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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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Abstract

Introduction: The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal functions has long been documented. However, review investigations on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents are scarce. The aim of current study was to assess the impact of various doses of vitamin D supplementation on serum 25-hydroxyvitamin D concentrations in children and adolescents, and to identify relevant determinants of variations in the effect of vitamin D supplementation.

Methods: PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to the 27-Sep-2017 will systematically be searched for randomized controlled trials of vitamin D supplementation compared with placebo, no intervention control, or comparative arm investigations. One reviewer will assess articles for eligibility according to prespecified selection criteria, after which data extraction and quality appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed using Jadad scales. Meta-analyses will be conducted where appropriate. We will express continuous measures (i.e serum 25-hydroxyvitamin D concentration) as mean differences (MDs) with 95% CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test on N-1 degrees of freedom, with a significance level of α=0.1. We will also assess the individual study and subgroup characteristics and perform a sensitivity analysis. Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

Trial registration number: PROSPERO CRD42017067179.

Keywords: Vitamin D; 25-hydroxyvitamin D; children; adolescents; meta-analysis

Strengths and limitations of this study

- This systematic review will comprehensively assess the effectiveness and safety of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations.
- The study screening, data extraction and quality assessment will be fulfilled by two independent reviewers.
- Some variables including sex, 25-hydroxy vitamin D baseline level, length of intervention, frequency of intervention, doses of vitamin D supplementation may cause considerable heterogeneity in this review.
- Studies may not systematically report all outcomes.
- The systematic review will include only published data.

Introduction

The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal functions has long been clarified. Currently, vitamin D deficiency is a global problem, and a recent systematic review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-hydroxyvitamin D [1]. Since childhood and adolescence life cycles increase vitamin requirements for the growth of muscle and bone, vitamin D deficiency is also significantly observed during this period. Low vitamin D status has recently been reported in children and adolescents across countries of the Middle East such as Iran [2, 3], Saudi Arabia [4], Jordan [5], and United Arab Emirates [6], as well as in South East Asia [7, 8], Europe [9], and the Unites States [10]. Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made for evaluating the influence of variable doses of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents [11], a factor crucial for stipulating dietary recommendations. Based on recommendations of the Institute of Medicine (IOM) in 2011, the recommended dietary allowance (RDA) is 600 IU for 9-18-year old children and adolescents [12], whereas based on recommendations of the Endocrine Society, 9-18-year old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000 IU of vitamin D is essential to maintain levels of 25-hydroxyvitamin D > 30 ng/ml [13]; this controversy may be explained by the fact that IOM recommendations are based on acieving the target level of ≥20 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on achieving ≥30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for adolescents at risk of vitamin D deficiency such as obesity [14], emphasizing the differences in recommendations of these two scientific societies.

Serum level of 25-hydroxyvitamin D is a commonly used marker of the long-term vitamin D nutritional status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the cultural beliefs of individuals. Supplementation of vitamin D and dietary intake of limited foods also increase 25-hydroxyvitamin D concentrations. Previous studies in adults showed that baseline 25-hydroxyvitamin D, concurrent calcium intakes, and the level of overweight and obesity are among other factors which may affect 25-hydroxyvitamin D in response to vitamin D supplementation [15]. Studies have shown a direct association of increase in body mass index (BMI) with decrease in both 25-hydroxyvitamin D and 1,25-hydroxyvitamin D and increase in parathyroid hormone [16-18]. A stronger correlation between the fat mass and concentration of 25-hydroxyvitamin D has also been reported due to reduction in calcium and vitamin D intake, bioavailability and subcutaneous synthesis of vitamin D, and activation of 25-hydroxyvitamin D, increase in vitamin D catabolism or 25-hydroxy vitamin D sequestration in fat tissue [19, 20]. A systematic review in adults found that the average increase in serum 25-hydroxyvitamin D concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [21]. Recently a review study from the Middle East and North Africa (MENA) region showed that intakes of intermediate vitamin D dose of 1000–2000 IU daily may be necessary to faciliate for achievement of optimal 25-hydroxyvitamin D level of 20 ng/ml in children and adolescents [11].

To the best of our knowledge, to date, no systematic review has been conducted on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents worldwide. In previous original studies also the optimum level of 25-hydroxyvitamin D had not been determined [22-24], and because of lower power, the graded response to vitamin D supplementation could not be explored. This review will therefore aim at determining the

effectiveness of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations and assessing the graded response to vitamin D supplementation.

Methods

Objectives

• To assess the effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents.

• To determine the effectiveness of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations.

• To determine if the effect of vitamin D supplementation on serum 25-hydroxyvitamin D varies by baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.

Types of studies

We will include randomized controlled trials of vitamin D supplementation compared with placebo, no intervention control, or comparative arm studies, which examine the response to different doses of vitamin D supplementation (with or without a placebo arm), irrespective of their endpoint of interest, but they must have reported 25-hydroxyvitamin D level at baseline and at the end of the study.

Types of participants

Healthy children and adolescents (aged ≤18 years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases that have no reason to have altered vitamin D metabolism.

Exclusion criteria:

a) Rickets in children characterized by low 25(OH)D, below 15 ng/ml with radiologic or laboratory evidence requires higher doses of vitamin D supplementation (higher than those recommended for the general population).

b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or below 30 ml/min), liver disease, heart failure (NYHA class 3 or more)

c) Individuals with conditions or on drug therapy that might affect vitamin D metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption, bypass surgery)

Types of intervention

Inclusion criteria:

Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with or without calcium supplementation

Exclusion criteria:

a) Studies that used active vitamin D supplementation as this type of supplementation is not recommended for the general population.

b) Studies that used vitamin D supplementation given intra muscularly

c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin cannot be defined accurately

Search methods for identification of studies

Electronic searches

We will perform a systematic search of published randomized trials on vitamin D intervention in subjects aged ≤18 years old in PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017 using eligible keywords in titles or abstracts (for details on search strategies see Supplementary File 1), using the following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or calcitriol] and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or controlled trial]. Inclusion criteria will be the ≤ 18 years (children and adolescents) age group. The first search will be done without language restrictions using various combinations of relevant keywords. If any excess relevant keywords are identified during any of the electronic or other searches, search strategies will be modified to incorporate these terms and document the changes; we will also perform a complete updated search on all databases available and identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our review.

