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Vitamin D and/or calcium to prevent fractures and falls: protocol for a systematic review and meta-analysis

Olivier Massé ,[1] Claudia Mei Mercurio,[1] Sébastien Dupuis,[1] Alexandra Arruda,[1] Katherine Desforges,[2,3] Nicolas Dugré,[1,3] Gabriel Dallaire,[1] David Williamson [1,4]

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[1]Department of pharmacy, Hôpital du Sacré-Coeur-de-Montréal, Montréal, Québec, Canada
[2]Department of pharmacy, McGill University Health Centre, Montréal, Québec, Canada
[3]Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada
[4]Research Centre, Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal, Montréal, Québec, Canada

Correspondence to
Olivier Massé;
olivier.masse.cnmtl@ssss.gouv.qc.ca

ABSTRACT

Background Previous systematic reviews on fracture and fall prevention have generally shown no efficacy with calcium or vitamin D alone and conflicting findings with that of vitamin D combined with calcium. Despite these findings, increases in vitamin D and calcium prescriptions have been reported in many countries, as many clinicians, guidelines and regulatory agencies still largely recommend universal supplementation to adults.

Methods and analysis We will conduct a systematic review of randomised controlled trials on the efficacy of vitamin D and/or calcium in fracture and fall prevention. A systematic search will be performed in Medline, Embase, CENTRAL, International Clinical Trials Registry Platform and Clinicaltrials.gov (1 January 2024). We will also hand search abstracts published in relevant congress and journals (2021–2023) and the reference lists of included trials. We will consider any trial involving the pharmacological administration of calcium alone, vitamin D alone or vitamin D combined with calcium against placebo or no treatment in adults. The primary outcome will be the number of participants with fractures at any site. The secondary outcomes will be the number of participants with hip fractures, non-vertebral fractures, vertebral fractures and falls, and the rate of falls. Two reviewers will independently screen and include the trials, extract the data and assess the risk of bias using the second version of the Cochrane risk-of-bias tool. We plan to pool outcomes to conduct random-effects meta-analyses and to appraise the certainty of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE). Many prespecified subgroup and sensitivity analyses will be performed to explore the potential heterogeneity and to test the robustness of our findings.

Ethics and dissemination This systematic review does not require research ethics approval. The results will be disseminated in peer-reviewed journals and help inform clinicians, guidelines and regulatory agencies.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We planned a comprehensive systematic review with broad eligibility criteria on the musculoskeletal benefits of vitamin D and/or calcium supplements.
⇒ We will assess the risk of bias of all trials using the second version of the Cochrane risk-of-bias tool and the certainty of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).
⇒ The subgroup and sensitivity analyses will help explore potential heterogeneity and test the robustness of our findings.
⇒ In including participants with very different fracture and fall risks using various doses of calcium and vitamin D, we expose our findings to clinical and methodological heterogeneity.
⇒ We will not extract safety data, thus limiting the full assessment of the risk–benefit ratio of vitamin D and/or calcium supplements.

INTRODUCTION

Falls and fractures are very common in older adults. As many as 30% and 50% of adults of 65 and 80 years or more experience at least one fall every year, respectively.[1 2] In older adults, falls are associated with fear of falling and restriction of physical activities. This can lead to deconditioning and to an even greater fall risk.[1] Injuries (eg, sprains, fractures, concussions) are common consequences of falls. In addition, 20% and 50% of men and women older than 50 years will experience a fragility fracture during their lifetime, most often after a fall.[3] Falls and fractures can lead to serious consequences, including pain, disabilities, reduced quality of life, hospitalisation, surgeries, surgical complications, institutionalisation and death.[2 3] Hip fractures, in particular, are a significant source of mortality and morbidity.[4] In Canada alone, the economic burden of fragility fractures was estimated at $4.6 billion in 2016.[5]

Vitamin D, a fat-soluble nutrient, has been extensively studied and prescribed to improve bone health.[6] Vitamin D3 (cholecalciferol) is currently the most prescribed form of vitamin D.[7] Usual doses of vitamin D3 range from 400 to 2000 units daily to 10 000–20 000 units weekly and to higher doses at greater intervals (eg, monthly, annually) in some clinical

trials and settings.[6] Vitamin D2 is also available in many countries, but it is rarely used due to its limited potency in improving serum vitamin D level.[7] Although vitamin D has long been recognised for its tolerability and safety, some randomised controlled trials (RCTs) have shown an increase in falls and fractures with large doses.[8 9] In North America, recommended dietary allowance for vitamin D ranges from 400 to 800 units/day, depending on gender and age.[10 11]

