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Comparative effectiveness of vitamin D supplementation via buccal spray versus oral supplements on serum 25-hydroxyvitamin D concentrations in humans: a systematic review protocol.

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Comparative effectiveness of vitamin D supplementation via buccal spray versus oral supplements on serum 25-hydroxyvitamin D concentrations in humans: a protocol for a systematic review

Introduction

Vitamin D with parathyroid hormone (PTH) regulates intestinal absorption of calcium, maintaining adequate concentrations for bone mineralization.[1,2] Vitamin D deficiency has been associated with the pathogenesis of several diseases including cardiovascular disease, some cancers and autoimmune diseases.[3-5] Many experts report of a major global pandemic of vitamin D deficiency and insufficiency, affecting one billion people worldwide.[6-8] Vitamin D deficiency is linked with bone metabolism disorders and reduced bone mineral density.[2] In view of the high prevalence of vitamin D deficiency and the risk to musculoskeletal health, professional societies and government bodies worldwide have in the past decade issued dietary reference intakes (DRI) for vitamin D. The DRI for the general population over one year of age is 10 micrograms (mcg) a day in UK, equivalent to 400 international units (IU), and 15 mcg (600 IU) in USA and the rest of Europe.[9-11]

Vitamin D exists in two forms; vitamin D3 (cholecalciferol) is a fat soluble vitamin that is mainly derived from 7-dehydrocholesterol upon exposure of the skin to UV-B radiation[1] and vitamin D2 (ergocalciferol) which is found in only a few foods including fatty fish, egg yolk and fortified foods.[1,2] The liver and kidney convert vitamin D2 and D3 into the biologically active form of vitamin D, calcitriol (1,25 dihydroxyvitamin D [1,25-OHD]). The widely accepted measure of vitamin D nutrient status is via measurement of serum 25-hydroxyvitamin D (25-OHD) concentration[12,13] because it has longer half-life (2-3 weeks versus 4 hours) than the active form (1,25-OHD).[1] In the adult population, serum 25-OHD concentration <12 ng/ml is considered deficient, 12-20 ng/ml insufficient and >20 ng/ml sufficient based on rickets prevention[10,14] however there is considerable international debate on the definition and optimal serum levels of vitamin D.[1,3,15]

Several factors influence vitamin D status in the human body: sun exposure, skin pigmentation, oral intake of the vitamin, its absorption from the intestine and its distribution in the body, as vitamin D is predominantly sequestered in adipose tissue.[1,16,17] Vitamin D deficiency often occurs in people who are not exposed to sufficient sunlight, and in individuals with intestinal malabsorption disorders (e.g. inflammatory bowel disease or short bowel syndrome) the prevalence may be as high as 78%.[9,18] Conventional vitamin D replacement is an oral dietary supplement, such as a tablet, but in patients with malabsorption, up to 2-3 times the usual amount of oral vitamin D may be required to achieve sufficiency.[15,19] Additionally, the response to supplementation in malabsorptive disorders can be unpredictable.[18,20,21]

Vitamin D absorption occurs through a combination of passive diffusion and active transport mechanisms involving membrane carriers and cholesterol transporters.[22,23] Vitamin D is lipid soluble and can be absorbed with long-chain triglycerides in the small intestine.[24,25] Ingested vitamin D is incorporated into chylomicrons which are released into the systemic circulation via the lymphatic system and then activated in the liver.[26,27] Absorption studies indicate that individuals with malabsorption are 30-70% less likely to absorb oral vitamin D.[21,28] The gastrointestinal tract is aqueous in nature; there is some evidence that vitamin D delivered in an oil-based formulation has improved solubility and ability to be incorporated into chylomicrons.[29,30] A systematic review that evaluated the impact of different vehicles (powders, lipids, ethanol) on the absorption of vitamin D supplements reported that absorption was greatest in the oil-based vehicle.[31] When the response to escalating doses of oral vitamin D supplements fails, intramuscular (IM) vitamin D is an alternative. However IM injections are associated with high inter-individual variability in absorption[32] and slower onset of repletion[33]. Additionally, an IM injection can be a painful procedure,[20] and also requires a visit to a healthcare facility at one to three month intervals, adding to the administrative burden. There is interest in the potential of vitamin D supplementation in people with malabsorption via the buccal and sublingual mucosa of the oral cavity which is able to circumvent the gastrointestinal tract.[34,35]