Searching other resources

To complete the data bank, we will try to detect other potentially relevant studies with a clinical trial design by examining the reference list of the extracted articles in review articles.

Data collection and analysis

Selection of studies

Two review authors (G.A., H.F.) will independently determine studies that should be evaluated further by scanning the abstract, title, or both, of every study retrieved based on inclusion/exclusion criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement through consensus or consultation with a third review author for resolving differences and reaching concensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study selection [25].

Data extraction and management

Two review authors (G.A., H.F.) will independently extract data based on inclusion and exclusion criteria including the method used (randomized clinical trial vs. other studies), and participant and intervention characteristics as described above. In first step the review authors will select articles via keywords or search reference lists of relevant studies, and in the second, full texts of selected articles will be retrieved and screened using inclusion and exclusion criteria. Finally, in third step, we will extract the relevant data from the articles selected in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or consultation with a third review author for resolving differences (F.H.).

Dealing with duplicate and companion publications

In case of duplicate papers or multiple publications of a primary study, we will enhance yield of information by collating all available data and use the most complete dataset aggregated across all known publications.

Quality of assessment

The quality of each included study will be assessed independently by two review authors (G.A., H.F.). We will assess the quality assessment, focusing on the following criteria: Randomization, allocation concealment, blinding of personnel and of participants, incomplete outcome data, selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve disagreements in quality assessments by consensus, or by consultation with a third review author (F.H.).

Data synthesis

We will present data of all included studies and provide a description of results, including population studies, interventions, and outcome in details in both summary tables and the text. Also, a meta-analysis using fixed- or random-effects modeling will be conducted to summarize weigthed mean differences and 95% CI in 25-OH-D from baseline to follow-up during the supplementation [27, 28]. We first perform graphical exploration of variability of changes in 25-hydroxyvitamin D levels due to vitamin D doses. A potential nonlinear or linear dose-response relationship between vitamin D supplementation and serum 25-hydroxyvitamin D concentration will be modelled by using restricted cubic splines. We will fit meta-regression models for prediction of linear change in 25-hydroxyvitamin D concentration. We will complete statistical analyses based on the statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions [29].

If we are faced with any missing data in some studies in the process of analysis and data extraction and if we have proper evidence that indicate the randomness of these missing data, we will use data from existence data analysis, otherwise we will obtain the missing data from the study authors if possible; an alternate method where the value of some indices, including mean

or standard deviation are not reported for outcomes is to impute these values by assuming the mean, standard deviation of the missing data to be the average of the mean or standard deviation of data from those studies where this information was given. To investigate the impact of imputation on meta-analyses, we will use sensitivity analysis.

Assessment of heterogeneity

Any clinical, methodological or statistical heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test on N-1 degrees of freedom (df), with significance level of $\alpha = 0.1$. If the power of this test is low, we will also calculate heterogeneity by I^2, a transformation of the square root of the Chi^2 test divided by its df [30]. If the values of I^2 is high we will have greater heterogeneity [31]; should there be heterogeneity in our investigation, we will assess the individual study and subgroup characteristics and perform a sensitivity analyses to clarify the reasons of this heterogeneity [32].

Assessment of publication biases

Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33, 34]. We will only test for funnel plot asymmetry if the review has included over 10 studies that assess a specific outcome.

Subgroup analysis

After the final search and screening, if a sufficient number of studies are available, we will perform subgroup analyses and investigate interactions based on the following: Characteristics of participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level, puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length

of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of studies.

Sensitivity analysis

We will carry out sensitivity analyses because of the exploring the influence of following factors on effect sizes and validity of the estimations:

1. Investigation of the impact of quality assessment on the results
2. An analysis of the influence of various characteristics of studies using the following filters, including duration of intervention, sex, language of publication, country, and dose of administration
3. An assessment of the effect of different variance imputations.

Discussion

The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal functions has long been understood. However, to date, no systematic review has been conducted on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents worldwide. The findings of this review will provide the existing evidence regarding the effectiveness of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations. Our research will also provide guidance to general practitioners, nutritionist, and researchers on the skeletal and extra-skeletal outcomes and the long term safety of supplementation of various doses of vitamin D in this age group.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

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Provenance and peer review: Not commissioned; externally peer reviewed.

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PubMed (n=549)

(vitamin D[tiab] OR ergocalciferol[tiab] OR vitamin D2[tiab] OR cholecalciferol[tiab] OR vitamin D3[tiab] OR "ergocalciferols"[MeSH Terms] OR "cholecalciferol"[MeSH Terms]) AND (("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR controlled trial[all fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "intervention study"[All Fields])) AND ("25-hydroxyvitamin D"[tiab] OR "25-hydroxy vitamin D"[tiab] OR hydroxyvitamin D[tiab] OR "25-hydroxyvitamin D2"[tiab] OR "25-hydroxy vitamin D2"[tiab] OR "hydroxyvitamin D2"[tiab] OR "25-hydroxyvitamin D3"[tiab] OR "25-hydroxy vitamin D3"[tiab] OR "hydroxyvitamin D3"[tiab] OR "25OHD"[tiab] OR "25OHD2"[tiab] OR "25OHD3"[tiab] OR "25OH D"[tiab] OR "25OH D3"[tiab] OR "25(OH)D"[tiab] OR "25(OH)D2"[tiab] OR "25(OH)D3"[tiab] OR "25(OH) vitamin D"[tiab] OR "25(OH) vitamin D2"[tiab] OR "25(OH) vitamin D3"[tiab] OR "25OH vitamin D"[tiab] OR "25OH vitamin D3"[tiab] OR 25-hydroxycalciferol[tiab] OR hydroxycholecalciferol[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "25-OH cholecalciferol"[tiab] OR "25OH cholecalciferol"[tiab] OR "25-hydroxy cholecalciferol"[tiab] OR hydroxyergocalciferol[tiab] OR "25- hydroxyergocalciferol"[tiab] OR "25-hydroxy ergocalciferol"[tiab] OR calcitriol[tiab] OR calcidiol[tiab])

