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[Intervention Review]

Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism

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ABSTRACT

Background

Post-surgical hypoparathyroidism is a common complication after thyroid surgery. The incidence is likely to increase given the rising trend in the annual number of thyroid operations being performed. Measures to prevent post-thyroidectomy hypoparathyroidism including different surgical techniques and prophylactic calcium and vitamin D supplements have been extensively studied. The management of post-thyroidectomy hypoparathyroidism however has not been extensively evaluated. Routine use of calcium and vitamin D supplements in the postoperative period may reduce the risk of symptoms, temporary hypocalcaemia and hospital stay. However, this may lead to overtreatment and has no effect on long-term hypoparathyroidism. Current recommendations on the management of post-thyroidectomy hypoparathyroidism is based on low-quality evidence. Existing guidelines do not often distinguish between surgical and non-surgical hypoparathyroidism, and transient and long-term disease.

The aim of this systematic review was to summarise evidence on the use of calcium, vitamin D and recombinant parathyroid hormone in the management of post-thyroidectomy hypoparathyroidism. In addition, we aimed to highlight deficiencies in the current literature and stimulate further work in this field.

Objectives

The objective of this systematic review was to assess the effects of calcium, vitamin D and recombinant parathyroid hormone in managing post-thyroidectomy hypoparathyroidism.

Search methods

We searched CENTRAL, MEDLINE, PubMed, Embase as well as ICTRP Search Portal and ClinicalTrials.gov. The date of the last search for all databases was 17 December 2018 (except Embase, which was last searched on 21 December 2017). No language restrictions were applied.

Selection criteria

We planned to include randomised control trials (RCTs) or controlled clinical trials (CCTs) examining the effects of calcium, vitamin D or recombinant parathyroid hormone in people with temporary and long-term post-thyroidectomy hypoparathyroidism.

Data collection and analysis

Two review authors independently screened titles, abstracts and full texts for relevance.

Main results

Database searches yielded a total of 1751 records. We retrieved potentially relevant full texts and excluded articles on the following basis: not a RCT or CCT; intervention, comparator or both did not match prespecified criteria; non-surgical causes of hypoparathyroidism, and studies on prevention. None of the articles was eligible for inclusion in the systematic review.

Authors' conclusions

This systematic review highlights a gap in the current literature and the lack of high-quality evidence in the management of post-thyroidectomy temporary and long-term hypoparathyroidism. Further research focusing on clinically relevant outcomes is needed to examine the effects of current treatments in the management of temporary and long-term post-thyroidectomy hypocalcaemia.

PLAIN LANGUAGE SUMMARY

Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism

Review question

What are the effects of calcium, vitamin D and parathyroid hormone in the management of low parathyroid hormone following thyroid surgery?

Background

The parathyroid glands are four small glands attached to the thyroid gland. They produce parathyroid hormone which regulates blood calcium levels. These glands may be accidentally damaged during surgery, for example after removal of the thyroid gland. The consequence of this is low blood calcium levels. The damage to the parathyroid glands may be temporary or long term. The use of calcium and vitamin D supplements to normalise the blood calcium level is the mainstay of treatment in these people but the precise nature, dose and duration of these treatments vary across centres. Recent studies suggest the use of laboratory-engineered (recombinant) parathyroid hormone as a treatment option. Current guidelines on the management of post-thyroidectomy hypoparathyroidism are based on low-quality evidence. We aimed to review high-quality research evaluating the use of calcium, vitamin D and parathyroid hormone in this condition. In addition, we aimed to highlight gaps in the current literature and to stimulate further clinical studies in this field.

Study characteristics

We found no relevant randomised controlled trials (clinical trials where people are randomly allocated to one of two or more treatment groups) or controlled clinical trials that evaluated the use of calcium, vitamin D supplements and parathyroid hormone in this condition.

This evidence is up to date as of 17 December 2018.

Key results

Lack of high-quality evidence on the use of calcium, vitamin D and parathyroid hormone in the management of low parathyroid hormone after thyroid surgery.

Certainty of the evidence

We could not critically appraise the certainty of the evidence because we did not identify studies matching our inclusion criteria.

BACKGROUND

Description of the condition

Hypoparathyroidism is a common complication following bilateral thyroid surgery. It can also occur after parathyroid surgery and occasionally following extensive head and neck cancer resections (Shoback 2008). Estimated rates of temporary and long-term post-thyroidectomy hypoparathyroidism following bilateral thyroid surgery range from 19% to 38% and from 0% to 3%, respectively (Edafe 2014). Post-thyroidectomy hypoparathyroidism may be due to inadvertent excision, damage or devascularization of the parathyroid gland(s) (Sitges-Serra 2010).

Acute hypocalcaemia as a consequence of post-thyroidectomy hypoparathyroidism may present with paraesthesia (including numbness and tingling in fingers and toes), cramps, nausea and occasionally convulsions due to severe neuromuscular irritability (Hannan 2013). Long-term hypocalcaemia is associated with cataracts, abnormal teeth, renal impairment, ectopic calcifications and psychiatric illness (Hannan 2013).

