Vitamin D supplementation for obese adults undergoing bariatric surgery (Protocol)

Chakhtoura MT, Nakhoul NF, Akl EA, Safadi BY, Mantzoros CS, El-Hajj Fuleihan G

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[Intervention Protocol]

Vitamin D supplementation for obese adults undergoing bariatric surgery

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the effects of different doses of vitamin D supplementation (low dose ≤ 600 IU daily, moderate dose between 600 and 3500 IU daily, high dose ≥ 3500 IU daily, compared to each other or to placebo) in obese adults undergoing bariatric surgery.

BACKGROUND

Description of the condition

Obesity is a worldwide problem associated with a significant medical and economic burden (Imes 2014). Analysis of obesity trends in the United States shows that, in 2011 to 2012, 20% of adolescents had a body mass index (BMI) for age ≥ 95^{th} percentile of the Centers for Disease Control and Prevention (CDC) growth charts and 35% of adults had a BMI ≥ 30 kg/m² (Ogden 2014). Although in the last few years this prevalence has been relatively steady in the US population, it has been increasing in the developing countries (Ogden 2014). Obesity results in significant health problems and serious comorbidities, including obstructive sleep apnoea, hypertension, coronary artery disease, diabetes mellitus and the metabolic syndrome (Guh 2009).

Non-surgical weight loss interventions, such as lifestyle modifications and pharmacotherapy result in a modest weight loss as compared to surgical procedures (Colquitt 2014; McTigue 2003). Bariatric surgery is the most effective long-term measure for weight loss, regardless of the type of the surgical procedure (Chang 2014; Colquitt 2014). It is considered appropriate for persons with a BMI ≥ 40 kg/m² in the absence of comorbidities, or if BMI ≥ 35 kg/m² in the presence of a serious cardiovascular, metabolic, respiratory and gastro-intestinal comorbidity or impaired quality of life, that are expected to improve with weight loss (Mechanick

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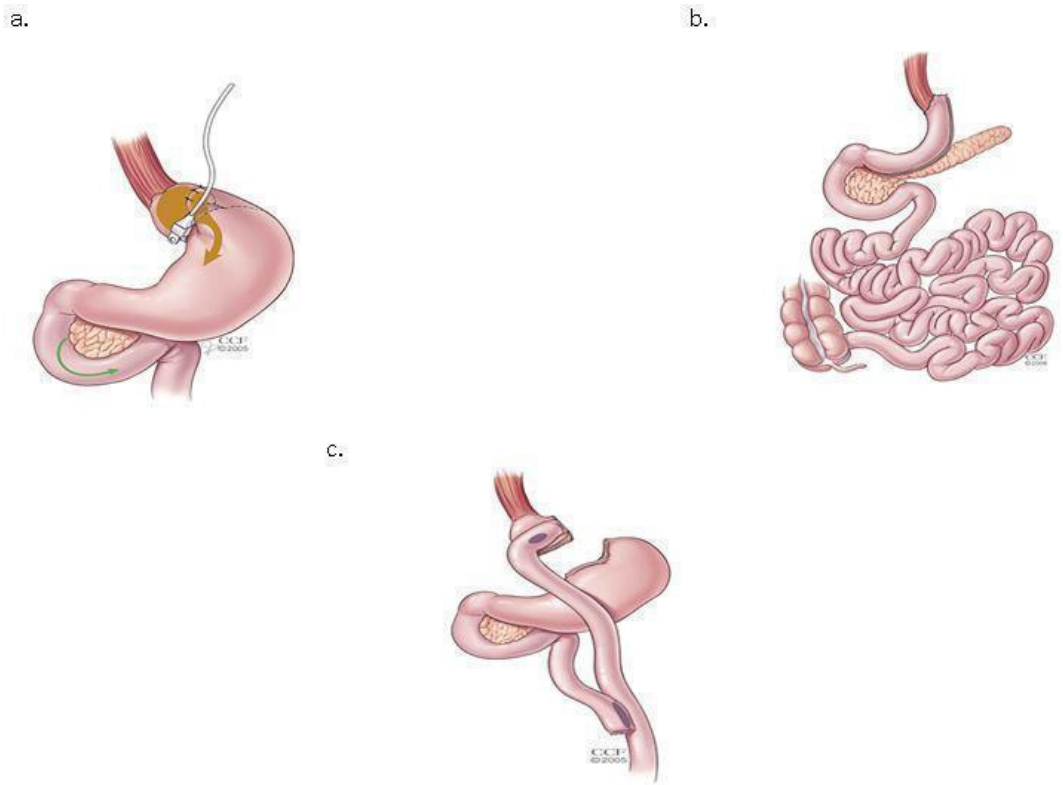
2013). In addition to weight loss, bariatric surgery demonstrated significant short- and long-term improvement in health-related quality of life and various metabolic and cardiovascular outcomes, including type 2 diabetes mellitus, hypertension and dyslipidaemia (Chang 2014; Colquitt 2014; Kwok 2014; Schauer 2014). Furthermore, a meta-analysis of observational studies showed a 50% decrease in mortality in individuals undergoing bariatric surgery, compared to controls, over a follow-up period of 2 to 14.7 years (Kwok 2014).

Bariatric surgeries are classified into restrictive, malabsorptive and combination procedures, although this classification is arbitrary and lacks scientific validation (Sawaya 2012) (Figure 1). Restrictive procedures reduce energy intake by limiting the stomach capacity and volume, using a synthetic band distal to the gastro-oesophageal junction in the laparoscopic adjustable gastric banding or by stapling the stomach in the vertical banded gastroplasty. Similarly, the sleeve gastrectomy, where two thirds of the stomach along the greater curvature are resected, is considered a restrictive procedure (Sawaya 2012). Malabsorptive procedures reduce caloric intake by decreasing food absorption, achieved by surgically bypassing various areas of the intestine, as in the duodenal switch, bilio-pancreatic diversion and the jejuno-ileal bypass (Sawaya 2012). The Roux-en-Y gastric bypass is considered a combination procedure, characterised by decreasing the stomach size and creating a Roux limb that bypasses some areas of the small bowel (Colquitt 2014; Sawaya 2012). Several hormonal changes follow sleeve gastrectomy, Roux-en-Y gastric bypass and bilio-pancreatic diversion, such as a drop in circulating ghrelin levels, an orexigenic hormone, and a rise in glucagon-like peptide-1, a gut hormone that potentiates insulin production (Hage 2012; Valverde 2005). These changes contribute to weight loss and to improvement in insulin resistance and glucose metabolism (Hage 2012; Lee 2011; Valverde 2005).