Limited by filter in the site to: Age birth to 18 years

Scopus (n=3303)

(TITLE-ABS (“vitamin D”) OR TITLE-ABS (ergocalciferol) OR TITLE-ABS (cholecaciferol) OR TITLE-ABS (“vitamin D2”) OR TITLE-ABS (“vitamin D3”)) AND (TITLE-ABS (“25-hydroxyvitamin D”) OR TITLE-ABS (“25-hydroxy vitamin D”) OR TITLE-ABS (“hydroxyvitamin D”) OR TITLE-ABS (“25-hydroxyvitamin D2”) OR TITLE-ABS (“25-hydroxy vitamin D2”) OR TITLE-ABS (“hydroxyvitamin D2”) OR TITLE-ABS (“25-hydroxyvitamin D3”) OR TITLE-ABS (“25-hydroxy vitamin D3”) OR TITLE-ABS (“hydroxyvitamin D3”) OR TITLE-ABS(25OHD) OR TITLE-ABS(25OHD2) OR TITLE-ABS(25OHD3) OR TITLE-ABS(“25-OH-D”) OR TITLE-ABS(“25-OH-D2”) OR TITLE-ABS(“25-OH-D3”) OR TITLE-ABS (“25(OH)D”) OR TITLE-ABS (“25(OH)D2”) OR TITLE-ABS (“25(OH)D3”) OR TITLE-ABS (“25-OH-vitamin D”) OR TITLE-ABS (“25-OH-vitamin D2”) OR TITLE-ABS (“25-OH-vitamin D3”) OR TITLE-ABS (hydroxycholecalciferol) OR TITLE-ABS (hydroxyergocalciferol) OR TITLE-ABS (calcitriol) OR TITLE-ABS (calcidiol)) AND (ALL (“clinical trial”) OR ALL (“controlled trial”))

Limited by the filter in the site: exclusion Adults

ISI Web of Science (n=320)

(TS="vitamin D" OR TS=ergocalciferol OR TS="vitamin D2" OR TS=cholecalciferol OR TS="vitamin D3") AND (TS="25-hydroxyvitamin D" OR TS="25-hydroxy vitamin D" OR TS= "hydroxyvitamin D" OR TS= "25-hydroxyvitamin D2" OR TS= "25-hydroxy vitamin D2" OR TS= "hydroxyvitamin D2" OR TS= "25-hydroxyvitamin D3" OR TS= "25-hydroxy vitamin D3" OR TS= "hydroxyvitamin D3" OR TS=25OHD OR TS= 25OHD2 OR TS= 25OHD3 OR TS= "25(OH)D" OR TS= "25(OH)D2" OR TS= "25(OH)D3" OR TS= "25OH D" OR TS= "25OH D2" OR TS= "25OH D3" OR TS= "25-OH-vitamin D" OR TS= "25-OH-vitamin D2" OR TS= "25-OH-vitamin D3" OR TS=hydroxycholecalciferol OR TS=hydroxyergocalciferol OR TS= calcitriol OR TS= calcidiol) AND (TS= "clinical trial" OR TS= "controlled trial") AND (TS=child* OR TS=adolesc*)

Cochrane Central Register of Controlled Trials (CENTRAL) (n=552)

("vitamin D":ti,ab,kw OR "ergocalciferol":ti,ab,kw OR "vitamin D-2":ti,ab,kw OR "vitamin D2":ti,ab,kw OR "cholecalciferol":ti,ab,kw O R"vitamin D-3":ti,ab,kw OR "vitamin D3":ti,ab,kw) AND

("25-hydroxyvitamin D":ti,ab,kw OR "25-hydroxy vitamin D":ti,ab,kw OR "hydroxyvitamin D":ti,ab,kw OR "25-hydroxyvitamin D2":ti,ab,kw OR "25-hydroxy vitamin D2":ti,ab,kw OR "25-hydroxyvitamin D3":ti,ab,kw OR "25-hydroxyvitamin D-3":ti,ab,kw OR "25-hydroxy vitamin D3":ti,ab,kw OR "hydroxyvitamin D3":ti,ab,kw OR "25OHD":ti,ab,kw OR "25OHD2":ti,ab,kw OR "25OHD3":ti,ab,kw OR "25OH D":ti,ab,kw OR "25OH D3":ti,ab,kw OR "25(OH)D":ti,ab,kw OR "25(OH)D2":ti,ab,kw OR "25(OH)D3":ti,ab,kw OR "25(OH) vitamin D":ti,ab,kw OR "25(OH) vitamin D2":ti,ab,kw OR "25(OH) vitamin D3":ti,ab,kw OR "25OH vitamin D":ti,ab,kw OR "25OH vitamin D3":ti,ab,kw OR "25-hydroxycalciferol":ti,ab,kw OR "hydroxycalciferol":ti,ab,kw OR "25-hydroxycholecalciferol":ti,ab,kw OR "hydroxycholecalciferol":ti,ab,kw OR "25-OH cholecalciferol":ti,ab,kw OR "25-hydroxy cholecalciferol":ti,ab,kw OR "hydroxyergocalciferol":ti,ab,kw OR "25- hydroxyergocalciferol":ti,ab,kw OR "calcitriol":ti,ab,kw OR "calcidiol":ti,ab,kw) AND

("Child":ti,ab,kw OR "adolescence":ti,ab,kw OR "adolescent":ti,ab,kw)

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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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Abstract

Introduction: The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been documented. However, review investigations on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents are scarce. The aim of current study was to assess the impact of various doses of vitamin D supplementation on serum 25(OH)D concentrations in children and adolescents, and to identify relevant determinants of variations in the effect of vitamin D supplementation.