Prevalence of chronic or long-term post-surgical hypoparathyroidism is estimated to be around 22 per 100,000 people in the Western world (Powers 2013; Underbjerg 2013). The condition is likely to increase in frequency with the rising number of thyroid surgical procedures being performed in the UK and globally in line with increasing detection and diagnosis of thyroid cancer (Mao 2016).

Preventive measures for post-thyroidectomy hypoparathyroidism include medications as well as haemostatic and surgical techniques (Antakia 2015). Prophylactic calcium and vitamin D supplementation reduces rates of temporary hypocalcaemia, symptoms and hospital stay (Antakia 2015). However, routine use may lead to overtreatment, masking of the diagnosis and inappropriate treatment of the condition in the long term.

Symptomatic or severe hypocalcaemia is amenable to rapid treatment with large doses of oral calcium and active vitamin D. Occasionally, intravenous calcium infusions are required. The standard treatment for long-term hypocalcaemia and hypoparathyroidism includes calcium and active vitamin D supplements (Perros 2014).

Surgical and non-surgical hypoparathyroidism are different disease entities. A number of genetic variants and autoimmune diseases are known to cause hypoparathyroidism (Lima 2011). Hypoparathyroidism due to deletion of a small piece of chromosome 22 (deletion syndrome) usually resolves after the neonatal period but may recur in later life due to physiological stress (e.g. infection, pregnancy) (Underbjerg 2015). Non-surgical causes of hypoparathyroidism are associated with increased risk of ischaemic heart disease and cataracts (Underbjerg 2015). In post-surgical hypoparathyroidism there is a lack of adequate, viable parathyroid tissue, but the tissue is inherently normal. Thus, the response to treatment may differ between these two patient groups. Most people with post-surgical hypoparathyroidism will recover, so there is potential to wean patients off vitamin D and calcium supplements (Sitges-Serra 2010). In addition, people with post-surgical hypoparathyroidism are not at an increased risk of osteoporosis and fractures (Underbjerg 2014).

Description of the intervention

Calcium and active vitamin D supplements are currently the mainstays of treatment for both temporary and long-term hypoparathyroidism. However, the optimal treatment strategies, objectives of treatment and monitoring in these patients are unclear.

In the UK, thyroid cancer management guidance includes recommendations for managing temporary and long-term hypocalcaemia following thyroid surgery (Perros 2014). The guidelines recommend early treatment for asymptomatic hypocalcaemia with calcium or non-active vitamin D supplements to achieve adjusted serum calcium above 2.10 mmol/L. In people with persistent (> 72 hours) hypocalcaemia despite calcium supplements, the active form of vitamin D is also recommended in addition to calcium. Clinicians are advised to use intravenous calcium in severe hypocalcaemia (adjusted calcium < 1.90 mmol/L) or for symptoms with calcium below the normal range. For long-term hypocalcaemia, the guidelines recommend alfacalcidol or calcitriol with close monitoring of serum calcium with a view to weaning patients off medication. These recommendations are not supported by good quality evidence.

A recent European Society of Endocrinology guideline advised the use of active vitamin and calcium supplements as the primary treatment for long-term hypoparathyroidism (Bollerslev 2015) aiming for a low normal serum calcium to reduce risks of hypercalciuria and renal calculi. Furthermore, the guideline recommended against the routine use of recombinant parathyroid hormone (PTH) in long-term hypoparathyroidism due to the potential risk of osteosarcoma, as reported in rat studies. These recommendations are also based on low-level evidence and do not address the management of temporary post-surgical hypoparathyroidism.

The American Thyroid Association briefly discussed the management of post-thyroidectomy hypocalcaemia in their statement on outpatient thyroidectomy (Terri 2013). They advised active vitamin D and calcium supplements in patients with low PTH after surgery. They also recommended oral calcium and active vitamin D in symptomatic hypocalcaemia, reserving intravenous calcium gluconate for severe symptomatic hypocalcaemia. The statement did not describe the evidence base for this recommendation.

A recent clinical review by the American College of Clinical Endocrinology and the American College of Endocrinology discussed the management of postoperative hypoparathyroidism (Stacks 2015). They recommended 1 g to 3 g of calcium daily in people with low postoperative calcium; and 3 g of oral calcium daily and 0.5 mg of calcitriol twice daily in patients with low calcium and low PTH. Intravenous calcium (1 g to 2 g of calcium gluconate) is reserved for severe hypocalcaemia. The review highlighted the lack of guidelines for managing long-term hypoparathyroidism.

Adverse effects of the intervention

Treatment with calcium and vitamin D supplements may result in hypercalcaemia and hypercalciuria. Hypercalciuria predisposes people to the development of renal calcifications (Adorni 2005; Bollerslev 2015). The use of recombinant PTH 1-84 has been associated with osteosarcoma in rat studies (Bollerslev 2015).