Calcium is available in various forms (eg, tablet, chewable, suspension) and salts (eg, carbonate, citrate, acetate, lactogluconate).[12] Although the carbonate salt is mostly prescribed, its poor absorption requires it to be taken with a meal. The citrate salt can be taken with or without a meal, and its absorption seems less influenced by achlorhydria. Usual supplement doses to prevent fractures range from 500 to 1200 mg daily.[6 12] Adverse effects are mainly gastrointestinal (eg, constipation, bloating, dyspepsia).[12] Particularly at high dose (greater than 1000 mg/day), calcium supplements have been inconsistently associated with increased risks of cardiovascular events and kidney stone formation.[13–15] In North America, the recommended dietary allowance for calcium ranges from 1000 to 1200 mg, depending on gender and age.[10 11]

Vitamin D plays a major role in the regulation of mineral and bone homeostasis.[7] Its active metabolites (in particular 1,25-dihydroxyvitamin D3) promote calcium absorption and regulate parathyroid hormone secretion. Muscles also express receptors for 1,25-dihydroxyvitamin D3, and low vitamin D levels can potentially alter muscle cell differentiation, metabolism and function.[16] As the main mineral ingredient of bones, calcium plays a major role in osteoblast bone formation activities.[12] To contract and function, muscle cells also need adequate calcium levels.[16] In a number of observational studies, low 25-hydroxyvitamin D blood concentrations and low calcium dietary intake have been associated with bone loss, muscle weakness, falls and fractures.[17–23] Consequently, many guidelines and regulatory agencies encourage vitamin D supplementation and calcium intake increase in diet or via supplements, particularly for older adults.[10 11 24] These recommendations promote that increasing intakes of vitamin D and/or calcium benefit musculoskeletal health and help reduce falls and fractures.

A recent umbrella systematic review on fractures identified 13 systematic reviews on vitamin D combined with calcium and 19 on vitamin D alone, compared with placebo or no treatment.[6] Except for four publications, all systematic reviews were considered of low or critically low quality. These reviews on fracture prevention generally showed no efficacy of vitamin D or calcium alone and conflicting findings with the vitamin D/calcium combination.[6] The effect of these supplements on falls is even more conflicting. Recent systematic reviews either showed no effect, a decrease or an increase in falls with vitamin D, depending on the review methodology, the population and the prescribed doses.[25–27] In brief, previous systematic reviews on musculoskeletal benefits of vitamin D and/or calcium were either limited by the selected population (eg, studying subgroup of adults, such as postmenopausal women or community-dwelling older adults), the interventions sought (eg, analysing specific vitamin D doses or not assessing the role of calcium combined with vitamin D), the comparator (eg, including low-dose vitamin D or calcium, thus promoting null effects) and the prespecified outcomes (with inconsistency in the reporting and definition of specific fractures or falls).[6] Some systematic reviews also excluded trials according to outcome occurrence and sample sizes, which limited the number of included trials. The most comprehensive systematic reviews were published a few years ago,[6] thus not including recent large-scale RCTs.[28–32] In addition, 34 guidelines were published between 2010 and 2020 on the musculoskeletal benefits of vitamin D in the adult population, of which 24 (70.6%) recommended or suggested supplementation.[24] Consequently, several observational studies have reported large increases in vitamin D prescriptions and serum vitamin D testing over the last 20 years, which can lead to significant costs while the real efficacy of these supplements remains controversial.[33–36]

In this systematic review and meta-analysis of RCTs, we aim to assess the efficacy of calcium alone, vitamin D alone and vitamin D combined with calcium in reducing fractures and falls compared with placebo or no treatment in adults. Although the Cochrane Handbook recommends always investigating safety data, we will consider conducting another systematic review on the safety (eg, cardiovascular events, kidney stones) of these supplements.[37] This review question warrants a larger search strategy and possibly the inclusion of observational studies.

METHODS AND ANALYSIS

Design

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guidelines (online supplemental appendix 1).[38] We will conduct and report this systematic review in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines.[37 39] This protocol is registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42023483915). We will report any protocol deviations in the supplements of the final manuscript.