Methods: PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to the 27-Sep-2017 will systematically be searched for randomized controlled trials of vitamin D supplementation. We considered articles with the following control groups as eligible: placebo control, control group without any supplementation, or a comparative arm investigation. Two reviewers will assess articles for eligibility according to pre-specified selection criteria, after which data extraction and quality appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed using Jadad scales. Meta-analyses will be conducted where appropriate. We will express continuous measures (i.e serum 25(OH)D concentration) as mean differences (MDs) with 95% CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test on N-1 degrees of freedom, with a significance level of α=0.1. We will also assess the individual study and subgroup characteristics and perform a sensitivity analysis. Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

Prospero registration number: PROSPERO CRD42017067179.

Keywords: Vitamin D; 25-hydroxyvitamin D; Children; Adolescents; Supplementation; Systematic review

Strengths and limitations of this study

- This systematic review will comprehensively assess the effectiveness and safety of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations.
- The study screening, data extraction and quality assessment will be fulfilled by two independent reviewers.
- Based on previous reviews dealing with vitamin D we expect considerable heterogeneity of our data that might be due to variables, including sex, 25(OH)D baseline level, length of intervention, frequency of intervention, doses of vitamin D supplementation.
- The systematic review will include only published data.

Introduction

The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been clarified [1]. Currently, vitamin D deficiency is a global problem, and a recent systematic review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-hydroxyvitamin D [2]. Since childhood and adolescence life cycles increase vitamin requirements for the growth of muscle and bone, vitamin D deficiency is also significantly observed during this period [3]. Low vitamin D status has recently been reported in children and adolescents across countries of the Middle East such as Iran [4, 5], Saudi Arabia [6], Jordan [7], and United Arab Emirates [8], as well as in South East Asia [9, 10], Europe [11], and the Unites States [12].

Serum level of 25(OH)D is a commonly used marker of the long-term vitamin D nutritional status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the cultural beliefs of individuals [3]. Dietary intake of limited foods such as fatty fish, egg yolk, cheese, and fortified foods with vitamin D and also supplementation of vitamin D may increase 25(OH)D concentrations [13, 14]. Previous studies in adults showed that baseline 25-hydroxyvitamin D, concurrent calcium intakes, and the level of overweight and obesity are among other factors which may affect 25(OH)D in response to vitamin D supplementation [15]. Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made for evaluating the influence of various doses of vitamin D supplementation on serum 25(OH)D levels in children and adolescents [16], a factor crucial for stipulating dietary recommendations. Based on recommendations of the Institute of Medicine (IOM) in 2011, the recommended dietary allowance (RDA) is 600 IU for 9-18-year old children

and adolescents [17], whereas based on recommendations of the Endocrine Society, 9-18-year old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000 IU of vitamin D is essential to maintain levels of 25(OH)D > 30 ng/ml [3]; this controversy may be explained by the fact that IOM recommendations are based on achieving the target level of ≥20 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on achieving ≥30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as obese ones [18], emphasizing the differences in recommendations of these two scientific societies.

Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin D, and parathyroid hormone levels [19-21]. A systematic review in adults found that the average increase in serum 25(OH)D concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [22]. Recently a review study from the Middle East and North Africa (MENA) region showed that intakes of intermediate vitamin D dose of 1000–2000 IU daily may be necessary to facilitate for achievement of 25(OH)D level of 20 ng/ml in children and adolescents [16].

To the best of our knowledge, to date, no systematic review has been conducted on the effect of vitamin D supplementation on serum 25(OH)D levels in children and adolescents worldwide. In previous original studies also the optimum level of 25(OH)D had not been determined [13, 23, 24], and because of lower power, the graded response to vitamin D supplementation could not be explored. This review will therefore aim at determining the effectiveness of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations and assessing the graded response to vitamin D supplementation. Secondly, we

aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.

Methods

Types of studies

We will include randomized controlled trials of vitamin D supplementation with placebo, no intervention control, or comparative arm studies. Comparative arm is an arm type in which a group of participants receives another dose of vitamin D, or fortified foods with vitamin D, or other micronutrients such as vitamin E during the clinical trial. Also, all of included studies must have reported 25(OH)D level at baseline and at the end of the study.

Types of participants

Healthy children and adolescents (aged ≤18 years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension, and etc.) that have no reason to have altered vitamin D metabolism.

Exclusion criteria:

a) Rickets in children characterized by low 25(OH)D , below 15 ng/ml with radiologic or laboratory evidence requires higher doses of vitamin D supplementation (higher than those recommended for the general population).

b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or below 30 ml/min), liver disease, heart failure (New York Heart Association class 3 or more)

c) Individuals with conditions or on drug therapy that might affect vitamin D metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption, bypass surgery)

Types of intervention

Inclusion criteria:

Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with or without calcium supplementation

Exclusion criteria:

a) Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of supplementation is not recommended for the general population.

b) Studies that used vitamin D supplementation given intra muscularly

c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin cannot be defined accurately

Search methods for identification of studies

Electronic searches

We will perform a systematic search of published randomized trials on vitamin D supplementation in subjects aged ≤18 years old in PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017 using eligible keywords in titles or abstracts (for details on search strategies see Supplementary File 1), using the following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or

calcitriol] and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or controlled trial]. Inclusion criteria will be the ≤ 18 years (children and adolescents) age group. The first search will be done without language restrictions using various combinations of relevant keywords. We will also perform a complete updated search on all databases available and identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our review.