However, the adverse effects associated with its long-term use in humans are not known.

How the intervention might work

Parathyroid hormone increases calcium levels by stimulating bone resorption, increasing renal reabsorption of calcium and synthesis of 1,25-dihydroxy vitamin D. In addition, PTH stimulates renal excretion of phosphate. Thus, low serum PTH leads to hypocalcaemia and hyperphosphataemia.

Routine treatment of hypoparathyroidism with oral calcium and vitamin D increases serum calcium. However, in the long term it is associated with ectopic calcification and hypercalciuria, as the lack of PTH increases renal leak of calcium.

Two different approaches (splinting and stimulating) have been proposed for managing postoperative hypoparathyroidism ([Stacks 2015](#)). Splinting involves treatment with calcium and vitamin D supplements to normalise serum calcium, thus allowing time for the parathyroid gland to recover ([Sitges-Serra 2010](#)). The stimulating approach aims to achieve a serum calcium at the lower end of the normal range, with a view to increasing the demand for PTH and allowing stimulation of parathyroid cell growth ([Walker Harris 2009](#)).

Studies have evaluated the role of recombinant PTH in postoperative hypoparathyroidism ([Ramakrishnan 2016](#)). This has the potential to reduce hypercalciuria as well as normalising serum calcium.

Why it is important to do this review

Current recommendations for managing post-surgical hypoparathyroidism are not based on good quality evidence. In addition, most primary and secondary research does not distinguish between surgical and non-surgical hypoparathyroidism ([Bollerslev 2015](#); [Perros 2014](#); [Stacks 2015](#)).

There is no robust evidence on the relative effectiveness of different approaches to treatment (for example, the splinting and stimulating approaches).

A systematic review of 11 studies (nine randomised controlled trials (RCTs) and two cohort studies) has evaluated the impact of recombinant PTH for managing hypoparathyroidism (both medical and surgical causes) ([Ramakrishnan 2016](#)). The review demonstrated that recombinant PTH was effective for correcting serum calcium levels in hypoparathyroidism. The adjuvant use of PTH 1-84 with calcium and vitamin D significantly reduced the daily requirements of calcium and active vitamin D supplements compared to placebo. Urinary calcium excretion was reduced with PTH 1-34 compared to conventional calcium and vitamin D supplements, but unchanged with PTH 1-84 (likely due to the once-daily regimen used in the studies). In addition, patients tolerated the use of recombinant PTH. The included studies were heterogeneous and hence a meta-analysis was not performed. Variability in studies included different recombinant PTH analogues, different treatment regimens, and the inclusion of people with surgical and non-surgical causes of hypoparathyroidism.

It is important to do this review not only to summarise existing evidence and compare the relative efficacy of reported strategies,

but also to highlight knowledge gaps and stimulate further primary work.

OBJECTIVES

To assess the effects of calcium, vitamin D and recombinant parathyroid hormone in managing post-thyroidectomy hypoparathyroidism.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs).

Types of participants

People who developed hypoparathyroidism following thyroidectomy.

Diagnostic criteria for hypoparathyroidism

Temporary hypocalcaemia and hypoparathyroidism: postoperative day one corrected calcium less than 2.10 mmol/L or ionised calcium less than 1.20 mmol/L ([Chadwick 2017](#)).

Long-term hypoparathyroidism: need for calcium, vitamin D supplements or both to maintain normocalcaemia at six months or more after surgery ([Chadwick 2017](#)).

We also considered studies using other definitions. Changes in diagnostic criteria may introduce significant variability in the clinical characteristics of the participants included as well as in the outcomes, and the plan was for these to be investigated through subgroup analyses. Trials involving participants with comorbid disorders were considered to be eligible for inclusion as long as the primary focus of the intervention was treatment for post-surgical hypoparathyroidism.

Types of interventions

We planned to investigate the following comparisons of intervention versus control/comparator.

- Oral calcium or vitamin D supplements versus placebo.
- Oral calcium plus vitamin D versus oral calcium plus placebo.
- Recombinant parathyroid hormone (1-84 or 1-34) plus oral calcium plus vitamin D versus placebo plus oral calcium plus vitamin D.

Concomitant interventions had to be the same in both the intervention and comparator groups to establish fair comparisons.

Minimum duration of intervention and follow-up

For temporary disease, participants should have been treated for a minimum period of one week prior to assessment of outcome. For long-term disease, the minimal duration of treatment and follow-up should have been six months.

Summary of specific exclusion criteria

- Studies on non-surgical hypoparathyroidism.
- Animal studies.

Types of outcome measures

Studies were not excluded if they failed to report one or several of the primary or secondary outcome measures listed below. If studies reported none of the primary or secondary outcomes listed below, they were not included but we planned to provide some basic information in an additional table.

Primary outcomes

- Health-related quality of life.
- Long-term hypoparathyroidism.
- Adverse events.

Secondary outcomes

- All-cause mortality.
- Occurrence of epilepsy.
- Hypercalcaemia.
- Socioeconomic effects.