The membranes of the oral cavity consist of the buccal membrane (inner cheek and gumline), palatal (roof of the mouth) and sublingual region (under the tongue)[36] however the buccal and sublingual routes have a higher membrane permeability.[37] Vitamin D is lipophilic (fat soluble) and sprays typically contain a solubilizing agent, such as oil in a micro-emulsified preparation and excipients including emulsifiers and permeation enhancers. This facilitates absorption across the oral membrane and into the systemic circulation, thus bypassing the gastrointestinal tract.[36-38] Buccal spray delivery may result in a more effective route of administration and could reduce the burden associated with the IM route.[37] To date, only one case study of sublingual vitamin D is identified in the literature, and corrected a vitamin D deficiency in an adult with Crohn's disease and end-ileostomy.[39] However, a few studies have investigated buccal vitamin D spray, in comparison to capsules or placebo and in all no safety concerns have been identified.[40-42]

In 2015, the first clinical trial of buccal spray vitamin D in humans was published. In an Indian study, Satia et al.[42] performed a two-way cross-over of buccal spray vitamin D versus equivalent dose gel capsule in a study lasting 30 days per treatment arm with a 30-day washout in between. A daily regimen of 3000 international units (IU) buccal spray significantly increased mean serum 25-OHD concentration as compared to the soft gelatin capsule, by 1.9 times in both healthy subjects (percentage change from baseline, 43% vs. 22%, $p < 0.0001$) and 2.6 times in those with intestinal malabsorption (118% vs. 36%, $p < 0.005$). In 2016, Todd et al.[40] investigated a daily dose of 3000 IU buccal spray versus capsules in healthy participants (n22) in a randomized, two-way cross-over study conducted in wintertime lasting four weeks with a 10 week washout between treatments. In contrast, both spray and capsule were equally effective in raising serum 25-OHD concentrations (percentage

change from baseline 44% and 51%, respectively, p = 0.313).[40] The discrepancies between these study results may in part result from differences in baseline vitamin D levels. In the former study by Satia et al.,[42] there was considerable intra-subject variability in baseline vitamin D levels between healthy subjects and those with malabsorption. It is known that 25(OH)D concentration has a significant inverse correlation with baseline 25(OH)D concentrations, with those that are deficient responding more rapidly to supplementation than those that are replete.[43,44] In 2017, Todd et al.[41] used 3000 IU buccal vitamin D spray per day over a study period of 12 weeks and corrected vitamin D deficiency in athletes (n42) verses placebo spray (p = 0.006) however the spray was used as a secondary endpoint. No other directly relevant reviews on buccal spray vitamin D are available in the literature and it is not clear whether other studies have investigated buccal spray to treat a low vitamin D level.

The primary objective of this review is to determine if there is enough evidence to conclude whether vitamin D supplementation via buccal spray is comparable in effectiveness to oral supplements, taken via the oral-gastric route. The secondary objective is to identify any adverse effects, as reported by the researcher. Safety is important to consider as treatments can be effective but are not useful if they have undesirable side effects. Effectiveness will be determined through evaluation of quantitative experimental studies using buccal spray vitamin D versus an oral comparator or placebo on measured serum 25-hydroxyvitamin D (25-OHD) levels. This will provide information on how the buccal spray compares in efficacy to another type of vitamin D supplement, or a placebo. It is anticipated that this information may help to inform clinical practice. We will consider experimental studies: randomized controlled trials (RCTs) and controlled studies (quasi-experimental studies) in both in adults and in children with no restriction imposed on health status (i.e. healthy subjects or patient groups).