Searching other resources

To complete the data bank, we will use snowballing techniques to complement the database searches by screening the reference lists of included articles for relevant studies.

Data collection and analysis

Selection of studies

Two authors (G.A., H.F.) will independently determine studies that should be evaluated further by scanning the title, abstract, or both, of every study retrieved based on inclusion/exclusion criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement through consensus or consultation with a third review author for resolving differences and reaching concensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study selection [25].

Data extraction and management

In the first step, two authors (G.A., H.F.) will independently select articles by title and abstract or search reference lists of relevant studies, and in the second, full texts of selected articles will be retrieved and screened using inclusion and exclusion criteria (study design, participants, and intervention). Finally, in the third step, we will extract the relevant data from the selected articles in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or consultation with a third author for resolving differences (F.H.).

Dealing with duplicate and companion publications

In case of duplicate papers or multiple publications of a primary study, we will enhance yield of information by collating all available data and use the most complete dataset aggregated across all known publications.

Quality of assessment

The quality of each included study will be assessed independently by two authors (G.A., H.F.). We will assess the quality assessment, focusing on the following criteria: Randomization, allocation concealment, blinding of personnel and of participants, incomplete outcome data, selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve disagreements in quality assessments by consensus, or by consultation with a third author (F.H.).

Data synthesis

We will present data of all included studies and provide a description of results, including study population, interventions, and outcome in details in both summary tables and the text. Also, a meta-analysis using fixed- or random-effects modeling will be conducted to summarize weigthed mean differences and 95% CI in 25(OH)D from baseline to follow-up during the

supplementation [27, 28]. We first perform graphical exploration of variability of changes in 25(OH)D levels due to vitamin D doses. A potential nonlinear or linear dose-response relationship between vitamin D supplementation and serum 25(OH)D concentration will be modelled by using restricted cubic splines. We will fit meta-regression models for prediction of linear change in 25(OH)D concentration. We will complete statistical analyses based on the statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions [29].

If we are faced with any missing data in some studies in the process of analysis and data extraction and if we have proper evidence that indicate the randomness of these missing data, we will use data from existence data analysis, otherwise we will obtain the missing data from the study authors if possible; an alternate method where the value of some indices, including mean or standard deviation are not reported for outcomes is to impute these values by assuming the mean, standard deviation of the missing data to be the average of the mean or standard deviation of data from those studies where this information was given. To investigate the impact of imputation on meta-analyses, we will use sensitivity analysis.

Assessment of heterogeneity

Any clinical, methodological or statistical heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test on N-1 degrees of freedom (df), with significance level of $\alpha = 0.1$. If the power of this test is low, we will also calculate heterogeneity by I^2, a transformation of the square root of the Chi^2 test divided by its df [30]. If the values of I^2 is high we will have greater heterogeneity [31]; should there be heterogeneity in our

investigation, we will assess the individual study and subgroup characteristics and perform a sensitivity analyses to clarify the reasons of this heterogeneity [32].

Assessment of publication biases

Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33, 34]. We will only test for funnel plot asymmetry if the review has included over 10 studies that assess a specific outcome.

Subgroup analysis

After the final search and screening, if a sufficient number of studies are available, we will perform subgroup analyses and investigate interactions based on the following: Characteristics of participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level, puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of studies.

Sensitivity analysis

We will carry out sensitivity analyses because of the exploring the influence of following factors on effect sizes and validity of the estimations:

1. Investigation of the impact of quality assessment on the results
2. An analysis of the influence of various characteristics of studies using the following filters, including duration of intervention, sex, language of publication, country, and dose of administration
3. An assessment of the effect of different variance imputations.

Patient and public involvement

Patients and/or public are not involved in this study.

Summary statement

The findings of this review will provide the existing evidence regarding the effectiveness of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations. Our research will also provide guidance to general practitioners, nutritionist, and researchers on the skeletal and extra-skeletal outcomes and the long term safety of supplementation of various doses of vitamin D in this age group.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

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Contributors: GA had the original idea of this work. GA, HF, and FH designed and conceived the protocol. NM designed the search strategies. PM proposed some important advice for the study design and revision PM and FA aided in developing the research questions. All authors critically revised the draft of the manuscript and approved its final version. GA and HF are the guarantors of the review.

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Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Last Updated September 27, 2017 (n=4019)

PubMed (n=549)

(vitamin D[tiab] OR ergocalciferol[tiab] OR vitamin D2[tiab] OR cholecalciferol[tiab] OR vitamin D3[tiab] OR "ergocalciferols"[MeSH Terms] OR "cholecalciferol"[MeSH Terms]) AND (("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR controlled trial[all fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "intervention study"[All Fields])) AND ("25-hydroxyvitamin D"[tiab] OR "25-hydroxy vitamin D"[tiab] OR hydroxyvitamin D[tiab] OR "25-hydroxyvitamin D2"[tiab] OR "25-hydroxy vitamin D2"[tiab] OR "hydroxyvitamin D2"[tiab] OR "25-hydroxyvitamin D3"[tiab] OR "25-hydroxy vitamin D3"[tiab] OR "hydroxyvitamin D3"[tiab] OR "25OHD"[tiab] OR "25OHD2"[tiab] OR "25OHD3"[tiab] OR "25OH D"[tiab] OR "25OH D3"[tiab] OR "25(OH)D"[tiab] OR "25(OH)D2"[tiab] OR "25(OH)D3"[tiab] OR "25(OH) vitamin D"[tiab] OR "25(OH) vitamin D2"[tiab] OR "25(OH) vitamin D3"[tiab] OR "25OH vitamin D"[tiab] OR "25OH vitamin D3"[tiab] OR 25-hydroxycalciferol[tiab] OR hydroxycholecalciferol[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "25-OH cholecalciferol"[tiab] OR "25OH cholecalciferol"[tiab] OR "25-hydroxy cholecalciferol"[tiab] OR hydroxyergocalciferol[tiab] OR "25- hydroxyergocalciferol"[tiab] OR "25-hydroxy ergocalciferol"[tiab] OR calcitriol[tiab] OR calcidiol[tiab])