Method and timing of outcome measurement

- Health-related quality of life: evaluated by a validated instrument such as Short-Form health survey and measured at any time during follow-up.
- Long-term hypoparathyroidism: defined as need for calcium, vitamin D supplement or both to maintain normocalcaemia at six months or more after surgery.
- Adverse events: such as hypercalcaemia, renal impairment (defined as a reduction of estimated glomerular filtration rate from baseline), renal calculi (defined as radiological evidence of stone within the kidney or renal tract) documented at any time after participants were allocated to intervention/comparator groups.
- All-cause mortality: death from any cause and measured at any time after treatment allocation.
- Hypercalcaemia: defined as adjusted calcium > 2.60 mmol/L in at least two samples.
- Occurrence of epilepsy: defined as seizures (of any type) recorded and occurring at any point during follow-up.
- Socioeconomic effects: such as direct costs defined as admission/readmission rates, average length of stay, visits to general practitioner, accident and emergency visits, medication consumption; indirect costs: defined as resources lost due to illness by the participant or their family member.

Specification of key prognostic variables

- PTH level at initiation of treatment.
- Vitamin D level at initiation of treatment.

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the specified date without restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (last searched on 17 December 2018).

- MEDLINE <Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to December 14> (last searched on 17 December 2018).
- PubMed (subsets not indexed for MEDLINE; last searched on 17 December 2018).
- Embase <1974 to 2016 Week 47> (last searched on 21 November 2018).
- ClinicalTrials.gov (www.clinicaltrials.gov) (last searched on 17 December 2018).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/) (last searched on 17 December 2018).

For detailed search strategies, see [Appendix 1](#).

Searching other resources

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

We defined grey literature as records detected in ClinicalTrials.gov or WHO ICTRP.

Data collection and analysis

Selection of studies

Two review authors (OE, CEM) independently screened the abstract, title, or both, of every record retrieved in the literature searches, to determine which trials required further assessment. The full texts of all potentially relevant records were retrieved and reviewed. Disagreements on eligibility were resolved through consensus or by recourse to a third review author (SPB). An adapted PRISMA flow diagram trial selection ([Liberati 2009](#)) shows the process of trial selection. Articles excluded after full-text assessment are listed in the [Characteristics of excluded studies](#) table along with reasons for exclusion.

Data extraction and management

We planned to extract independently key participant and intervention characteristics. We aimed to describe interventions according to the 'template for intervention description and replication' (TIDieR) checklist ([Hoffmann 2014](#); [Hoffmann 2017](#)).

Data on efficacy outcomes and adverse events would have been provided using standardised data extraction sheets from the CMED Group. We planned to resolve any disagreements by discussion or, if required, by consultation with a third review author (SPB).

We planned to provide information including trial identifier about potentially relevant ongoing trials, including the trial identifiers, in the Characteristics of ongoing studies table and in a joint appendix 'Matrix of trial endpoint (publications and trial documents)'. We also planned to find the protocol for each included study and aimed to report primary, secondary and other outcomes in comparison with data in publications in a joint appendix.

We planned to email all authors of included studies to enquire whether they would be willing to answer questions regarding their studies and to present the results of this survey in an appendix. We

aimed to seek relevant missing information on the study from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we would have maximised the information yield by collating all available data, and planned to use the most complete data set aggregated across all known publications. We would have listed duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study. Furthermore, we planned to list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included studies had been available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we planned to make full use of this information and extract the data. If there was also a full publication of the trial, we would have collated and critically appraised all available data. If an included study was marked as a completed study in a clinical trial register but no additional information (study results, publication or both) was available, we planned to add this study to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Two review authors (OE, CEM) would have independently assessed the risk of bias for each included study. We planned to resolve any disagreements by consensus or by consulting a third review author (SPB). If adequate information was unavailable from the publications, trial protocols or other sources, we planned to contact the study authors for more detail to request missing data on 'Risk of bias' items.

We planned to use the Cochrane 'Risk of bias' assessment tool ([Higgins 2017](#)), assigning assessments of low, high or unclear risk of bias (for details see [Appendix 2](#); [Appendix 3](#)). We wanted to evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein ([Higgins 2017](#)).

Summary assessment of risk of bias

We planned to present a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We wanted to distinguish between self-reported and investigator-assessed and adjudicated outcome measures.

We considered the following to be self-reported outcomes.

- Health-related quality of life.
- Adverse events.

We considered the following outcomes to be investigator-assessed.

- Long-term hypoparathyroidism.
- Hypercalcaemia.
- All-cause mortality.

- Adverse events: renal calculi.
- Adverse events: renal impairment.
- Epilepsy.
- Socioeconomic effects.

Measures of treatment effect

When at least two included studies were available for comparison of a given outcome, we planned to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg) we planned to estimate the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we planned to calculate the standardised mean difference (SMD). We planned to express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We planned to take into account the level at which randomisation occurred, such as cross-over trials and cluster-randomised trials; and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we planned to either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants did not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons ([Higgins 2011](#)).