Figure 1. a. Laparoscopic bandingb. Gastric sleevec. Roux-en-Y gastric bypassReprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2005-2015. All Rights Reserved.



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Acute and late complications following bariatric surgery have been widely described. These include peri-operative comorbidities, nutritional deficiencies, metabolic and gastrointestinal complications (Colquitt 2014; Sawaya 2012; Shikora 2007). Macro- and micronutrients deficiencies are common and depend mainly on the type of the surgical procedure as well as the pre-operative vitamin and mineral status (Saltzman 2013). Although malabsorptive procedures are associated with the highest risk, nutrient deficiencies can complicate all types of bariatric surgery (Shikora 2007). Vitamin B12, folate and iron deficiency are the most common deficiencies following bariatric surgery (Sawaya 2012). Deficiencies in vitamins B1, B2 and C, and biotin have been also reported (Bal 2012). Fat soluble vitamins malabsorption frequently occurs following malabsorptive and combination bariatric surgery procedures (Sawaya 2012). A cohort study showed that vitamins A and K deficiencies occur in 50% to 69% of individuals at one to four years following bilio-pancreatic diversion or duodenal switch (Slater 2004). Vitamin D and calcium malabsorption have been extensively described (Bal 2012; Sawaya 2012). Some causes of vitamin D deficiency are directly related to obesity, such as sedentary lifestyle, decreased sun exposure (Vanlint 2013), vitamin D sequestration in adipose tissue (Wortsman 2000), and altered vitamin D metabolism (Wamberg 2012). Other causes are related to the malabsorptive and combination procedure per se, resulting in fat malabsorption (Shikora 2007). In addition, limited intake of dairy products due to dietary intolerance and non-adherence to multivitamin supplementation concur to worsen hypovitaminosis D, even in the isolated gastric procedures (Saltzman 2013; Shikora 2007). Finally, hypoalbuminaemia, reflecting protein malnutrition, occurs in 3% to 18% of persons undergoing bilio-pancreatic diversion and duodenal switch (Bal 2012). Therefore, bariatric surgery clinical practice guidelines recommend prophylactic post-operative supplementation with multivitamins and minerals, including calcium, vitamin D, iron, thiamin, vitamin B12, folate, vitamin A and in specific conditions vitamin B1, copper, zinc, and selenium (Fried 2014; Heber 2010; Mechanick 2013).

Description of the intervention

Vitamin D is a fat soluble vitamin. The skin constitutes its major source and few food naturally contain vitamin D, such as cod liver, salmon and other seafood (Holick 2005). The 25-hydroxyvitamin D [25(OH)D] level is the best indicator of vitamin D status and results from liver hydroxylation (Holick 2005). The active form of vitamin D, 1,25 dihydroxyvitamin D ($1,25(OH)_2D$), results from additional 1α-hydroxylation at the level of the kidneys; $1,25(OH)_2D$ interacts with the intranuclear vitamin D receptor (VDR) and is responsible for the biologic effects of vitamin D (Holick 2005). Vitamin D has been classically known to be responsible of maintaining calcium haemostasis, through stimulation of intestinal calcium absorption and bone resorption (Holick 2005). High parathyroid hormone levels, low calcium and low phosphate are potent stimulators of vitamin D renal hydroxylation (Holick 2005).

Vitamin D supplements are available in different forms such as ergocalciferol (D2) or cholecalciferol (D3), or the hydroxylated forms: calcidiol (25-hydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D). Enteral and parenteral preparations are over the counter. Various dosing regimens have been assessed. Daily, weekly and monthly regimens are almost equivalent in terms of achieving serum 25(OH)D levels (Ish-Shalom 2008), whereas less frequent dosing is suboptimal (Kearns 2014). Various supplementation regimens have been assessed in observational studies conducted on bariatric surgery populations, ranging from daily equivalent doses of 200 IU daily to 28,000 IU daily, with variable improvements in vitamin D status (De Luis 2008; Hewitt 2013; Manco 2005). Supplementation with high doses of vitamin D has been recommended in obese individuals, in patients with malabsorption (Holick 2011) and in individuals undergoing bariatric surgery (Heber 2010; Mechanick 2013).

Despite the controversy in defining the optimal vitamin D level (Holick 2011; Ross 2011), vitamin D supplementation randomised controlled trials showed improved muscle function, decreased fractures (hip and non vertebral fractures) and decreased falls with daily doses $\geq$ 800 IU (Bischoff-Ferrari 2009; Bischoff-Ferrari 2012). In addition to the classic effects of vitamin D supplementation on skeletal health, extra-skeletal effects have been recently elucidated, given the wide expression of vitamin D receptor and 25(OH)D3-1α-hydroxylase in various tissues (Norman 2010). Therefore, a possible protective effect of vitamin D in multiple diseases has been suggested, including diabetes mellitus (Mitri 2014), auto-immune diseases (Souberbielle 2010), cancer (Bjelakovic 2014a), cardiovascular diseases (Zittermann 2014a), brain and mental health (Holick 2014), in addition to neonatal and maternal outcomes (Hypponen 2014; Weinert 2014), and even mortality (Bjelakovic 2014b).

