregnancy, LT_4 was titrated to keep TSH and FT_4 within the normal range.	
Turker 2006	N/A	N/A	N/D	Normal ranges, analytical sensitivities, intra-assay coef-ficients of variation (CV) and inter-assay CV are as follows: Anti-TPOAb: (< 100 IU/mL); 4 IU/mL; 4.26%; 8.45%.	N/A	N/A
Footnotes FT_4: free thyroxine; LT_4: levothyroxine; N/A: not applicable, N/D: not defined; RIA: radio-immunoassay: TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone						

Appendix 8. Adverse events (I)

Characteristic	Intervention(s) and comparator (s)	Randomised / Safety [N]	Deaths [N]	Deaths [%]	All adverse events [N]	All adverse events [%]	Severe/serious adverse events [N]	Severe/serious adverse events [%]
Karanikas 2008	I: LT_4 + sodium selenite	18	-	-	-	-	-	-
	C: LT_4 + placebo	18	-	-	-	-	-	-
	all:	36	-	-	-	-	-	-

(*Continued*)

Krysiak 2011	I1: levothyroxine sodium	42	-	-	1	2.4	-	-
	I2: selenomethionine	43	-	-	0	0	-	-
	I3: levothyroxine sodium + selenomethionine	43	-	-	1	2.3	-	-
	C: placebo	42	-	-	0	0	-	-
	all:	170/165	0	0	2	1.2	0	0
Negro 2007	I: selenomethionine	85	-	-	-	-	-	-
	C: placebo	84	-	-	-	-	-	-
	all:	169	-	-	-	-	-	-
Turker 2006	I: LT_4 + selenomethionine	48	-	-	1	2.1	-	-
	C: LT_4 + placebo	40	-	-	0	0	-	-
	all:	88	-	-	1	1.1	-	-

Footnotes
"-" denotes not reported
LT_4: levothyroxine

Appendix 9. Adverse events (II)

Characteristic	Intervention(s) and comparator (s)	Randomised / Safety [N]	Left study due to adverse events [N]	Left study due to adverse events [%]	Hospitalisation [N]	Hospitalisation [%]	Outpatient treatment [N]	Outpatient treatment [%]

(*Continued*)

Karanikas 2008	I: LT_4 + sodium selenite	18-	-	-	-	-	-	-
	C: LT_4 + placebo	18	-	-	-	-	-	-
	all:	18						
Krysiak 2011	I1: levothyroxine sodium	42	1	2.4	-	-	-	-
	I2: selenomethionine	43	-	-	-	-	-	-
	I3: levothyroxine sodium + selenomethionine	43	1	2.3	-	-	-	-
	C: placebo	42	-		-	-	-	-
	all:	170/165	2	1	0	0	0	0
Negro 2007	I: selenomethionine	85	-	-	-	-	-	-
	C: placebo	84	-	-	-	-	-	-
	all:							
Turker 2006	I: LT_4 + selenomethionine	48	-	-	-	-	-	-
	C: LT_4 + placebo	40	-	-	-	-	-	-
	all:	88	-	-	-	-	-	-

Footnotes
"-" denotes not reported
LT_4: levothyroxine

Appendix 10. Survey of authors providing information on trials

Characteristic Study ID	Study author contacted	Study author replied	Study author asked for additional information	Study author provided data
Karanikas 2008	Yes	Yes	1. Sequence generation. You report in the text that "Enrolled patients were randomized into two groups according to their initial TPOAb titer, age, and supposed duration of the disease". This indicates that participants were randomly assigned (to one or other interventions) according to baseline criteria and therefore most definitely not at random. Randomisation ensures that each participant has an equal chance of being allocated to one or another intervention; what you described is selective (i.e. biased) allocation. However, as this may have involved stratification or minimisation, would you please clarify how this judgement was made (i.e. what were the cut-off points for TPOAb titer, age and disease duration that dictated allocation to sodium selenite or placebo?)? 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i. e. participants and investigators enrolling participants could not foresee the upcoming assign-	Reply 9-10-12: Unfortunately I have to tell you that our working group (thyroid immunology) does not exist anymore since 4 years ago. Most of the co-workers removed to other hospitals or retired. I also changed my scientific orientation and moved to hybrid diagnostic modal- ities (positron emission tomography (PET)/computed tomography (CT)) 4 years ago