Eligibility criteria

We formulated the eligibility criteria according to the PICO (Population, Intervention, Comparator and Outcome) approach.

Type of studies

We will only include RCTs, including cluster RCTs.

Types of participants

The population of interest is adults (≥ 18 years) who are not chronic users of corticosteroids or antiosteoporosis drugs.

Types of interventions and comparators

We will consider any trial involving the administration of calcium alone, vitamin D alone or vitamin D combined with calcium compared with placebo or no treatment. We will exclude trials when the intervention is provided as a dietary intake or as an active vitamin D analogue. We decided to exclude dietary sources of calcium or vitamin D as they usually contain other nutrients, minerals and vitamins, thus making it difficult to assess the real impact of calcium or vitamin D alone. We will include trials regardless of vitamin D type, calcium salts, doses used, method of administration and duration of intervention. We will include studies accepting non-trial supplements of calcium and/or vitamin D. We expect that the majority of trials would limit (without prohibiting) the use of these supplements or not report clear instructions for participants. Trials of calcium and/or vitamin D used with other interventions (eg, hormonal therapy, dietary instructions, other supplements, exercise training) will be included if both arms receive the co-intervention(s).

Types of outcomes

Primary outcome

1. Proportion of participants with one or more fractures at any site.

Secondary outcomes

2. Proportion of participants with one or more hip fractures.
3. Proportion of participants with one or more non-vertebral fractures.
4. Proportion of participants with one or more vertebral fractures.
5. Proportion of participants with one or more falls (risk of falling).
6. Rate of falls (falls per person-year).

We will include all trials reporting data on at least one of these efficacy outcomes. We selected fractures at any site as the primary outcome as we expect this outcome to be more frequently reported. Although sometimes less clinically significant, vertebral fractures were included due to their high prevalence and their negative consequences (eg, pain, loss of function, low health-related quality of life).[3 40 41] We will not restrict our analyses to fragility fractures for two reasons. First, based on prior systematic reviews, only a few RCTs report the trauma fracture level.[6] Second, a large prospective study on postmenopausal women recently showed that all fractures may increase the risk of future fractures regardless of the trauma level.[42]

Although fractures imply more direct clinical consequences, falls can also have serious consequences, such as injuries, healthcare use, morbidity and mortality.[1–3] In a comprehensive approach, we selected any fall as an outcome regardless of their clinical consequences. We decided to investigate the effect of vitamin D and/or calcium both on risk of falling and rate of falls. Although the risk of falling can be used along absolute fall risk to help inform shared decision-making with patients, this measure can lead to loss of information, for example, when a small number of participants sustain multiple falls.[43]

We will not include data on any intermediate outcomes (eg, bone mineral density, biochemical markers, parameters of muscle function) as data on fractures and falls are sufficient to establish the musculoskeletal benefits of vitamin D and/or calcium.

Data sources and search strategy

The search strategy aims to identify studies regardless of language or publication status. The strategy will follow a two-step approach, as many systematic reviews have already been published.[6] First, we will search Medline and Embase (from 2014 until 1 January 2024) to identify published systematic reviews of RCTs evaluating the effects of calcium alone, vitamin D alone or vitamin D combined with calcium on fractures or falls. We will use the Canadian Agency for Drugs and Technologies in Health (CADTH) filter for systematic reviews. Second, we will search Medline, Embase and CENTRAL (from 2017 until 1 January 2024) using the CADTH filter for RCTs to identify new trials not captured by the included systematic reviews. We chose to perform this second search as the most comprehensive systematic reviews searched the literature until 2017–2018.[26 44–46] We will manually search abstracts from scientific meetings published in the last 3 years from the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and in major osteoporosis journals (*Bone*, *Journal of Bone and Mineral Research*, *Osteoporosis International*, *Calcified Tissue International* and *Archives of Osteoporosis*). Unpublished and ongoing trials will be sought through the International Clinical Trials Registry Platform and Clinicaltrials.gov. We will also manually search the reference lists of included trials to identify potentially eligible trials. The full search strategy is available in online supplemental appendix 2. We adapted the search strategies from previous Cochrane reviews and revised the final search strategy with a healthcare librarian.[46–48]

Study selection

Two reviewers (from all authors) will independently and in duplicate complete title, abstract and full-text screening for eligibility assessment of systematic reviews and RCTs. Disagreements will be resolved through consensus and discussion with a third reviewer (DW and ND) when needed. Systematic reviews will be included if they report results from at least one RCT with fracture or fall data. Once we include all pertinent systematic reviews, we will screen citations from the RCT search and the included systematic reviews. When necessary, we will contact trial authors for additional

information to assess the eligibility. Following the literature search, we will use EndNote (version X7.5.3 Thomson Reuters, New York) and Covidence software (Veritas Health Innovation, Melbourne) to manage and screen the citations.