To our knowledge, this is the first review to have been conducted on the effectiveness of buccal spray vitamin D on serum 25-OHD levels. A search of the *JBI Database of Systematic Reviews and Implementation Reports* and *JBI Registered Systematic Reviews*, Cochrane Systematic Review Database, MEDLINE (Ovid), DARE, PROSPERO, EPISTEMONIKOS, and ACCESSSS on 12/06/18 reveals no systematic or review paper on buccal spray vitamin D.

Review Question

What is the effectiveness of vitamin D supplementation via buccal spray compared to oral supplements on serum 25-hydroxyvitamin D concentrations in humans?

Keywords

Buccal spray; Comparative effectiveness; 25-hydroxyvitamin D; Supplements; Vitamin D

Inclusion and Exclusion Criteria

A summary of the inclusion criteria can be found in Appendix I: Inclusion and exclusion criteria

Population

This review will consider both children and adults with no restriction on age, gender, ethnicity or health status. In vitro or studies in animals are excluded. The purpose of the study is to evaluate the effectiveness of vitamin D supplementation via spray in humans. Findings from both the adult and pediatric population are relevant as they will provide important information regarding the effectiveness of buccal spray vitamin D delivery on serum vitamin D levels. In addition, no restriction is placed on the health status of the study population. A preliminary search reveals studies in both healthy and malabsorption populations, with and without vitamin D deficiency. One study has combined both healthy and malabsorption populations together for comparison. In such an under-researched area, restricting the review to only select populations would exclude potentially relevant studies which address the research question. It may also highlight studies in which population groups were compared, which may facilitate sub-group analysis.

Intervention(s)

This review will consider studies that evaluate vitamin D supplementation of oral or buccal vitamin D spray (either vitamin D2 or vitamin D3) administered to the buccal mucosa. A preliminary scope of the literature reveals that the majority of studies use buccal vitamin D3 spray. Although most authorities advise that vitamin D3 is more effective than vitamin D2,[12,14] restricting the review to vitamin D3 may potentially exclude relevant studies. In some studies, the term 'oral spray' is used and in two studies, oral spray was administered to the buccal mucosa which is the area of interest. Studies which supplemented individuals with oral spray vitamin D not specifically to the buccal membrane but to the mouth will be excluded as the absorption of spray may be reduced on the surface of the tongue due to saliva[36]. This review will also exclude studies using sublingual vitamin D supplementation, via spray or liquid, as there may be differences in the membrane permeability which may not be comparable to the buccal route. [36] Furthermore, no studies have been identified in preliminary scoping.

Comparator(s)

We will consider for inclusion studies that compared the intervention to orally ingested vitamin D; vitamin D3 (cholecalciferol), vitamin D2 (ergocalciferol), at any dose, formulation, duration, or placebo. Comparing the intervention with all existing alternative interventions may help to identify its effectiveness against supplements which are conventionally prescribed. A sub-group analysis based on these different forms (i.e. vitamin D2 or vitamin D3) and formulations (i.e. tablet, capsule, liquid) will be considered. We will allow concomitant comparators (i.e. intervention and comparator vs. intervention). Additionally, inclusion of a comparator that is a placebo may also provide additional information of the spray's efficacy which will be useful to evaluate.

Outcomes

The primary outcome is selected to represent effects of buccal spray vitamin D versus comparator on serum vitamin D levels as measured by 25-hydroxyvitamin D or 25-OHD at baseline and at follow-up (pre-and post). Studies must report 25-OHD at baseline and at follow-up or the change in 25-OHD level from baseline to the end of the study and the significance between intervention and comparator.

We will include studies which report 25-OHD as nmol/L or ng/ml. For consistency, throughout the study, vitamin D will be reported as IU (1 IU = 0.025 μg) and serum 25-OHD will be reported as ng/mL (1ng/mL = 2.5 nmol/L).[9] No restriction will be placed on the methodology used to measure serum 25-OHD. Many laboratory methods are used to measure 25-OHD (e.g. liquid chromatography-tandem mass spectrometry, chemiluminescence immunoassay and enzyme linked immunosorbent assay). These differing techniques result in notable intra- and inter-assay variability.[14] Internationally, there are efforts to standardize the measurement of vitamin D via the Vitamin D Standardization Program (VDSP) however entering into this program is voluntarily and there is presently no obligation to abide with these standards.[45]

We will consider including studies of buccal spray vitamin D in which serum 25-OHD was measured as a secondary endpoint (surrogate outcome). The review question is to evaluate the effectiveness of buccal spray on serum 25-OHD levels and exclusion of studies using the spray in such an under-researched area could exclude potentially relevant studies.