(*Continued*)

			ment; this is not the same as blinding). 3. The specific measures used to blind study participants and personnel from knowledge of which intervention a participant received. 4. Were there any losses to follow-up? If so, how many in each group? 5. Were all participants who were randomly assigned and received treatment included in the analysis of all outcomes (i.e. the full data set)? Repeated the e-mail on 1-1-2013. Repeated the e-mail on 9-1-2013.	
Krysiak 2011	Yes	Yes	1. The method used to generate the allocation sequence. 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i.e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding)). 3. The specific measures used to blind study participants and personnel from knowledge of which intervention a participant received. Repeated the e-mail on 1-1-2013. 3-1-2013 additional mail: Could the participants	Reply 3-1-2013: Allocation sequence in this study was generated by a computer on the basis of the results of mathematical calculation. The formula required a record number and an identity card number for each participant. Because our study was carried out by only two investigators (not counting a person performing laboratory assays), we were forced to ask two other persons to help us with the allocation procedure and drug distribution (based on the results of allocation). During all visits, both investigators were unaware of a record number and an identity card number, having received participant documentation that

(*Continued*)

			not see which tablet they received (on the package, or on the tablet)?	did not contain these data. The person helping us to perform laboratory assays (a technician) worked in another building and received samples that had previously been coded to protect participant identity. With the exception of the withdrawn participants, investigators had access to participant allocation only after the study had been completed. The participants, although they knew their own identity card numbers, did not know their record numbers, had no access to their documentation and were unaware of the method (formula) used for allocation sequence Reply 3-1-2013 second mail: It is very difficult or even impossible to answer this question. Our study was conducted some time ago, and presently I do not have contact with one of the persons who performed the allocation procedure and drug distribution. As far as I remember, the names of drugs had not been placed on the packages or on the drugs. However, levothyroxine, selenomethionine and placebo were stored on different shelves, but the same for each drug. Although the participants

(*Continued*)

				were not informed about this, theoretically, they may see from which shelves they received their drugs. For the reasons already mentioned, I cannot say whether this fact may have helped some participants to find out which drug they were given
Negro 2007	Not necessary			
Turker 2006	Yes	No	1. Sequence generation. You report in the text, "Patients were randomised into two groups according to their initial serum TPOAb and TSH concentrations and ages to exclude any difference in serum TPOAb and TSH levels or age". This indicates that participants were randomly assigned (to one or other interventions) according to baseline criteria and therefore most definitely not at random. Randomisation ensures that each participant has an equal chance of being allocated to one or another intervention; what you described is selective (i.e. biased) allocation. However, as this may have involved stratification or minimisation, would you please clarify how this judgement was made (i.e. what were the cut-off points for TPOAb titer, TSH level and age that dictated allocation to L-selenomethionine or placebo?)?	

(*Continued*)

			2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i. e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding)). 4. Were there any losses to follow-up? If so how many in each group? 5. Were all participants who were randomly assigned and received treatment included in the analysis of all outcomes (i. e. the full dataset)? Repeated the e-mail on 1-1-2013. Repeated the e-mail on 9-1-2013.	
Ongoing study: EudraCT2007-001107-38	Yes	No	We are conducting a Cochrane systematic review on selenium for Hashimoto and the trial you are sponsoring "Dose finding study to investigate efficacy and tolerability of a 6 month oral treatment with selenium in patients with auto-immune thyroiditis" appears to be eligible for inclusion in our review. We tried to look for the authors emails to contact regarding the trial but could not find them. We would highly appreciate it if you could send us the authors' emails or provide us with the information needed. We would	

(*Continued*)

			like to know whether the trial has been published. In case it has not, we would like to know when it is expected to be completed or published? Repeated mail 16-1-2013.	
Ongoing study: ISRCTN26633557	Yes	Yes	Asked in Dutch whether study was published or was about to be published, and if we can receive data	Is submitted for publication, no further reply.
Ongoing study: NCT01465867	Yes	Yes	We are conducting a Cochrane systematic review on selenium for Hashimoto, and your trial "Selenium Supplementation in Pregnancy (Serena)" appears to be eligible for inclusion in our review. We would highly appreciate it if you could inform us whether your trial has been published. In case it has not, could you please inform us when it is expected to be completed or published? Repeated mail 16-1-2013.	18-1-2013: The Serena trial is actively recruiting. Recruitment is expected to be completed by Oct 2013. Publication is expected by mid 2014. The trial is double-blind randomised; therefore we cannot anticipate any data on the participants that are already included. Best regards, Andrea Isidori
Excluded study: Duntas 2003	Yes	Yes	1. The method used to generate the allocation sequence. 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i.e. participants and investigators enrolling participants could not foresee the upcoming assignment	I am providing you the requested trial details of the study: 1. The allocation sequence has been ensured by numbering 1,3, 5 & 2, 4, 6,…, respectively 2. The allocation sequence was concealed by complete randomisation and stratification (confounders: TSH, anti-TPO levels) 3. All participants who