Data extraction and management

Two reviewers (from all authors) will independently and in duplicate extract data from all included trials. Disagreements will be resolved through consensus and discussion with a third reviewer (DW and ND) when needed. We will use a data extraction form developed by one author (OM), pretested with three potentially eligible trials by three authors (OM, DW and KD) and improved with the comments from all authors.[29 32 49] The data extracted will include publication details, trial and participant characteristics, and details on interventions, controls, co-interventions and outcomes. The complete list of variables sought can be found in online supplemental appendix 3. We will capture all outcomes at the longest follow-up available. For the proportion of participants with one or more fractures at any site, hip fractures, non-vertebral fractures, vertebral fractures and falls, we will extract the sum of the events and sample size across arms. For the rate of falls, we will preferably extract the unadjusted rate ratio (RaR) with 95% CIs or adjusted RaR if the unadjusted one is unavailable (except if the adjustment is provided for cluster RCTs). If the rate of falls is unavailable, we will extract the number of falls in each group and the corresponding number of patient-years of follow-up to calculate an RaR. If the number of patient-years is unavailable, we will calculate this data with the number of participants across arms and the mean length of follow-up.

When a trial reports fracture data using different reporting sources, we will prioritise fracture source in this order: confirmed by radiography, through medical or clinical review, through clinicians, through insurance claims or self-reported. If data on fractures at any site are not provided, we will use the largest number of participants with non-vertebral or osteoporotic fractures (defined as a fracture due to a fall from no more than standing height). If data on vertebral fractures are not provided, we will consider clinical vertebral fractures as vertebral fractures. If data on any falls are not provided, we will preferably use data (in this order) on injurious falls, falls resulting in a healthcare visit or falls requiring hospitalisation. We will contact trial authors for clarification on missing or unclear data whenever necessary. If we are unable to obtain unpublished data through personal communications and these data are provided in another systematic review, we will perform data extraction from this review.

Assessment of risk of bias

Two reviewers (from all authors) will independently and in duplicate perform risk-of-bias assessment. Disagreements will be resolved through consensus and discussion with a third reviewer (DW) when needed. As recommended by the Cochrane Handbook, we will use the updated version of the Cochrane risk-of-bias tool (RoB 2) which assesses the randomisation process, adherence to interventions, missing outcome data, outcome measurements and selection of results.[37] The Revised Cochrane risk-of-bias tool for cluster RCTs (RoB2 CRT), which also assesses the timing of identification or recruitment of participants, will be used for cluster RCTs. We will perform the risk-of-bias assessment on fracture at any site or, if not sought, on a secondary outcome. Each domain will be evaluated as having low risk of bias, raising some concerns or having high risk of bias. Based on the assessment for each domain, we will propose an overall risk of bias assessment (low risk, some concerns or high risk).

Statistical analysis

We will categorise trials into three groups: (a) calcium alone versus placebo or no treatment; (b) vitamin D alone versus placebo or no treatment; (c) vitamin D combined with calcium versus placebo or no treatment. For the proportion of participants with one or more fractures at any site, hip fractures, non-vertebral fractures, vertebral fractures and falls, we will conduct a meta-analysis to estimate treatment effects as risk ratios (RR) with 95% CIs. For the rate of falls, we will conduct a meta-analysis to estimate treatment effects as RaR with 95% CIs. For multiple vitamin D and/or calcium arms included in a trial, we will pool the different treatment groups. All analyses will be performed on an intention-to-treat basis using Review Manager software (RevMan 5.3, Nordic Cochrane Centre, Cochrane Collaboration). For cluster RCTs, we will adjust extracted values according to the method described in the Cochrane Handbook to include their results in the meta-analysis.[37] Due to the high probability of heterogeneity in participants and interventions, we will use random-effects methods. We are aware that our meta-analysis will probably include trials with at least one arm with zero event, thus potentially affecting the validity of this meta-analytic model.[37] However, as we expect to include a very large number of trials, we consider this risk of bias to be low. Statistical heterogeneity will be investigated through visual inspection of the forest plots and the I^2 statistics. The I^2 values will be interpreted as follows: 0%–40% might not be important heterogeneity; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity; 75%–100% may represent considerable heterogeneity.[37] If an analysis contains more than 10 trials for any outcome, we will explore publication bias with funnel plots and Begg's and Egger's tests. Asymmetry on the funnel plot or a p value of <0.05 will indicate possible bias.