Adverse effects of the intervention

Although the upper limit of vitamin D intake in adults, defined by the Institute of Medicine is 4000 IU daily, doses up to 10,000 IU daily have been used over weeks to months without evidence of adverse events**.** The risk of vitamin D toxicity appears only when 25(OH)D level becomes higher than 100 to 150 ng/mL (Bouillon 2013; Holick 2005; Vieth 2007). At such high levels, the buffering effect of vitamin D binding protein is exceeded, therefore, leading to increased free $1,25(OH)_2D$ levels (Vieth 2006; Vieth 2007). Symptoms of vitamin D toxicity are related to hypercalcaemia and hypercalciuria, including gastrointestinal symptoms, loss of appetite, polyuria, polydipsia and kidney stones (Alshahrani 2013).

How the intervention might work

Vitamin D dose response has been assessed in several studies. In normal weight individuals, the increase in 25(OH)D in response

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to vitamin D supplementation varied, from 0.37 ng/mL/mcg in postmenopausal women at a high latitude (Boston) (Holick 2008), to 0.7 ng/mL/mcg in young men at a high latitude (Omaha) (Heaney 2003), and reached 1.2 ng/mL/mcg in elderly women in France (Chapuy 1992). This increment tends to reach a plateau with high doses (Cashman 2011; Gallagher 2013). In fact, multiple variables influence 25(OH)D levels reached following supplementation, including baseline vitamin D status, age, vitamin D supplementation type, dose and duration (Autier 2012; Cashman 2011; Shab-Bidar 2014). In addition, BMI significantly affects vitamin D dose response curve, whereby, even with high doses, the increment in 25(OH)D level barely achieves 0.2 ng/mL/mcg in obese individuals (Drincic 2012; Wamberg 2013).

Bone changes following bariatric surgery have been recently reviewed (Hage 2014; Yu 2014a). Although bone loss detected after bariatric surgery may, in part, be artifactual and related to weight loss rather than bone loss per se, volumetric bone mineral density assessment using quantitative computed tomography showed significant drops in spine bone mineral density (Yu 2014b). In addition to surgery type, the degree of weight loss and the effect of changes of various hormones affecting bone metabolism, vitamin D deficiency plays a pivotal role in bone changes following weight loss surgery (Hage 2014; Scibora 2012). Although multiple observational studies showed significant bone loss despite vitamin D supplementation, dosing regimen and patients' compliance remain a major limitation preventing the achievement of a desirable 25(OH)D level and confounding the bone mineral density results in these studies (Scibora 2012).

Vitamin D deficiency is commonly accompanied with secondary hyperparathyroidism in bariatric surgery patients (Ybarra 2005; Youssef 2007). In addition to serum 25(OH)D levels, age and ethnic origin are other risk factors, further complicating metabolic bone disease following bariatric surgery (Youssef 2007). Indeed, vitamin D supplementation post-operatively decreases secondary hyperparathyroidism rate (Flores 2015).

Osteomalacia presenting with the typical symptoms of bone pain and tenderness, myalgia, proximal muscle weakness, difficulty walking and stooping posture, is a less common complication of various malabsorptive weight loss surgeries, and requires aggressive vitamin D replacement (Al-Shoha 2009; Bhan 2010; Collazo-Clavell 2004).

The extra skeletal manifestations of vitamin D deficiency in bariatric surgery have not been well established. One study from Italy failed to show a significant association between 25(OH)D level and insulin sensitivity following bilio-pancreatic diversion (Manco 2005).

Why it is important to do this review

Vitamin D deficiency following bariatric surgery results in an increased risk of hypocalcaemia, secondary hyperparathyroidism and bone loss (Hage 2014; Stein 2014; Yu 2014a). Therefore, vitamin D replacement seems to be crucial in this specific population as it will remedy disturbances in mineral metabolism, and possibly other complications. Major professional societies, including the Endocrine Society (Heber 2010), the American Association of Clinical Endocrinologists (AACE), the Obesity Society (TOS), the American Society for Metabolic & Bariatric Surgery (ASBMS) (Mechanick 2013), and the Interdisciplinary European Guidelines (Fried 2014), have all recommended vitamin D supplementation as part of the post-operative care of bariatric surgery patients. The Endocrine Society recommends 50,000 IU vitamin D one to three times weekly (Heber 2010). The AACE/TOS/ASBMS guidelines recommend vitamin D 3000 to 6000 IU daily (Mechanick 2013). The dose increases to 50,000 IU one to three times daily in case of severe malabsorption (Heber 2010; Mechanick 2013). These recommendations were based on expert opinion, rather than an evidence based systematic review of available prospective interventional and randomised controlled trials. No previous systematic review of randomised controlled trials (RCTs) has assessed the effects of vitamin D supplementation following bariatric surgery.

In light of the substantial repercussions of hypovitaminosis D on mineral and skeletal metabolism, the current knowledge gap, the availability of RCTs and current ongoing studies, a systematic review and meta-analysis is pressing. This systematic review will help define the optimal dosing of vitamin D supplementation in persons undergoing bariatric surgery. The results will help inform and update vitamin D replacement guidelines in this specific population.

OBJECTIVES

To compare the effects of different doses of vitamin D supplementation (low dose $\leq$ 600 IU daily, moderate dose between 600 and 3500 IU daily, high dose $\geq$ 3500 IU daily, compared to each other or to placebo) in obese adults undergoing bariatric surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs and controlled clinical trials (CCTs) with vitamin D supplementation for at least three months and a follow-up duration of at least three months.

Types of participants

We will include obese individuals who have undergone bariatric surgery, according to the American Association of Clinical Endocrinologists, the Obesity Society and the American Society for

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Metabolic & Bariatric Surgery indications as follows (Mechanick 2013).

- Body mass index (BMI) ≥ 40 kg/m².
- BMI ≥ 35 kg/m² with one or more comorbidities related to obesity such as type 2 diabetes mellitus, hypertension, dyslipidaemia, obstructive sleep apnoea, obesity hypoventilation syndrome, non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, pseudo tumour cerebri, gastro-oesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life.

We will exclude following types of participants.

- Undergoing bypass surgery for malignancy.
- Who have chronic illnesses (chronic kidney disease, chronic liver disease other than non-alcoholic steatohepatitis, heart failure, or malabsorption prior to bariatric surgery).
- Who are on drugs that interfere with vitamin D metabolism (steroids, anti-fungals, or anti-convulsants).