We planned to re-analyse cluster-RCTs that did not appropriately adjust for potential clustering of participants within clusters in their analyses. The variance of the intervention effects would have been inflated by a design effect. Calculation of a design effect involves estimation of an intracluster correlation coefficient (ICC). We planned to obtain estimates of ICCs by contacting study authors or imputing the ICC values by using either estimates from other included trials that reported ICCs or external estimates from empirical research (e.g. [Bell 2013](#)). We would have examined the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we wanted to obtain missing data from the authors of the included studies. We planned to evaluate carefully important numerical data such as screened, randomly assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We wanted to investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and planned to critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In trials where the standard deviation (SD) of the outcome was not available at follow-up or could be created, we planned to standardise by the mean of the pooled baseline SD from those studies that reported this information.

Where included studies did not report means and SDs for outcomes and we did not receive the necessary information from study authors, we planned to impute these values by estimating the mean

and variance from the median, range and the size of the sample (Hozo 2005).

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we wanted to report for every outcome which trials had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not plan to report trial results as the pooled effect estimate in a meta-analysis.

We wanted to identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard χ^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we wanted to also consider the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we found heterogeneity, we would have attempted to determine the possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

If we had included 10 or more studies that investigated a particular outcome, we planned to use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small trials) and publication bias (Sterne 2017). Therefore we planned to interpret the results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display) a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence showed homogeneous effects across studies of different methodological quality, we planned primarily to summarise low risk of bias data using a random-effects model (Wood 2008). We would have interpreted random-effects meta-analyses with due consideration to the whole distribution of effects and wanted to present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we planned to use the Peto's odds ratio method, provided that there was no substantial imbalance between intervention and comparator group sizes and intervention effects were not exceptionally large. In addition, we planned to perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and planned to carry out the following subgroup analyses including investigation of interactions (Altman 2003).

- Type of thyroid surgery, further stratified by benign and malignant thyroid disease.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published studies.
- Effect of risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section.
- Very large studies or studies with long follow-up to establish the extent to which they dominate the results.
- Using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

We also wanted to test the robustness of results by repeating the analyses using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We planned to present the overall certainty of evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results. Two review authors (OE, CEM) would have independently rated the certainty of evidence for each outcome. We planned to resolve any differences in assessment by discussion or consulting the third review author (SPB).

We wanted to include an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we planned to use the GRADEpro Guideline Development Tool (GDT) software and would have presented evidence profile tables as an appendix (GRADEproGDT 2015). We planned to present results for the outcomes as described in the [Types of outcome measures](#) section. If meta-analysis was not possible, we would have presented the results in a narrative format in a 'Summary of findings' table. We would have justified all decisions to downgrade the quality of trials using footnotes, and we planned to make comments to aid the reader's understanding of this Cochrane Review where necessary.

'Summary of findings' table

We planned to present a summary of the evidence in a 'Summary of findings' table. This would have provided key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome and a rating of overall confidence in effect estimates for each outcome. We planned to create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017) using Review Manager (RevMan 5.3) table editor (RevMan 2014).

Interventions presented in the 'Summary of findings' table were oral calcium or vitamin D supplements or recombinant parathyroid hormone (1-84 or 1-34) plus oral calcium plus vitamin D, and

comparators were placebo, oral calcium plus placebo and placebo plus oral calcium plus vitamin D.

We planned to report the following outcomes, listed according to priority.

- Health-related quality of life.
- Long-term hypoparathyroidism.
- Adverse events.
- All-cause mortality.
- Hypercalcaemia.
- Occurrence of epilepsy.

- Socioeconomic effects.

RESULTS

Description of studies

No study was eligible for inclusion in the systematic review.

Results of the search

We screened a total of 1751 records ([Figure 1](#)). Twenty-nine full-text articles (involving 25 studies) were retrieved following title and abstract screen. None met our inclusion criteria as specified in the protocol ([Edafe 2017](#)). We did not identify any ongoing trials.

Figure 1. Trial flow diagram.

Figure 1. (Continued)

Included studies

No study could be included.

Excluded studies

All 29 full-text articles retrieved were excluded from review. We excluded studies mainly because of study design (not RCT/CCT) and inclusion of patients with non-surgical causes of hypoparathyroidism.

Risk of bias in included studies

Appraisal of risk of bias was not possible because no study could be included.

Allocation

Appraisal of selection bias was not possible because no study could be included.

Blinding

Appraisal of blinding was not possible because no study could be included.

Incomplete outcome data

Appraisal of attrition bias was not possible because no study could be included.

Selective reporting

Appraisal of reporting bias was not possible because no study could be included.

Other potential sources of bias

Appraisal of potential sources of bias was not possible because no study could be included.

Effects of interventions

Evaluation of the effects of interventions was not possible because no study could be included.