Subgroup analyses

The subgroup analysis plan is available in online supplemental appendix 4. The main subgroup analysis will compare trials with high-risk population versus low-risk population. High-risk population is defined as a mean age of 80 years and older, living in institutions, having a

fracture or fall history and having a diagnosis of osteoporosis or a baseline 25OHD level of<25 nmol/L. To explore potential heterogeneity and subgroup interactions, we will conduct other subgroup analyses according to age of participants (≥ 65 years vs <65 years and ≥80 years vs <80 years), sex (women-only vs both sex or men trials), type of residence (institutionalised vs community dwelling), fracture history (previous vs no previous fracture), fall history (previous vs no previous fall), osteoporosis diagnosis (with vs without a diagnosis), baseline vitamin D deficiency (25OHD level <25 vs ≥ 25 nmol/L) or insufficiency (< 50 vs ≥ 50 nmol/L), baseline dietary calcium intake (< 800 mg vs ≥ 800 mg), type of vitamin D (vitamin D2 vs D3), frequency of administration of vitamin D (daily to monthly administration vs intermittent bolus), mean chronic daily dose of vitamin D excluding trials with intermittent bolus (< 1000 vs 1000–2000 vs >2000 units/day), trial size (< 1000 vs ≥ 1000 participants) and mean follow-up (≤ 1 vs > 1 year). We will conduct the main subgroup analysis for all interventions and comparisons, but we will only conduct the other subgroup analyses if at least 10 trials are included for an intervention and outcome. We will use a random-effects method to pool data in all subgroup analyses.[37] We will perform the interaction tests between subgroups available in RevMan 5.3 and report the p value for interaction (with p <0.05 considered significant).

Sensitivity analysis

Robustness of our findings will be assessed through these variables :

1. The choice of the statistical model (in conducting fixed-effects analysis).
2. The risk of bias of the trials (in excluding trials at high risk of bias).
3. The effect of each individual study (in using the leave-one-out method).
4. The inclusion of trials potentially without enough statistical power (not reporting at least 1000 patient-years of follow-up) (in excluding these trials).
5. The inclusion of trials accepting non-trial supplements of vitamin D and/or calcium or not giving clear instructions about non-trial supplements (in excluding these trials).

GRADE assessment

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to appraise the certainty of evidence of all findings.[50] This approach systematically explores risk of bias, indirectness, heterogeneity, imprecision and publication bias to provide the extent to which the estimates of effect are close to the true estimates. We will grade the evidence as 'very low', ''low'', 'moderate' or 'high' in accordance with the GRADE handbook. Two authors (OM and DW) will independently and in duplicate conduct the GRADE assessment. Disagreements will be resolved through consensus and discussion with a third reviewer (ND) when needed. The GRADE assessment will also be presented to all authors for final approval. The results will be synthesised in three 'Summary of findings' tables. We will present the findings using a standardised description based on the GRADE guidelines.[51] Baseline risks will be expressed for the overall population or according to the main subgroup analysis (low-risk or high-risk population), depending on the number of included trials and the presence of a difference in baseline risks. If the test for interaction between high-risk and low-risk populations is significant, we will consider using the relative effect of each subgroup to present the findings. We expect to use the treatment effect of the main statistical analysis in our GRADE assessment in most cases.

ETHICS AND DISSEMINATION

This systematic review does not require research ethics approval. The results will be disseminated in peer-reviewed journals and help inform clinicians, guidelines and regulatory agencies.

Contributors Conceptualisation: OM. Design and methodology: All authors. Developed the search strategy: OM and DW. Design data extraction: All authors. Pilot data extraction: OM, DW and KD. Drafting the manuscript: OM. Critical revision of the manuscript: All authors. All authors reviewed the content of the protocol and approved the final version. Guarantor of the review: OM.

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ORCID iDs

Olivier Massé http://orcid.org/0009-0004-1764-4520
David Williamson http://orcid.org/0000-0003-3360-4831

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