The secondary outcome will be any reports of adverse effects, as reported by the researcher. Studies will not be excluded if they do not acknowledge adverse effects. In the event of non-disclosure of safety or adverse effects, researchers will be contacted to provide this information.

Study Types

This review will include experimental study designs: randomized controlled trials (RCTs), and quasi-experimental studies (non-randomized studies). RCTs are arguably the best study type to inform of clinical effectiveness.[46]

Study Setting

No restriction will be placed on the context of study designs, both hospital inpatients, outpatients and free dwelling individuals will be considered.

Methods

This systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence. Available from:

Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Search Strategy

The search strategy aims to find both published and unpublished studies in any setting and in both adults and children. Gray literature can make important contributions to a systematic review and can help to reduce the risk of publication bias i.e. from null or negative results.[47] This will illustrate the full available research evidence and may identify gaps in the research base.[48]

A three-step search strategy will be utilized in this review. The initial search strategy and terms will be chosen in discussion with a medical librarian and information specialist with expertise in systematic review methodology. An initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, forward and backward citation searching will be conducted using the reference lists and citations of all identified reports and articles to search for additional studies. The initial keywords and search terms will include:

(oral OR buccal) AND (spray) AND (vitamin D OR cholecalciferol OR ergocalciferol OR 25-hydroxyvitamin D).

Due to resource limitations of translation, the search will be restricted to studies written in the English language. To our knowledge, the first quantitative study to report on buccal spray vitamin D supplementation was in 2015. Studies published between 2008 to the present will be included. Extending the inclusion date to 10 years is more likely to reflect current buccal spray formulations. Studies will be excluded if they are published before 2008. If relevant, the reviewers intend to contact authors of primary studies for further information. The search will be limited to humans.

A full search strategy for MEDLINE (Ovid) and CINAHL is detailed in Appendix II: Search strategy.

Information Sources

A total of six databases will be searched: MEDLINE (Ovid), 2008-Present dataset, Epub Ahead of Print; EMBASE (Ovid), 2008-Present, Epub Ahead of Print; PubMed, CINAHL, AMED and The Cochrane Library.

The search for unpublished studies (gray literature) will include: a search of the Cochrane Handbook of gray literature databases, ProQuest Dissertation Publishing (PQDP) and search engines will be used with keywords relating to the research question.

Trial registers to be searched include: The Cochrane Central Register of Controlled Trials (CENTRAL), U.S. National Library of Medicine (ClinialTrials.gov) database; World Health Organization International Clinical Trials Registry Platform (ICTRP); All Trials (alltrials.net) and Restoring Invisible and Abandoned Trials (RIAT).

Study Selection

Following the search, all identified citations will be collated and uploaded into Endnote X8 citation management system and duplicates removed.[49] Titles and abstracts will then be screened by two independent reviewers for assessment against the pre-defined (a priori) inclusion criteria for the review. Studies that meet the inclusion criteria will be retrieved in full and their details imported into JBI SUMARI. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.[50] Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Assessment of Methodological Quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardized critical appraisal instruments from the Joanna Briggs Institute.[51] All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible). Any disagreements that arise will be resolved through discussion, or with a third reviewer.

Data Extraction

The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question. Authors of papers will be contacted to request missing or additional data where required. Two attempts will be made to contact the corresponding authors for missing information.