Limited by filter in the site to: Age birth to 18 years

Scopus (n=3303)

(TITLE-ABS (“vitamin D”) OR TITLE-ABS (ergocalciferol) OR TITLE-ABS (cholecaciferol) OR TITLE-ABS (“vitamin D2”) OR TITLE-ABS (“vitamin D3”)) AND (TITLE-ABS (“25-hydroxyvitamin D”) OR TITLE-ABS (“25-hydroxy vitamin D”) OR TITLE-ABS (“hydroxyvitamin D”) OR TITLE-ABS (“25-hydroxyvitamin D2”) OR TITLE-ABS (“25-hydroxy vitamin D2”) OR TITLE-ABS (“hydroxyvitamin D2”) OR TITLE-ABS (“25-hydroxyvitamin D3”) OR TITLE-ABS (“25-hydroxy vitamin D3”) OR TITLE-ABS (“hydroxyvitamin D3”) OR TITLE-ABS(25OHD) OR TITLE-ABS(25OHD2) OR TITLE-ABS(25OHD3) OR TITLE-ABS(“25-OH-D”) OR TITLE-ABS(“25-OH-D2”) OR TITLE-ABS(“25-OH-D3”) OR TITLE-ABS (“25(OH)D”) OR TITLE-ABS (“25(OH)D2”) OR TITLE-ABS (“25(OH)D3”) OR TITLE-ABS (“25-OH-vitamin D”) OR TITLE-ABS (“25-OH-vitamin D2”) OR TITLE-ABS (“25-OH-vitamin D3”) OR TITLE-ABS (hydroxycholecalciferol) OR TITLE-ABS (hydroxyergocalciferol) OR TITLE-ABS (calcitriol) OR TITLE-ABS (calcidiol)) AND (ALL (“clinical trial”) OR ALL (“controlled trial”))

Limited by the filter in the site: exclusion Adults

ISI Web of Science (n=320)

(TS="vitamin D" OR TS=ergocalciferol OR TS="vitamin D2" OR TS=cholecalciferol OR TS="vitamin D3") AND (TS="25-hydroxyvitamin D" OR TS="25-hydroxy vitamin D" OR TS= "hydroxyvitamin D" OR TS= "25-hydroxyvitamin D2" OR TS= "25-hydroxy vitamin D2" OR TS= "hydroxyvitamin D2" OR TS= "25-hydroxyvitamin D3" OR TS= "25-hydroxy vitamin D3" OR TS= "hydroxyvitamin D3" OR TS=25OHD OR TS= 25OHD2 OR TS= 25OHD3 OR TS= "25(OH)D" OR TS= "25(OH)D2" OR TS= "25(OH)D3" OR TS= "25OH D" OR TS= "25OH D2" OR TS= "25OH D3" OR TS= "25-OH-vitamin D" OR TS= "25-OH-vitamin D2" OR TS= "25-OH-vitamin D3" OR TS=hydroxycholecalciferol OR TS=hydroxyergocalciferol OR TS= calcitriol OR TS= calcidiol) AND (TS= "clinical trial" OR TS= "controlled trial") AND (TS=child* OR TS=adolesc*)

Cochrane Central Register of Controlled Trials (CENTRAL) (n=552)

("vitamin D":ti,ab,kw OR "ergocalciferol":ti,ab,kw OR "vitamin D-2":ti,ab,kw OR "vitamin D2":ti,ab,kw OR "cholecalciferol":ti,ab,kw O R"vitamin D-3":ti,ab,kw OR "vitamin D3":ti,ab,kw) AND

("25-hydroxyvitamin D":ti,ab,kw OR "25-hydroxy vitamin D":ti,ab,kw OR "hydroxyvitamin D":ti,ab,kw OR "25-hydroxyvitamin D2":ti,ab,kw OR "25-hydroxy vitamin D2":ti,ab,kw OR "25-hydroxyvitamin D3":ti,ab,kw OR "25-hydroxyvitamin D-3":ti,ab,kw OR "25-hydroxy vitamin D3":ti,ab,kw OR "hydroxyvitamin D3":ti,ab,kw OR "25OHD":ti,ab,kw OR "25OHD2":ti,ab,kw OR "25OHD3":ti,ab,kw OR "25OH D":ti,ab,kw OR "25OH D3":ti,ab,kw OR "25(OH)D":ti,ab,kw OR "25(OH)D2":ti,ab,kw OR "25(OH)D3":ti,ab,kw OR "25(OH) vitamin D":ti,ab,kw OR "25(OH) vitamin D2":ti,ab,kw OR "25(OH) vitamin D3":ti,ab,kw OR "25OH vitamin D":ti,ab,kw OR "25OH vitamin D3":ti,ab,kw OR "25-hydroxycalciferol":ti,ab,kw OR "hydroxycalciferol":ti,ab,kw OR "25-hydroxycholecalciferol":ti,ab,kw OR "hydroxycholecalciferol":ti,ab,kw OR "25-OH cholecalciferol":ti,ab,kw OR "25-hydroxy cholecalciferol":ti,ab,kw OR "hydroxyergocalciferol":ti,ab,kw OR "25- hydroxyergocalciferol":ti,ab,kw OR "calcitriol":ti,ab,kw OR "calcidiol":ti,ab,kw) AND