(*Continued*)

			(this is not the same as blinding)). 3. Were there any losses to follow-up? If so, how many in each group? 4. Were all participants who were randomly assigned and received treatment included in the analysis of all outcomes (i. e. the full dataset)? Additional e-mail 22-12-12: Thank you for your reply. Unfortunately, odd and even is a predictable sequence and is not random. It is quasi-randomised The second reply does not concern concealment but rather sequence generation. Please look at our question again. How could the allocation not be foreseen? Even/odd numbers are easily foreseen by investigators Last reply is clear. Repeated e-mail of 22-12-12 on 1-1-2013.	received treatment were included in the analyses, and no losses were reported following recruitment Follow-up mail 8-1-2013: Concealment of allocation remained unclear.
Excluded study: Gärtner 2002	Yes	Yes	1. The method used to generate the allocation sequence. 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i. e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding)). 3. The specific measures	Recruitment was obtained from the patients coming to our outpatient clinic and suffering from auto-immune thyroiditis. We were advertising that we planned a study. After agreement to participate (71 out of 92), participants were allocated according to the concentration of the TPOAb in group A or B by an independent physician, who had access only to the lab tests, without names, but with age and ap-

(*Continued*)

			used to blind study participants and personnel from knowledge of which intervention a participant received. 4. Were there any losses to follow-up? If so, how many in each group? 5. Were all participants who were randomly assigned and received treatment included in the analysis of all outcomes (i. e. the full dataset)? 19-12-2012: We sent an additional mail: Thank you for your replies to our questions. To be sure whether I understood you well, regarding the first study after the independent physician had the participants with high TPOAB titers, comparable age and disease duration, participants were allocated consecutively to A or B (on alternation)? Further questions 21-12-2012: Thanks for your reply. If you are using titre, age and disease duration, and you assign to A or B on the basis of previous assignments, then you can predict next allocation, thus not implementing allocation concealment? So if it was indeed AB AB AB, we consider this to be quasi-randomised. We need to be sure if this is what happened before we can include or exclude the studies (the one of 2003 sounded like AB AB as well)	proximate duration of the disease. The independent physician also did not know whether A or B was placebo. This was done consecutively, meaning after the TPOAb concentration was received, those with high titers and comparable age and duration of disease were randomly assigned to A or B, so that especially the TPOAb concentration was comparable in both groups. Se- lenium and placebo were blinded and the medication handed to the participants. The numbers of tablets were counted, and tablets were handled in similar blinded boxes. The physician who distributed the medication also did not know whether A or B was placebo. Only one participant in the verum group got pregnant and was excluded, All participants had completed the follow-up, and for all, the data were complete Extra reply 19-12-2012 after our second mail: Yes, that is as we did it: on alternation. Last reply 21-12-2012: It is correct that we used AB AB and so on, so it was quasi-randomised

(*Continued*)

Excluded study: Gärtner 2003	Yes	Yes	1. The method used to generate the allocation sequence. 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i. e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding))	In the second cross-over study, participants were asked whether they wanted to continue, and 47 agreed. We built four groups before un-blinding the results, and participants were randomly assigned (number one from group A to B, the next to A,and so forth; the same was done in group B). All 47 participants finished the study, and no data were missed, but the QL questionnaire was not continued
Excluded study: Nacamulli 2010	Yes	Yes	1. The method used to generate the allocation sequence. 2. The method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (i. e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding)). 3. The specific measures used to blind study personnel from knowledge of which intervention a participant received. 4. Were there any losses to follow-up? If so, how many in each group? 5. Were all participants who were randomly assigned and received treatment included in the analysis of all outcomes (i. e. the full dataset)?	Reply 3-1-2013: 1-2. Participants were recruited consecutively from outpatients afferent in our Operative Unit, and each participant was randomly assigned to group 0 or group 1. As the minimum sample size was achieved in each group, subsequent participants were assigned to Group 1 because it was likely that some participants would not complete the study, stopping to assume selenium. Indeed, we needed to achieve the most accurate test reliability in group 1, as the main comparison of the study regarded just the variation of each parameter in treated participants at every follow-up point. Evidence of any improvement in group 1 should be considered a significant result in itself