Types of interventions

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

Intervention

(a) Vitamin D (D2 or D3) of any dose, given orally, as daily, weekly or monthly supplementation, initiated pre- or immediately post-surgery, for a duration of at least three months.
(b) Vitamin D (as described above) + calcium or other vitamins.

Comparator

- Placebo alone or concomitantly with another therapy (calcium or other vitamins) compared with (a) or (b) as mentioned above, respectively.
- Various doses of vitamin D (alone or concomitantly with other therapy, as described above) compared to one another.

Concomitant interventions will have to be the same in the intervention and comparator groups to establish fair comparisons.
We define vitamin D dose categories as:

- Low dose ≤ 600 IU daily.
- Moderate dose between 600 and 3500 IU daily.
- High dose ≥ 3500 IU daily.

Vitamin D dose of 600 IU daily is the dose recommended by the Institute of Medicine for the general adult population (IOM 2011). Vitamin D dose of 3500 IU daily is an intermediate dose between the vitamin D supplementation dose recommended by the AACE/TOS/ASBMS for individuals undergoing bariatric surgery, which is 3000 IU daily (Mechanick 2013), and the tolerable upper intake level of vitamin D recommended by the Institute of Medicine (IOM 2011)

Exclusion criteria

We will exclude studies where the intervention consists of:

- Biologically active vitamin D (calcitriol).
- Parenteral vitamin D administration (intra muscular, topical).
- Vitamin D administration at frequency less than once monthly.
- Vitamin D administration for less than three months.
- Vitamin D supplementation as fortified food.

Types of outcome measures

Clinically relevant outcomes considered in RCTs of vitamin D replacement in obese persons undergoing bariatric surgery are prespecified. By comparing two vitamin D dose categories (low versus high, low versus moderate, moderate versus high) or any vitamin D dose category versus placebo, we will assess the following outcomes.

Primary outcomes

- Vitamin D status.
- Adverse events.
- Fractures.

Secondary outcomes

- All-cause mortality.
- Specific adverse events.
- Bone density change.
- Diabetes resolution rate.
- Secondary hyperparathyroidism.
- Bone turnover markers.
- Health-related quality of life.
- Metabolic profile:
    - Insulin resistance.
    - Glycaemic profile
    - Dyslipidaemia.
    - Liver function.
- Blood pressure.
- Anthropometric measures: weight, BMI, waist circumference.
- Muscle strength.
- Fat mass.
- Socioeconomic effects.

Method and timing of outcome measurement

- Vitamin D status: measured by 25-hydroxyvitamin D level, using automated or manual 25-hydroxyvitamin D, competitive protein-binding assays and immunoassays and measured at any time point after three months post-operatively.
- Adverse events defined as total incidence of adverse events (hypercalcaemia, hypercalciuria, kidney stones, gastrointestinal

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symptoms or any other adverse event reported in trials) occurring at any time post-operatively.

- Fractures: defined as the proportion of participants who experience any low trauma fracture at any time point post-operatively.
- All-cause mortality: defined as mortality from any cause, occurring at any time point post-operatively.
- Specific adverse events, measured at any time point post-operatively, specified as:
    - Hypercalcaemia incidence defined as the proportion of participants who have a serum calcium level above the upper limit of normal.
    - Hypercalciuria incidence defined as the proportion of participants who have a 24-hour urine collection of calcium > 250 mg in women and > 300 mg in men (Hodgkinson 1958) or > 4 mg/kg in both sexes (Coe 1977).
    - Nephrolithiasis incidence defined as the proportion of participants who experience a kidney stone clinically or radiologically.
    - Gastro-intestinal symptoms incidence defined as the proportion of participants who experience constipation, anorexia, nausea, vomiting, or epigastric pain.
- Bone density change: defined as a decrease or increase in bone mineral density at hip, lumbar spine or forearm, measured by dual energy x-ray absorptiometry scan at any time point after three months post-operatively. The difference in bone change between two treatment arms will be considered significant if it exceeds the least significant change defined in each study, depending on the precision of each bone mineral density testing facility. When such information is lacking, the change in bone density is considered significant when it exceeds 5% at the lumbar spine, 5% at the total hip and 6.9% at the femoral neck (Baim 2008).
- Diabetes resolution rate: defined as the proportion of participants who were not taking any glucose lowering agent and had a glycosylated haemoglobin (HbA1c) of 6% or less, at any time point post-operatively.
- Secondary hyperparathyroidism: assessed by parathyroid hormone level, measured at any time point after three months post-operatively.
- Bone turnover markers: assessed by alkaline phosphatase, C-telopeptide of type I collagen, and osteocalcin levels measured at any time point after three months post-operatively.
- Health-related quality of life: evaluated by a validated instrument such as the CDC health-related quality of life questionnaire and measured at any time point post-operatively.
- Metabolic profile, assessed by:
    - Insulin resistance: assessed by insulin levels or other indices such as homeostasis model assessment of insulin resistance (HOMA) or quantitative insulin sensitivity check index (QUICKI), measured at any time point after three months post-operatively.
    - Glycaemic profile: measured by HbA1c, fasting blood glucose or two-hour value in an oral glucose tolerance test (OGTT) or randomly, measured at any time point after three months post-operatively.
    - Lipid profile: assessed by low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides levels, measured at any time point after three months post-operatively
    - Liver function: assessed by aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases, gamma glutamyl-transpeptidase levels, measured at any time point after three months post-operatively.
- Blood pressure: assessed by systolic and diastolic blood pressure, measured at any time point post-operatively.
- Anthropometric measures: defined as weight or BMI and waist circumference measured at any time point after three months post-operatively.
- Muscle strength: measured by hand grip or jump height at any time point after three months post-operatively.
- Fat mass: measured by dual energy x-ray absorptiometry at any time point after three months post-operatively.
- Socioeconomic effects: including cost of treatment, visits to clinics or hospitals, resources lost due to illness by the participants or absence from work and measured at any time point after three months post-operatively.

Summary of findings

We will present a 'Summary of finding' table to report the following outcomes, listed according to priority.