DISCUSSION

This Cochrane Review aimed to evaluate the effects of calcium, vitamin D and parathyroid hormone in the management of post-thyroidectomy hypocalcaemia. The lack of studies fulfilling the pre-specified inclusion criteria highlighted gaps in the evidence-based management of post-thyroidectomy hypocalcaemia. A number of randomised controlled trials (RCTs) have however examined the use of vitamin D and PTH in the management of non-surgical and surgical hypoparathyroidism.

[Choe 2011](#) compared the combination of oral calcium with different vitamin D supplements, i.e. cholecalciferol or calcitriol in the management of post-thyroidectomy hypocalcaemia. this study included 65 participants in their analysis and monitored serum calcium six hours following administration of supplements. Serum

calcium was higher on postoperative days 10 to 20 in participants who received calcitriol. The study did not evaluate long-term hypocalcaemia or adverse effects.

In a 10-week cross-over RCT, Winer and colleagues compared recombinant PTH 1-34 versus calcitriol and calcium in 10 participants with hypoparathyroidism (Winer 1996). Calcitriol was administered twice daily (at 9 AM and 9 PM) and PTH once daily (at 9 AM). The study included participants with either non-surgical and post-surgical hypoparathyroidism. They found serum calcium was maintained with both calcitriol and PTH after two and 10 weeks of treatment. PTH administration caused a significant decrease in urine calcium and 24-hour urine calcium excretion. There were no substantial differences in the rates of hypercalcaemia between the two groups. Other adverse events were reported in two patients receiving PTH (one had bone pain, and the other had mild nausea and headache). A subsequent RCT compared PTH 1-34 versus calcitriol in the management of hypoparathyroidism (Winer 2003). Participants received a twice-daily regimen of PTH or calcitriol. Over the three-year follow-up, there was no substantial difference in serum calcium between PTH and calcitriol. The PTH arm had normal 24-hour urinary calcium excretion during the study period while those receiving calcitriol had elevated levels. However, there was no clear difference in the creatine clearance between the two groups. The authors reported no substantial differences in adverse events such as neuromuscular instability, bone pain, joint pain or fatigue. Mild bone pain occurred in seven participants in the PTH group and three participants in the calcitriol group. No participants developed osteosarcoma. Another small RCT (comparing PTH 1-34 versus calcitriol) of 12 participants with chronic non-surgical hypoparathyroidism found no substantial differences in serum calcium, urine calcium and creatinine clearance (Winer 2010).

Sikjaer and colleagues investigated the effects of adding PTH 1-84 to calcium and vitamin D in participants with surgical and non-surgical causes of hypoparathyroidism for the management of long-term hypoparathyroidism (Sikjaer 2011). They randomised 62 participants to daily treatment with PTH 1-84 or placebo as an addition to conventional treatment (calcium and active vitamin D) over six months. Calcium and vitamin D were down-titrated in the event of hypercalcaemia or elevated urinary calcium excretion. Ionised calcium levels were higher in the PTH 1-84 group but normalised at the end of the study following dose titration. However, 96% of hypercalcaemic episodes happened in the PTH group compared to 4% in the placebo group. In addition, nausea was more common in the PTH 1-84 group. PTH 1-84 reduced the required daily dose of calcium and vitamin D supplements. The 24-hour urinary calcium excretion was also higher in the PTH group, but there was no substantial difference after 12 weeks between the groups. There were no substantial differences in health-related quality of life between PTH 1-84 and placebo (Sikjaer 2014, report from Sikjaer 2011).

In another RCT, Mannstadt and colleagues compared PTH 1-84 with placebo as add on to conventional treatment for long-term of surgical and non-surgical hypoparathyroidism (Mannstadt 2013). The primary endpoint of this study was as follows: $\geq 50\%$ reduction in baseline oral calcium dose, $\geq 50\%$ reduction in active vitamin D dose and maintenance of stable corrected calcium $\geq$ baseline concentration and $\leq$ upper limit of normal. A higher proportion of participants in the PTH group achieved all three components of the primary endpoint compared to placebo (53% versus 2%). In

addition, 43% of participants in the PTH group were able to stop taking active vitamin D compared to 5% in the placebo group. At the end of the study, there was no substantial difference in mean 24-hour urinary calcium excretion between the two groups. The incidence of adverse events were similar between the two groups; hypocalcaemia was the commonest adverse event.

In another RCT, Winer and colleagues compared an once-daily versus twice-daily PTH 1-34 regimen for the management of hypoparathyroidism (Winer 1998). They included participants with surgical and non-surgical hypoparathyroidism. At 14 weeks after treatment, there were no substantial differences in serum calcium between once- and twice-daily regimens (i.e. calcium levels were similar in both groups). Participants with calcium sensing receptor abnormalities had a lower serum calcium with the 'once a day' regimen compared to other aetiologies (idiopathic or surgical). Reported adverse events with PTH included bone pain, nausea, nocturia and fatigue.