(*Continued*)

			Repeated the e-mail on 1-1-2013: New mail on 3-1-2013: 1'. Regarding sequence generation and allocation concealment. It is still not clear to me how each participant was "randomly assigned". What was the method? How was it made 'at random´ ? 2'. And was it possible for inves- tigators or participants to know how this randomisation method was performed? I mean, could the investigator and/or participant know in which group a participant would end up? How was it protected that investigators and participants did not know in which group they were included? Your reply on question 3 is clear. 4/5 I understand that four people in group 0 did not finish the study, but were these participants included in the final analysis, or was the analysis done only on those who finished the treatment period? How many participants stopped in group 15 who finished only the first 6 months? And were not included in the analysis at 12 months? Repeated mail on 9-1-2013: New mail 12-1-2013: What I understand is that participants were assigned	because the natural history of AIT is characterised by progressive thyroid structure and functional impairment. Anyway, we have also included a control group that, as expected, showed the same trend of the general AIT population. 3. No specific measures were used to blind study personnel from knowledge of which intervention a participant received because all critical measurements were operator independent. 4-5. Four participants in group 0 did not complete the study and have been replaced using the same criteria. Five participants assumed selenium only for 6 months and have been considered part of the treated group only for the duration of 6 months Reply to additional questions: 1- 2. Participants were "randomly assigned" in the sense that any participant with the proper characteristics had the same probability to be assigned alternatively to group 1 or group 0. Clearly, if one participant refused to assume selenium, he was recruited in group 0, and the next participant was a candidate for group 1,

(*Continued*)

			on alternation to group 0 or group 1. that is right? Thank you for clarifying the other details.	and so on. 4-5. The four participants in group 0 lost at control were eliminated from the study and were replaced with four other participants. The primary endpoint in our study consisted of the paired data comparison of thyroid echogenicity as expression of thyroid damage in Se-treated participants. The secondary endpoint was the paired data comparison of serum level antibodies as an indirect expression of the grade of auto-immune response. Therefore, the five participants with only 6 months' treatment cannot be included in the analysis at 12 months. Answer 14-1-2013: Yes, it is right. Conclusion: on alternation, quasi-randomised.

Footnotes
QL: quality of life; TPOAb: anti-thyroid peroxidase antibodies; TSH: thyroid-stimulating hormone

WHAT'S NEW

Last assessed as up-to-date: 2 October 2012.

Date	Event	Description
12 June 2013	Amended	Errata: Replacement of 'sodium selenite' with 'selenomethionine' in abstract, PLS, effects of interventions, summary of main results and appendixes

CONTRIBUTIONS OF AUTHORS

Esther J van Zuuren (EvZ): protocol draft, acquiring trial copies, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

Amira Y Albusta (AYA): protocol draft, search strategy development, acquisition of trial copies, trial selection, data extraction, review draft and future review updates.

Zbys Fedorowicz (ZF): protocol draft, data extraction, data analysis, data interpretation, review draft and future review updates.

Ben Carter (BC): protocol draft, data analysis, data interpretation, review draft and future review updates.

Hanno Pijl (HP): protocol draft, review draft and future review updates.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of report, Bahrain.
- No sources of report, UK.
- No sources of report, Netherlands.

External sources

- No sources of support, Bahrain.
- No sources of report, UK.
- No sources of report, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following statement was not followed: "We will also test the robustness of the results by repeating the analysis using different measures of effect size (RR, odds ratio (OR), etc). On reflection, the additional benefit derived does not warrant the additional complexity.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Hashimoto Disease [*therapy]; Randomized Controlled Trials as Topic; Selenomethionine [*administration & dosage]; Sodium Selenite [*administration & dosage]; Thyroxine [administration & dosage]

MeSH check words

Adult; Humans