("Child":ti,ab,kw OR "adolescence":ti,ab,kw OR "adolescent":ti,ab,kw)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line/page numbers
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3, line 24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 13, lines 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 13, lines 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 6, lines 52-74
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pages 6-7, lines 79-83
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 7-8, lines 85-113
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 8, lines 116-119
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pages 8-9, lines 116-130
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 10, lines 141-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 10, lines 141-146
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 10, lines 141-146
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 10-11, lines 158-162
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7, lines 89-90
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 10, lines 152-156
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pages 10-11, lines 158-176
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pages 11-12, lines 178-184
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 12, lines 189-203
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12, lines 186-188
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10, lines 152-156

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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Abstract

Introduction: The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been documented. However, review investigations on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D (25(OH)D) levels in children and adolescents are scarce. The aim of current study was to assess the impact of various doses of vitamin D supplementation on serum 25(OH)D concentrations in children and adolescents, and to identify relevant determinants of variations in the effect of vitamin D supplementation.

Methods: PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to the 27-Sep-2017 will systematically be searched for randomized controlled trials of vitamin D supplementation. We considered articles with the following control groups as eligible: Placebo control, control group without any supplementation, or a comparative arm investigation. Two reviewers will assess articles for eligibility according to pre-specified selection criteria, after which data extraction and quality appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed using Jadad scales. Meta-analyses will be conducted where appropriate. We will express continuous measures (i.e serum 25(OH)D concentration) as mean differences (MDs) with 95% CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test on N-1 degrees of freedom, with a significance level of α=0.1. We will also assess the individual study and subgroup characteristics and perform a sensitivity analysis. Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

Ethics and dissemination: Ethics approval is not required because the work will be carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

Prospero registration number: PROSPERO CRD42017067179.

Keywords: Vitamin D; 25-hydroxyvitamin D; Children; Adolescents; Supplementation; Systematic review

Strengths and limitations of this study

- This systematic review will comprehensively assess the effectiveness and safety of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations.
- The study screening, data extraction and quality assessment will be fulfilled by two independent reviewers.
- Based on previous reviews dealing with vitamin D, we expect considerable heterogeneity of our data, which might be due to variables, including sex, 25(OH)D baseline level, length of intervention, frequency of intervention, doses of vitamin D supplementation.
- The systematic review will include only published data.

Introduction

The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been clarified [1]. Currently, vitamin D deficiency is a global problem, and a recent systematic review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-hydroxyvitamin D (25(OH)D) [2]. Since during childhood and adolescence, vitamin D requirements increase for the growth of muscle and bone, vitamin D deficiency is often observed during this period [3]. Low vitamin D status has recently been reported in children and adolescents across countries of the Middle East such as Iran [4, 5], Saudi Arabia [6], Jordan [7], and United Arab Emirates [8], as well as in South East Asia [9, 10], Europe [11], and the United States [12].

Serum level of 25(OH)D is a commonly used marker of the long-term vitamin D nutritional status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the cultural beliefs of individuals [3]. Dietary intakes of limited foods such as fatty fish, egg yolk, cheese, and fortified foods with vitamin D and also supplementation of vitamin D may increase 25(OH)D concentrations [13, 14]. Previous studies in adults showed that baseline 25-hydroxyvitamin D, concurrent calcium intakes, and levels of overweight and obesity are among other factors which may affect 25(OH)D in response to vitamin D supplementation [15]. Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made to evaluate the effects of various doses of vitamin D supplementation on serum 25(OH)D levels in children and adolescents [16], a factor crucial to stipulating dietary recommendations. Based on recommendations of the Institute of Medicine (IOM) in 2011, the recommended daily dietary allowance (RDA) is 600 IU for 9-18-year old

children and adolescents [17], whereas based on recommendations of the Endocrine Society, 9-18-year old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000 IU of vitamin D is essential to maintain levels of 25(OH)D > 30 ng/ml [3]; this controversy may be explained by the fact that IOM recommendations are based on achieving the target level of ≥20 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on achieving ≥30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as obese adolescents [18], emphasizing the differences in recommendations of these two scientific societies.

Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin D, and parathyroid hormone levels [19-21]. A systematic review in adults found that the average increase in serum 25(OH)D concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [22]. Recently a review study from the Middle East and North Africa (MENA) region showed that intakes of an intermediate vitamin D dose of 1000–2000 IU daily may be necessary to achievement of level in 20 ng/ml 25(OH)D in children and adolescents [16].

To the best of our knowledge, to date, no systematic review has been conducted on the effect of vitamin D supplementation on serum 25(OH)D levels in children and adolescents worldwide. In previous original studies also the optimum level of 25(OH)D had not been determined [13, 23, 24], and because of lower power, the graded response to vitamin D supplementation could not be explored. This review will therefore aim at determining the effectiveness of various doses of vitamin D supplementation in children and adolescents for improving serum 25(OH)D concentrations and assessing the graded response to vitamin D supplementation. Secondly, we

aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.

Methods

Types of studies

We will include randomized controlled trials of vitamin D supplementation with one of the following: Placebo, no control, or comparative arm studies. Comparative arm is an arm type in which a group of participants receives another dose of vitamin D, or fortified foods with vitamin D, or other micronutrients such as vitamin E during the clinical trial. Also, all the included studies must have reported 25(OH)D level at baseline and at the end of the study.