Bilezikian and colleagues randomised 42 participants with hypoparathyroidism to 25 μg versus 50 μg daily of subcutaneous recombinant PTH 1-84 to evaluate the effects of a lower-dose regimen (Bilezikian 2017). Primary end points were the proportion of participants at eight weeks who met a reduction of oral calcium of ≤ 500 mg/day, a reduction in calcitriol supplement to ≤ 0.25 μg /day and maintaining a corrected calcium between 1.875 mmol/L and the upper limit of normal. The secondary endpoints used in this study were the same as the primary endpoints by Mannstadt and colleagues described above (Mannstadt 2013). There were no substantial differences between the 25 μg and 50 μg group in achieving the primary (21% versus 26%) and secondary (11% versus 26%) outcomes. No serious adverse events were reported.

In the six-month cross-over RCT, Winer and colleagues compared pump versus twice-daily injections for the administration of PTH 1-34 in the treatment of eight adults with long-term post-thyroidectomy hypoparathyroidism (Winer 2012). There were no substantial differences in serum calcium between pump and injection groups. Urinary calcium excretion was lower in the pump group compared to the injection group, however, there were no substantial differences in creatine clearance between the two groups. Participants on the pump regimen required a lower daily dose of PTH 1-34 compared to the twice-daily injection regimen.

In another RCT comparing PTH 1-34 pump versus injections in children with congenital hypoparathyroidism, Winer and colleagues found that pump delivery produced near normalisation of mean serum calcium compared to injection. In addition, pump delivery normalised mean 24-hour urinary excretion; however, there were no substantial differences compared to injections (Winer 2014).

Our review protocol specified strict inclusion and exclusion criteria (including the requirement to only include participants with hypoparathyroidism after thyroid surgery) as our aim was to examine the effects of interventions in a homogeneous group of patients without being influenced by disorders affecting calcium homeostasis. Patients with primary hyperparathyroidism have a different metabolic profile with associated osteoporosis and renal impairment (Khan 2017). Also, patients with non-surgical hypoparathyroidism may have other associated endocrine abnormalities and genetic defects (Bilezikian 2017) that may affect calcium homeostasis.

Summary of main results

Summary was not possible because no study could be included.

Overall completeness and applicability of evidence

Appraisal of completeness and availability of evidence was not possible because no study could be included.

Quality of the evidence

Appraisal of the quality of evidence was not possible because no study could be included.

Potential biases in the review process

The search for eligible published manuscripts was comprehensive as outlined previously. It is possible that studies that have not been published have good quality data that was not available for inclusion. Appraisal of potential biases in data collection, analyses and reporting of data was not possible because no study could be included.

Agreements and disagreements with other studies or reviews

Evaluation of agreement and disagreements with other studies or reviews was not possible because no study could be included.

AUTHORS' CONCLUSIONS

Implications for practice

Calcium and vitamin D supplements form the mainstay of treatment of post-thyroidectomy hypocalcaemia. Current guidelines on the nature and dose of these medications; monitoring of their effects; and nature and duration of long-term follow-up are based on low-quality evidence. Given this, practice will continue to be based on clinicians' experience and judgement and not on empiric data from appropriate clinical trials.

Implications for research

Findings highlighted deficiencies in the current literature in the management of post-thyroidectomy hypocalcaemia. Randomised controlled trials (RCTs) evaluating the use of calcium, vitamin D and PTH in post-thyroidectomy hypocalcaemia are needed. In addition, research comparing different treatment strategies (stimulating versus splinting) and the evaluation of adverse events and health-related quality of life in the long term is needed.

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Edafe 2017

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Añón 2015	This was a case report
Bilezikian 2017	Different regimens of parathyroid hormone were compared
Brenton 1977	This was a case report
Cayo 2012	This was a study on preventing temporary hypoparathyroidism using postoperative serum PTH measure to direct supplementation
Choe 2011	Different types of vitamin D were compared
Coiro 2008	The group of interest (i.e. participants who developed postoperative hypocalcaemia) were not randomised
Dymling 1968	Not a randomised/clinical controlled trial
Fåhræus 1973	This was a case report
Gabryś 1965	Not a randomised/clinical controlled trial
Gossmann 1976	This was a non interventional study
Gutiérrez-Cerecedo 2016	Not a randomised/clinical controlled trial
Mannstadt 2013	This study included participants with non-surgical causes of hypoparathyroidism
Mazzuoli 1968	Not a randomised/clinical controlled trial
Pak 1970	Not a randomised/clinical controlled trial
Palermo 2016	This was a study on prevention of post-thyroidectomy hypocalcaemia
Rubin 2010	Not a randomised/clinical controlled trial
Santonati 2015	Not a randomised/clinical controlled trial
Shah 2015	Not a randomised/clinical controlled trial