Data Synthesis

Data will be initially analysed through a narrative synthesis method. During analysis, if a subset of data appears comparable, it may be possible to perform a meta-analysis. To be eligible for meta-analysis, a trial must report the mean change in 25-OHD levels from baseline for each trial group and the corresponding standard deviation or standard error. Where possible, quantitative data will be pooled in a statistical meta-analysis using the JBI Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). All results will be subject to double data entry. Effect sizes will be expressed as either odds ratios (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals (CIs) will be calculated for analysis. Relative risks and 95% CIs will be calculated for dichotomous data. Analysis of continuous data will be undertaken using the mean and standard deviation values to derive weighted mean differences (WMDs) and their 95% CIs. Heterogeneity will be assessed statistically using the standard Chi-squared and I squared tests and also explored using subgroup analyses, i.e. buccal spray and comparator. If this indicates a high level of heterogeneity among the trials included in an analysis, a random effects meta-analysis will be performed for the overall summary. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru et al.[52] Sensitivity analysis will be performed to test decisions regarding subgroup analysis. If 10 or more studies are included in a

meta-analysis, a funnel plot will be presented, with the aims of assessing for signs of asymmetry with respect to publication bias. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate. Where statistical pooling is not possible, the findings will be presented in narrative format including tables and figures to aid in data presentation where appropriate.

Assessing Confidence

The study findings will be reported in narrative form and a 'summary of findings' table will be created using GRADEPro GDT software. The GRADE approach for grading the quality of evidence will be followed. The 'Summary of Findings' table will present the following information where appropriate: the risk of bias assessments for each aspect of methodological quality (randomization; blinding; measurement; statistical analysis) for each individual study and the overall risk of bias of the entire set of included studies.

Conflicts of Interest

The authors declare no conflict of interest.

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Appendix I: Inclusion and exclusion criteria (PICO)

PICO	Inclusion	Exclusion
Population	Humans: - Adults and children - Healthy or disease state We will allow concomitant populations (i.e. healthy and disease status)	No restrictions
Intervention	Buccal or oral vitamin D spray: - vitamin D2 or vitamin D3 applied to the buccal mucosa	Sublingual vitamin D Oral vitamin D spray applied to mouth not buccal mucosa
Comparator	Vitamin D in either form: - vitamin D3 (cholecalciferol), or - vitamin D2 (ergocalciferol) at any dose, duration, and formulation (i.e. tablet, capsule, liquid) or placebo We will allow concomitant comparators (i.e. intervention and comparator vs. intervention)	No comparator
Outcome	Total serum 25-hydroxyvitamin D (25-OHD) levels (pre- and post)	Total serum 25-hydroxyvitamin D (25-OHD) levels not reported

Appendix II: Search strategy

MEDLINE (Ovid)

Search #	Searches
1	administration, buccal
2	oral sprays.sh.
3	#1 OR #2
4	buccal.ti,ab,kw.
5	oral*.ti,ab,kw.
6	#4 OR #5
7	spray*.ti,ab,kw.
8	#6 AND #7
9	#3 OR #8
10	vitamin D/
11	vitamin D*.ti,ab,kw.
12	c?olecalciferol*.ti,ab,kw.
13	ergocalciferol*.ti,ab,kw.
14	25-hydroxyvitamin D*.ti,ab,kw.
15	#10 OR #11 OR #12 OR #13 OR #14
16	#9 AND #15
17	Publication Year: 2008-Current

CINAHL Plus with Full-Text

Search #	Searches
1	(MH “Administration, Buccal”)
2	TI buccal
3	AB buccal
4	TI oral
5	AB oral
6	#2 OR #3 OR #4 OR #5
7	TI spray
8	AB spray
9	#7 OR #8
10	#6 AND #9
11	#1 OR #10
12	(MH “Vitamin D+”)
13	TI vitamin D*
14	AB vitamin D*
15	(MH “Cholecalciferol”)
16	TI cholecalciferol*
17	AB cholecalciferol*
18	(MH “Ergocalciferols”)
19	TI ergocalciferol*
20	AB ergocalciferol*
21	TI “25-hydroxyvitamin D”
22	AB “25-hydroxyvitamin D”
23	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	#11 AND #23
25	Publication Date: 2008-2018

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