Types of participants

Healthy children and adolescents (aged ≤18 years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension, and etc.) that have no reason to have altered vitamin D metabolism.

Exclusion criteria:

a) Rickets in children characterized by low 25(OH)D, (below 15 ng/ml) with radiologic or laboratory evidence requiring higher doses of vitamin D supplementation (higher than those recommended for the general population).

b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or below 30 ml/min), liver disease, heart failure (New York Heart Association class 3 or more)

c) Individuals with conditions or on drug therapy both of which may affect vitamin D metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption, bypass surgery)

Types of intervention

Inclusion criteria:

Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with or without calcium supplementation

Exclusion criteria:

a) Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of supplementation is not recommended for the general population.

b) Studies that used vitamin D supplementation given intra muscularly

c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin cannot be defined accurately

Patient and public involvement

Patients and/or public are not involved in this study.

Search methods for identification of studies

Electronic searches

We will perform a systematic search of published randomized trials on vitamin D supplementation in subjects aged ≤18 years in PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017, using eligible keywords in titles or abstracts (for details on search strategies see Supplementary File 1), using the following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or calcitriol] and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or controlled trial]. Inclusion criteria will be the ≤ 18 year (children and adolescents age group). The first search will be done without language restrictions using various combinations of relevant keywords. We will also perform a complete updated search on all databases available and identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our review.

Searching other resources

To complete the data bank, we will use snowballing techniques to complement the database searches by screening the reference lists of included articles for relevant studies.

Data collection and analysis

Selection of studies

Two authors (G.A., H.F.) will independently determine studies that should be evaluated further by scanning the title, abstract, or both, of every study retrieved based on inclusion/exclusion criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement through consensus or consultation with a third review author for resolving differences and reaching concensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study selection [25].

Data extraction and management

In the first step, two authors (G.A., H.F.) will independently select articles by title and abstract or search reference lists of relevant studies, and in the second, full texts of selected articles will be retrieved and screened using inclusion and exclusion criteria (study design, participants, and intervention). Finally, in the third step, we will extract the relevant data from the selected articles in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or consultation with a third author for resolving differences (F.H.).

Dealing with duplicate and companion publications

In case of duplicate papers or multiple publications of a primary study, we will enhance yield of information by collating all available data and use the most complete dataset aggregated across all known publications.

Quality assessment

The quality of each included study will be assessed independently by two authors (G.A., H.F.). We will assess the quality assessment, focusing on the following criteria: Randomization, allocation concealment, blinding of personnel and of participants, incomplete outcome data, selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve disagreements in quality assessments by consensus, or by consultation with a third author (F.H.).

Data synthesis

We will present data of all included studies and provide a description of results, including study population, intervention, and outcome in details in both summary tables and the text. Also, a meta-analysis using fixed- or random-effects modeling will be conducted to summarize weigthed mean differences and 95% CI in 25(OH)D from baseline to follow-up during the supplementation [27, 28]. We will first perform graphical exploration of variability of changes in 25(OH)D levels due to vitamin D doses. A potential nonlinear or linear dose-response relationship between vitamin D supplementation and serum 25(OH)D concentration will be modelled by using restricted cubic splines. We will fit meta-regression models for prediction of linear change in 25(OH)D concentration. We will complete statistical analyses based on the statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions [29].

If faced with any missing data in some studies in the process of analysis and data extraction and if we have proper evidence that indicats the randomness of these missing data, we will use data from existing data analyses, otherwise we will obtain the missing data from the study authors if possible; an alternate method where the value of some indices, including mean or standard deviation are not reported for outcomes is to impute these values by assuming the mean, standard deviation of the missing data to be the average of the mean or standard deviation of data from those studies where this information was given. To investigate the impact of imputation on meta-analyses, we will use sensitivity analysis.

Assessment of heterogeneity

Any clinical, methodological or statistical heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi^2 test with N-1 degrees of freedom (df), and

significance level of α = 0.1. If the power of this test is low, we will also calculate heterogeneity by I^2, a transformation of the square root of the Chi^2 test divided by its df [30]. If the values of I^2 is high we will have greater heterogeneity [31]; should there be heterogeneity in our investigation, we will assess the individual study and subgroup characteristics and perform a sensitivity analysis to clarify the reasons of this heterogeneity [32].

Assessment of publication biases

Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33, 34]. We will only test for funnel plot asymmetry if our review includes over 10 studies that assess a specific outcome.

Subgroup analysis

After the final search and screening, if a sufficient number of studies are available, we will perform subgroup analyses and investigate interactions based on the following: Characteristics of participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level, puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of studies.

Sensitivity analysis

We will carry out sensitivity analyses because of the exploring the influence of following factors on effect sizes and validity of the estimations:

1. Investigation of the impact of quality assessment on the results

2. An analysis of the influence of various characteristics of studies using the following filters: Duration of intervention, sex, language of publication, country, and dose of administration
3. An assessment of the effect of different variance imputations.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

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Contributors: GA had the original idea of this work. GA, HF, and FH designed and conceived the protocol. NM designed the search strategies. PM proposed some important advice for the study design and revision and PM and FA aided in developing the research questions. All authors critically revised the draft of the manuscript and approved its final version. GA and HF are the guarantors of the review.

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Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line/page numbers
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3, line 24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 13, lines 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 13, lines 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 6, lines 52-74
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pages 6-7, lines 79-83
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 7-8, lines 85-113
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 8, lines 116-119
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pages 8-9, lines 116-130
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 10, lines 141-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 10, lines 141-146
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 10, lines 141-146
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 10-11, lines 158-162
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7, lines 89-90
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 10, lines 152-156
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pages 10-11, lines 158-176
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pages 11-12, lines 178-184
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 12, lines 189-203
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12, lines 186-188
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10, lines 152-156

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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