Study	Reason for exclusion
Sikjaer 2011	This article included participants with non-surgical causes of hypoparathyroidism (obtained from reference list search)
Wang 2009	Not a randomised/clinical controlled trial. In addition, the article includes non-surgical causes of hypoparathyroidism
Winer 1996	This study included participants with non-surgical causes of hypoparathyroidism
Winer 1998	This study (from reference list search) included participants with non-surgical causes of hypoparathyroidism. In addition, the study compared two different PTH regimes
Winer 2003	This study included participants with non-surgical causes of hypoparathyroidism
Winer 2012	Different PTH regimens were compared
Winer 2014	This study only included participants with congenital hypoparathyroidism

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Hypocalcemia EXPLODE ALL TREES
2. hypocal*:TI,AB,KY
3. MESH DESCRIPTOR Hypoparathyroidism EXPLODE ALL TREES
4. MESH DESCRIPTOR Thyroidectomy EXPLODE ALL TREES
5. thyroidectom*:TI,AB,KY
6. surg*:TI,AB,KY
7. #1 OR #2 OR #3
8. #4 OR #5 OR #6
9. #7 AND #8

PubMed (subsets not indexed for MEDLINE)

1. hypocal*[tw] OR hypoparathyroidism[tw]
2. thyroidectom*[tw] OR surg*[tw]
3. random*[tw] OR groups[tw] OR trial[tw]
4. #1 AND #2 AND #3
5. #4 NOT medline[sb] NOT pmcbook

MEDLINE (Ovid)

(Continued)

1. exp Hypocalcemia/ or hypocalcaemia.mp.
2. "hypocal*".tw.
3. hypoparathyroidism.mp. or exp Hypoparathyroidism/
4. or/1-3
5. thyroidectomy.mp. or exp Thyroidectomy/
6. "thyroidectom*".tw.
7. "surg*".tw.
8. or/5-7
9. 4 and 8

[10-20: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. or/10-17
19. exp animals/ not humans.sh.
20. 18 not 19
21. 9 and 20

Embase (Ovid)

1. hypocalcaemia.mp. or exp hypocalcemia/
2. "hypocalc*".tw.
3. hypoparathyroidism.mp. or exp hypoparathyroidism/
4. or/1-3
5. exp thyroidectomy/ or thyroidectomy.mp.
6. "thyroidectom*".tw.
7. "surg*".tw.
8. or/5-7
9. 4 and 8

[10. Wong 2006 "sound treatment studies" filter – best optimization of sens. and spec. version]

10. random*.tw. or placebo*.mp. or double-blind*.tw.
-

(Continued)

11. 9 and 10

ClinicalTrials.gov (Advanced search)

Conditions: hypocalcaemia OR hypocalcemia OR hypoparathyroidism OR thyroidectomy

Intervention: vitamin OR vitamins OR "vitamin D" OR cholecalciferol OR calcitriol OR calcium OR supplement OR supplements OR teriparatide OR PTH OR "parathyroid hormone"

ICTRP Search Protal (Standard search)

hypoparathyroidism AND thyroidectomy OR hypoparathyroidism AND surg* OR hypocal* AND thyroidectomy OR hypocal* AND surg*

Appendix 2. Assessment of risk of bias

Risk of bias domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included trial, we planned to describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We considered the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We planned to describe for each included trial the method used to conceal allocation to interventions prior to assignment and we assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also planned to evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias ([Corbett 2014](#)). Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we planned to distinguish between trials that we rated as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judged as being at low risk of bias on the basis of baseline similarity alone ([Corbett 2014](#)). We will reclassify judgements of unclear, low or high risk of selection bias as specified in Appendix 18.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)

We planned to evaluate the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We planned to note whether end-points were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judged that the outcome was unlikely to have been influenced by lack of blinding.

(Continued)

- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We planned to evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We planned to note whether end-points were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it was unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judged that the outcome measurement was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included trial and/or each outcome, we planned to describe the completeness of data, including attrition and exclusions from the analyses. We planned to state whether the trial reported attrition and exclusions, and report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also planned to note if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We would have considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We planned to assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis would have formed the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias

(Continued)

- Low risk of bias: the trial appears to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials reporting unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information^a

Reported randomisation and allocation concealment methods	Risk of bias judgment using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly randomised, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk

^aTaken from [Corbett 2014](#); judgments highlighted in grey indicate situations in which the addition of baseline assessments would change the judgment about risk of selection bias, compared with using methods reporting alone.

^bImbalance identified that appears likely to be due to chance.

^cDetails for the remaining important prognostic variables are not reported.

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

DECLARATIONS OF INTEREST

Ovie Edafe (OE): none known.

Claudia E Mech (CEM): none known.

Sabapathy P Balasubramanian (SPB): none known.

NOTES

Portions of the background and methods sections, the appendices, additional tables and Figure 1 of this review are based on a standard template established by the Cochrane Metabolic and Endocrine Disorders.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium, Dietary [*therapeutic use]; Dietary Supplements; Hypoparathyroidism [*prevention & control]; Parathyroid Hormone [*therapeutic use]; Thyroidectomy [*adverse effects]; Vitamin D [*therapeutic use]

MeSH check words

Humans