1. Vitamin D status.
2. Adverse events.
3. Fracture rates.
4. All-cause mortality.
5. Diabetes resolution rate
6. Health-related quality of life.
7. Socioeconomic effects.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception of each database to the specified date and will place no restrictions on the language of publication.

- Cochrane Library:
    - Cochrane Database of Systematic Reviews (CDSR).
    - Cochrane Central Register of Controlled Trials (CENTRAL).
    - Database of Abstracts of Reviews of Effects (DARE).
    - Health Technology Assessment (HTA).
- MEDLINE.
- PubMed (subsets not available on Ovid).

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- LILACS.
- EMBASE.

We will also search for trials in the following databases.

- ClinicalTrials.gov (https://clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Protal (http://apps.who.int/trialsearch/), which is a meta-register of studies with links to several trial registers, including:
    - Australian New Zealand Clinical Trials Registry.
    - ClinicalTrials.gov.
    - EU Clinical Trials Register.
    - International Standard Randomised Controlled Trial Number (ISRCTN) Registry.
    - Brazilian Clinical Trials Registry.
    - Chinese Clinical Trial Registry.
    - Clinical Trials Registry - India.
    - Clinical Research Information Service - Republic of Korea.
    - Cuban Public Registry of Clinical Trials.
    - German Clinical Trials Register.
    - Iranian Registry of Clinical Trials.
    - Japan Primary Registries Network.
    - Pan African Clinical Trial Registry.
    - Sri Lanka Clinical Trials Registry.
    - The Netherlands National Trial Register.
    - Thai Clinical Trials Register.

We will continuously apply MEDLINE (via Ovid platform), PubMed, and EMBASE email alert services to identify newly published studies using the same search strategy as described for each of the databases (Appendix 1). After supplying the final review draft for editorial approval, the Cochrane Metabolic and Endocrine Disorders (CMED) Group will perform a complete updated search on all databases available at the editorial office and will send the results to the review authors. Should we identify new studies for inclusion we will evaluate these, incorporate findings in our review and resubmit another review draft (Beller 2013).

If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes.

Searching other resources

We will try 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. We will also contact study authors of included trials to identify any further studies that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (MC, NN) will independently scan the abstract, title, or both, of every record retrieved, to determine which studies we should assess further. We will investigate the full text articles of all potentially-relevant articles. We will resolve any discrepancies through consensus or recourse to a third review author (GEHF). If we cannot resolve a disagreement, we will categorise the study as a 'study awaiting classification' and we will contact study authors for clarification. We will present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

For studies that fulfil inclusion criteria, two review authors (MC, NN) will independently extract key participant and intervention characteristics. We will report data on efficacy outcomes and adverse events using standard data extraction templates supplied by the CMED Group. We will resolve any disagreements by discussion, or, if required, by consulting a third review author (GEHF). We will provide information including trial identifier about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table and in a joint appendix 'Matrix of study endpoint (publications and trial documents)'. We will try to find the protocol for each included study and will report primary, secondary, and other outcomes in comparison with data in publications in a joint appendix'.

We will email all authors of included studies to enquire whether they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary author(s) of the article, if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximise the information yield by collating all available data and using the most complete dataset aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (MC, NN) will independently assess the risk of bias of each included study. We will resolve any disagreements by consensus, or by consultation with a third review author (GEHF). We will use the Cochrane's risk of bias assessment tool (Higgins 2011a; Higgins 2011b), and will evaluate the following criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).

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- Imbalances in baseline characteristics (chance bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other potential sources of bias.

We will judge the above 'Risk of bias' criteria as 'low risk', 'high risk', or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will present a risk of bias graph and a risk of bias summary. We will assess the impact of individual bias domains on study results at the endpoint and study levels. In case of high risk of selection bias, we will mark all endpoints investigated in the associated study as high risk.
We will evaluate whether imbalances in baseline characteristics existed and how these were addressed (Egbewale 2014; Riley 2013). For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessors) we will evaluate the risk of bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures.
We will consider the implications of missing outcome data from individual participants per outcome such as high drop-out rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between study arms).
We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of study endpoints (publications and trial documents)' (Boutron 2014; Mathieu 2009) and the appendix 'Examination of outcome reporting bias' (Kirkham 2010). This analysis will form the basis of the judgement of selective reporting (reporting bias).
We will distinguish between self-reported, investigator-assessed and adjudicated outcome measures.
We define the following endpoints as self-reported outcomes.

- Adverse events, reported by participants.
- Specific adverse events, reported by participants.
- Health-related quality of life.
- Blood pressure, measured by participants.
- Weight or BMI, measured by participants.
- Waist circumference, measured by participants.
- Muscle strength, measured by participants.

We define the following endpoints as investigator-assessed outcomes.

- Vitamin D status.
- Adverse events, evaluated by study personnel.
- Fractures.
- Bone density change.
- All-cause mortality.
- Specific adverse events, evaluated by study personnel.
- Diabetes resolution rate.
- Secondary hyperparathyroidism.
- Bone turnover markers levels.
- Metabolic profile.
- Blood pressure, measured by study personnel.
- Weight or BMI, measured by study personnel.
- Waist circumference, measured by study personnel.
- Muscle strength, measured by study personnel.
- Fat mass.
- Socioeconomic effects.

Measures of treatment effect

When at least two studies are available for a comparison (comparing two vitamin D dose categories or a vitamin D dose category to placebo) for a given outcome, we will express dichotomous data as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs), continuous data as mean differences (MDs) with 95% CIs, and time-to-event data as hazard ratios (HRs) with 95% CIs.
We will conduct a meta-regression using the SPSS or STATA software (SPSS Software; STATA Software), if at least 10 eligible studies are identified for a given comparison. Accordingly, we plan to establish a dose response curve of vitamin D supplementation in participants undergoing bariatric surgery, taking into consideration several covariates that affect the vitamin D level following supplementation.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data

If possible, we will obtain missing data from study authors, and carefully evaluate important numerical data such as screened, randomised participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations. We will investigate attrition rates, e.g. drop-outs, losses to follow up and withdrawals, and critically appraise issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).
Where means and standard deviations (SD) for outcomes have not been reported and we have not received the needed information from study authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005), or by assuming the SD of the missing outcome to be the average of the SD from those studies where this information was reported.
We will investigate the impact of imputation on meta-analyses by performing sensitivity analysis, using the methods suggested in previous papers (Ebrahim 2013; Ebrahim 2014).

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Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) through visual inspection of the forest plots and by using a standard Chi² test with a significance level of α = 0.1. In view of the low power of this test, we will also consider the I² statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); where an I² statistic of 75% or more indicates a considerable level of heterogeneity (Higgins 2011a).

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics, based on the following: baseline 25(OH)D level, baseline BMI, type of the surgical procedure.

Assessment of reporting biases

If we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully (Sterne 2011).

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarise, in a sensitivity analysis, primarily low risk of bias data using a random-effects model (Wood 2008). We will perform statistical analyses according to the statistical guidelines contained in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results. Two review authors (MC, NN) will independently rate the quality for each outcome. We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences, for each relevant comparison of alternative management strategies, numbers of participants, and studies addressing each important outcome and the rating of the overall confidence in effect estimates for each outcome. We will create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will present results for the outcomes as described in Types of outcome measures section. If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table .

In addition, we will establish a 'Checklist to aid consistency and reproducibility of GRADE assessments' to help with standardisation of the 'Summary of findings' tables (Meader 2014).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity and plan to carry out subgroup analyses with investigation of interactions

- BMI class (≤ 40 kg/m² or > 40 kg/m²) pre-operatively.
    - Body weight is one of the predictors of the response to vitamin D supplementation (Zittermann 2014b).
- Baseline 25-hydroxyvitamin D level (≤ 10 ng/ml versus >10 ng/ml).
    - Lower 25-hydroxyvitamin D levels at baseline respond better to vitamin D supplementation compared to higher levels (Autier 2012; Shab-Bidar 2014)
- Type of bariatric surgery (restrictive versus malabsorptive).
    - Nutrient deficiencies are more common in malabsorptive procedures compared to restrictive procedures, secondary to bypassing regions of the small intestine, diverting biliopancreatic secretions or both, which would result in various macro- and micronutrients malabsorption (Sawaya 2012).

Sensitivity analysis

We plan to perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes by restricting the analysis to:

- Published studies.
- Taking into account risk of bias, as specified in the 'Assessment of risk of bias in included studies' section.
- Very long or large studies to establish the extent to which they dominate the results.
- Studies using the following filters: source of funding (industry versus other).
- country.

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

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Cochrane Library
1. [mh "Vitamin D"]
2. [mh "Vitamin D Deficiency"]
3. vitamind*:ti,ab,kw
4. ((vitamin* or hydroxyvitamin* or dihydroxyvitamin*) next ("d" or d?)):ti,ab,kw
5. (colecalciferol* or cholecalciferol* or calciol* or calcitriol* or ergocalciferol* or calcifediol* or calcidol* or calcidiol* or calciferol* or ercalcidiol* or ercalcitriol*):ti,ab,kw
6. (hydroxyergocalciferol* or hydroxycalciferol* or hydroxycolecalciferol* or hydroxycholecalciferol* or dihydroxycolecalciferol* or dihydroxycholecalciferol*):ti,ab,kw
7. (dihydrotachyst* or ("dihydro" next tachyst*)):ti,ab,kw
8. (alphacalcidol or alphacalcidiol or alfacalcidol or alfacalcidiol):ti,ab,kw
9. {or #1-#8}
10. [mh ^"Bariatric Surgery"]
11. [mh ^"Gastric Bypass"]
12. [mh ^Gastroplasty]
13. [mh ^"Jejunoileal Bypass"]
14. [mh ^Gastroenterostomy]
15. [mh ^Gastrectomy]
16. [mh ^"Biliopancreatic Diversion"]
17. [mh ^"Gastric Balloon"]
18. [mh ^"Stomach"/SU]
19. [mh ^"Anastomosis, Roux-en-Y"]

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(*Continued*)

20. ((obes* or "weight loss" or "weight reduction" or antiobes* or "metabolic" or "gastric" or laparoscop*) next surg*):ti,ab,kw
21. ("bariatric" next (surg* or operation* or procedure* or patient*)):ti,ab,kw
22. (surg* next (procedure* or intervention* or treatment* or "management")):ti,ab,kw
23. ("gastric" near/4 (band* or imbrication* or plication* or "sleeve" or stapl* or resection* or reduction* or "stimulation")):ti,ab,kw
24. (("gastroileal" or "jejunoileal" or "biliopancreatic" or "gastric" or "stomach") next "bypass"):ti,ab,kw
25. gastrojejunostom*:ti,ab,kw
26. (pancreatico next jejunostom*):ti,ab,kw
27. gastrectom*:ti,ab,kw
28. gastroplast*:ti,ab,kw
29. "biliopancreatic diversion":ti,ab,kw
30. (malabsorpti* next (procedure* or surg*)):ti,ab,kw
31. "lap band":ti,ab,kw
32. "LAGB":ti,ab,kw
33. "LSG":ti,ab,kw
34. (RYGB* or "roux en y"):ti,ab,kw
35. "duodenal switch":ti,ab,kw
36. "stomach stapl*":ti,ab,kw
37. "scopinaro":ti,ab,kw
38. (("mason" or "rose" or "stomaphyx") next "procedure"):ti,ab,kw
39. (("gastric" or "intragastric") next balloon*):ti,ab,kw
40. (("endoluminal" or "bypass") next "sleeve"):ti,ab,kw
41. "endobarrier":ti,ab,kw
42. {or #10-#41}
43. #9 and #42

MEDLINE (Ovid SP)

1. exp Vitamin D/
2. exp Vitamin D Deficiency/
3. vitamind*.tw.
4. ((vitamin* or hydroxyvitamin* or dihydroxyvitamin*) adj d?).tw.
5. (c?olecalciferol* or calciol* or calcitriol* or ergocalciferol* or calcifediol* or calcid?ol* or calciferol* or ercalcidiol* or ercalcitriol*).tw.
6. (hydroxyergocalciferol* or hydroxycalciferol* or hydroxyc?olecalciferol* or dihydroxyc?olecalciferol*).tw.
7. (dihydrotachyst* or dihydro tachyst*).tw.
8. (alphacalcid?ol or alfacalcid?ol).tw.
9. or/1-8
10. Bariatric Surgery/
11. Gastric Bypass/
12. Gastroplasty/
13. Jejunoileal Bypass/
14. Gastroenterostomy/
15. Gastrectomy/
16. Biliopancreatic Diversion/
17. Gastric Balloon/
18. Stomach/su [Surgery]
19. Anastomosis, Roux-en-Y/
20. ((obes* or weight loss or weight reduction or antiobes* or metabolic or gastric or laparoscop*) adj1 surg*).tw.
21. (bariatric adj2 (surg* or operation? or procedure? or patient*)).tw.

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(*Continued*)

22. (surg* adj1 (procedure? or intervention? or treatment? or management)).tw.
23. (gastric adj3 (band* or imbrication? or plication? or sleeve or stapl* or resection? or reduction? or stimulation)).tw.
24. ((gastroileal or jejunoileal or biliopancreatic or gastric or stomach) adj1 bypass).tw.
25. gastrojejunostom*.tw.
26. pancreatico jejunostom*.tw.
27. gastrectom*.tw.
28. gastroplast*.tw.
29. biliopancreatic diversion.tw.
30. (malabsorpti* adj1 (procedure* or surg*)).tw.
31. lap band.tw.
32. LAGB.tw.
33. LSG.tw.
34. (RYGB* or roux en y).tw.
35. duodenal switch.tw.
36. stomach stapl*.tw.
37. scopinaro.tw.
38. ((mason or rose or stomaphyx) adj1 procedure).tw.
39. ((gastric or intragastric) adj1 balloon).tw.
40. ((endoluminal or bypass) adj1 sleeve).tw.
41. endobarrier.tw.
42. or/10-41
43. 9 and 42

[Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

44. randomized controlled trial.pt.
45. controlled clinical trial.pt.
46. randomi?ed.ab.
47. placebo.ab.
48. drug therapy.fs.
49. randomly.ab.
50. trial.ab.
51. groups.ab.
52. or/44-52
53. exp animals/ not humans/
54. 52 not 53
55. 43 and 54

PubMed (not medline[sb])

#1 weight loss surger*[tw] OR weight reduction surger*[tw] OR obesity surger*[tw] OR antiobesity surger*[tw] OR bariatric[tw] OR metabolic surger*[tw] OR "gastric bypass"[tw] OR "jejunoileal bypass"[tw] OR "gastroileal bypass"[tw] OR "biliopancreatic bypass"[tw] OR band*[tw] OR sleeve*[tw] OR resection*[tw] OR jejunostom*[tw] OR "biliopancreatic diversion"[tw] OR gastrojejunostom*[tw] OR gastrectom*[tw] OR gastroplast*[tw] OR gastroenterostom*[tw] OR LAGB[tw] OR LSG[tw] OR RYGB*[tw] OR "roux en y"[tw] OR "duodenal switch"[tw] OR stomach stapl*[tw] OR balloon*[tw] OR endobarrier[tw]
#2 vitamin d*[tw] OR hydroxyvitamin d*[tw] OR dihydroxyvitamin d*[tw] OR calciol[tw] OR calcidiol[tw] OR calcidol[tw] OR calcitriol[tw] OR calcifediol[tw] OR calciferol[tw] OR ercalcidiol[tw] OR ercalcitriol[tw] OR ergocalciferol[tw] OR doxercalciferol[tw] OR colecalciferol[tw] OR cholecalciferol[tw] OR paricalcitol[tw] OR alphacalcidol[tw] OR dihydrotachyst*[tw]
#3 #1 AND #2
#4 (medline[sb] or pmcbook)
#5 #3 NOT #4

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(*Continued*)

EMBASE (Ovid SP)

1. exp Vitamin D/
2. exp Vitamin D Deficiency/
3. vitamind*.tw.
4. ((vitamin* or hydroxyvitamin* or dihydroxyvitamin*) adj d?).tw.
5. (c?olecalciferol* or calciol* or calcitriol* or ergocalciferol* or calcifediol* or calcid?ol* or calciferol* or ercalcidiol* or ercalcitriol*).tw.
6. (hydroxyergocalciferol* or hydroxycalciferol* or hydroxyc?olecalciferol* or dihydroxyc?olecalciferol*).tw.
7. (dihydrotachyst* or dihydro tachyst*).tw.
8. (alphacalcid?ol or alfacalcid?ol).tw.
9. or/1-8
10. Bariatric Surgery/
11. Biliopancreatic Bypass/
12. Gastric Banding/
13. Sleeve Gastrectomy/
14. Stomach surgery/
15. Gastrectomy/
16. Stomach Bypass/
17. Gastroenterostomy/
18. Intestine Bypass/
19. Jejunoileal Bypass/
20. Intestine anastomosis/
21. Roux Y anastomosis/
22. Gastroenterostomy/
23. Gastric Balloon/
24. Gastric Band/
25. ((obes* or weight loss or weight reduction or antiobes* or metabolic or gastric or laparoscop*) adj1 surg*).tw
26. (bariatric adj2 (surg* or operation? or procedure? or patient*)).tw
27. (surg* adj1 (procedure? or intervention? or treatment? or management)).tw
28. (gastric adj3 (band* or imbrication? or plication? or sleeve or stapl* or resection? or reduction? or stimulation)).tw
29. ((gastroileal or jejunoileal or biliopancreatic or gastric or stomach) adj1 bypass).tw
30. gastrojejunostom*.tw.
31. pancreatico jejunostom*.tw.
32. gastrectom*.tw.
33. gastroplast*.tw.
34. biliopancreatic diversion.tw.
35. (malabsorpti* adj1 (procedure* or surg*)).tw.
36. lap band.tw.
37. LAGB.tw.
38. LSG.tw.
39. (RYGB* or roux en y).tw.
40. duodenal switch.tw.
41. stomach stapl*.tw.
42. scopinaro.tw.
43. ((mason or rose or stomaphyx) adj1 procedure).tw.
44. ((gastric or intragastric) adj1 balloon).tw.
45. ((endoluminal or bypass) adj1 sleeve).tw.

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(*Continued*)

46. endobarrier.tw.
47. or/10-46
48. 9 and 47
[49: Wong 2006 *"sound treatment studies" filter - BS version]*
49. random*.tw. or clinical trial*.mp. or exp health care quality/
50. 48 and 49

LILACS (iAHx)

(MH:"Vitamin D" OR MH:"Vitamin D Deficiency" OR "vitamin d" OR "vitamina d" OR "vitamin d3" OR "vitamina d3" OR calciol OR calcidiol OR calcitriol OR calcifediol OR calciferol OR ercalcidiol OR ercalcitriol OR ergocalciferol OR doxercalciferol OR colecalciferol OR paricalcitol OR alfacalcidol OR alphacalcidol OR dihidrotaquist$ OR dihydrotachyst$) AND (MH:"Bariatric Surgery" OR MH:"Gastroenterostomy" OR MH:"Obesity/surgery" OR MH:"Obesity, Morbid/surgery" OR MH:"Obesity, Abdominal/surgery" OR ((bariatric$ OR obes$ OR gastric$) AND (surg* OR cirug* OR cirurg*)) OR (gastr$ AND (band$ OR bypass OR sleeve OR vertic$ OR derivac$)) OR gastrojejun$ OR (biliopancreatic AND (diversion OR derivac$ OR bypass)) OR gastroplast$)

ClinicalTrials.gov (Expert Search via Advanced Search)

((surgery OR surgical OR bariatric OR gastric OR gastrectomy OR gastroplasty OR gastroenterostomy OR gastrojejunostomy OR jejunostomy OR band OR banding OR balloon OR "bileopancreatic diversion" OR roux OR bypass OR "duodenal switch" OR sleeve OR endobarrier) AND ("vitamin d" OR "vitamin d3" OR calciol OR calcidiol OR calcitriol OR calcifediol OR calciferol OR ercalcidiol OR ercalcitriol OR ergocalciferol OR doxercalciferol OR colecalciferol OR paricalcitol OR alphacalcidol OR dihydrotachysterol)) AND (obese OR obesity OR overweight OR bariatric) [DISEASE]

ICTRP Search Portal (Standard search)

bariatric AND vitamin d* OR
bariatric AND calciol OR
bariatric AND calcidiol OR
bariatric AND calcitriol OR
bariatric AND calcifediol OR
bariatric AND calciferol OR
bariatric AND ercalcidiol OR
bariatric AND ercalcitriol OR
bariatric AND ergocalciferol OR
bariatric AND doxercalciferol OR
bariatric AND colecalciferol OR
bariatric AND paricalcitol OR
bariatric AND alphacalcidol OR
bariatric AND dihydrotachyst* OR
obes* AND surg* AND vitamin d* OR
obes* AND surg* AND calciol OR
obes* AND surg* AND calcidiol OR
obes* AND surg* AND calcitriol OR
obes* AND surg* AND calcifediol OR
obes* AND surg* AND calciferol OR
obes* AND surg* AND colecalciferol OR
obes* AND bypass* AND vitamin d* OR
obes* AND bypass* AND calciol OR

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(*Continued*)

obes* AND bypass* AND calcidiol OR
obes* AND bypass* AND calcitriol OR
obes* AND bypass* AND calcifediol OR
obes* AND bypass* AND calciferol OR
obes* AND bypass* AND colecalciferol OR
obes* AND gastr* AND vitamin d* OR
obes* AND gastr* AND calciol OR
obes* AND gastr* AND calcidiol OR
obes* AND gastr* AND calcitriol OR
obes* AND gastr* AND calcifediol OR
obes* AND gastr* AND calciferol OR
obes* AND gastr* AND colecalciferol OR
obes* AND band* AND vitamin d* OR
obes* AND band* AND calciol OR
obes* AND band* AND calcidiol OR
obes* AND band* AND calcitriol OR
obes* AND band* AND calcifediol OR
obes* AND band* AND calciferol OR
obes* AND band* AND colecalciferol

CONTRIBUTIONS OF AUTHORS

The tasks protocol drafting correspond to the protocol version of this Cochrane review, the other tasks correspond to planned activities for the review version.

Marlene T Chakhtoura (MC): protocol drafting, acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

Nancy F Nakhoul (NFN): protocol drafting acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

Elie A Akl (EA): protocol drafting acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

Christos Mantzor (CM): protocol drafting acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

Bassem Y Safadi (BS): protocol drafting acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

Ghada El-Hajj Fuleihan (GEHF): protocol drafting acquiring study reports, selecting studies for inclusion, data extraction, data analysis, data interpretation, review drafting, and future review updates.

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DECLARATIONS OF INTEREST

MC: none known.

NFN: none known.

EA: none known.

CM: none known.

BS: Bassem Y Safadi is member of the board Surgical Innovations, Leads UK, (laparoscopic surgery manufacturing company, international advisory board) and consultant of Covidien Johnson and Johnson (organizing workshops and giving lectures on laparoscopic surgery). The relationship with the stated companies has no competing interest with this review.

GEHF: Ghada El-Hajj Fuleihan has received funding as primary investigator, from the American University of Beirut, to conduct an investigator initiated vitamin D trial in pregnancy. She is also co-primary investigator on an investigator initiated protocol to investigate vitamin D supplementation in patients post bariatric surgery.

Note from the CMED Group: for all ongoing and finished trials in which one of the review authors participated all data will be extracted and critically appraised by the editorial office.

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Internal sources

- Internal sources, Other.

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NOTES

We have based parts of the Methods and Appendix 1 sections of this Cochrane Protocol on a standard template established by the CMED Group.

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