REVIEW

Evaluation of vehicle substances on vitamin D bioavailability: A systematic review

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Vitamin D insufficiency is a common medical condition. Vitamin supplements can be ingested to improve vitamin D status. It is not known if the vehicle substance that is combined with the vitamin D tablet influences the bioavailability of vitamin D. The purpose of this review is to examine the impact of different vehicles on vitamin D bioavailability. A comprehensive literature search identified studies that directly compared the absorption of vitamin D from two or more vehicles. The change in mean serum 25(OH)D per average daily dose of vitamin D supplemented was calculated and compared among the studies. We identified four clinical studies that compared two different vehicles of vitamin D. Vitamin D in an oil vehicle produced a greater 25(OH)D response than vitamin D in a powder or an ethanol vehicle in healthy subjects. There are limited studies that have compared the influence of the vehicle substance on vitamin D bioavailability. Future studies should examine bioavailability among different vehicle substances such as oil, lactose powder, and ethanol and examine if there are any differences in bioavailability among different patient populations including those with fat malabsorption.

Keywords:
Bioavailability / Cholecalciferol / Ergocalciferol / Vitamin D

1 Introduction

Vitamin D is an important nutrient well known for its role in promoting optimal intestinal absorption of calcium and proper mineralization of the skeleton. Recently, the known functions of vitamin D have grown to include roles in immune function, cardiovascular health, and cancer prevention [1–4]. It has also been recognized that vitamin D insufficiency is highly prevalent, especially in industrialized countries [5, 6]. Therefore, there has been increased interest in optimizing supplementation strategies for vitamin D in populations at risk for vitamin D insufficiency and chronic disease, such as the elderly, obese individuals, and chronic kidney disease [7–9].

Serum vitamin D and 25(OH)D levels are dependent upon several factors: cutaneous production of vitamin D₃, dietary intake and intestinal absorption of D₃ and D₂, and the metabolic activation and subsequent conversion of vitamin D to its metabolites for excretion. Vitamin D is a secosteroid hormone that is made in the skin from 7-dehydrocholesterol upon exposure of the skin to UV-B radiation. Vitamin D is also obtained in the diet primarily from vitamin D fortified foods or by the use of vitamin D supplements [10]. However, several studies have reported differences in the bioavailability of vitamin D supplements in some populations [11]. Decreased bioavailability may be due to altered absorption of vitamin D from the small intestine or it may be due to altered metabolism of vitamin D in the body. Intestinal malabsorption disorders may cause a decrease in vitamin D absorption due to a decreased ability to absorb lipids. Obesity has also been found to be associated with decreased 25(OH)D levels and may reflect the larger body volume of obese individuals or the sequestration of vitamin D in excess adipose tissue [9].

In order to make recommendations for vitamin D intake for the general population, it is important to consider how the different vehicles may influence the bioavailability of vitamin D. Vehicles such as oils, powders, and ethanol can be used in

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vitamin D supplements; however, there has been little
research to determine the most effective vehicle. Holick et al.
[12] suggested that the the vehicle has an impact on the
bioavailability of vitamin D supplements. However, the extent
to which the vehicle impacts the bioavailability of vitamin D is
still not known. The mechanism of vitamin D absorption
from the gastrointestinal tract is similar to the absorption of
other lipids. A seco-steroid, vitamin D is classified as a lipid-
soluble vitamin. In the intestine, vitamin D is associated with
micelles and is taken up with other lipids by passive diffusion
into the enterocytes. The presence of fat in the duodenum
stimulates the release of bile acids to facilitate lipid absorption
[13]. Vitamin D may require other lipids to stimulate the
release of bile acids and with which to associate in micelles to
facilitate its absorption by the intestinal mucosa. Therefore,
vitamin D may exhibit differential efficacy in absorption when
solubilized in oil, lactose powders, cellulose powders or
ethanol.

The bioavailability of a supplement is partially dependent
on the dissolution of the supplement tablet or capsule
which increases its absorption. The coating of the supple-
ment and the solubility of the supplement formulation
contribute to its dissolution. The formulation of the
supplement includes the active ingredients and the expe-
dients, such as the vehicle and fillers. Vehicles are inactive
substances that function to stabilize the active ingredient of
a supplement and aid in the administration and absorption
of the active ingredient.

The main objective of this review is to determine if there
is enough evidence to conclude how the type of vehicle
affects the bioavailability of vitamin D supplements in
humans and to determine where more research may be
needed to determine the most bioavailable vehicles for
vitamin D supplementation. We conducted a systematic
review of the published literature to examine differences in
the bioavailability of vitamin D supplements across three
categories of vehicles: powders, lipids, and ethanol. We
examined the bioavailability of vitamin D in prospective
clinical studies that compared the absorption of vitamin D
supplements from two or more vehicles.

2 Methods

Eligible manuscripts were obtained using an electronic
search of the PubMed database (from inception to July 31,
2009). The following Mesh terms were used to perform
our search: cholecalciferol (vitamin D3) and ergocalciferol
(vitamin D2). Limits were set to include manuscripts from
clinical and randomized controlled trials. Additional
manuscripts were extracted from the references of the
eligible manuscripts. The search was also limited to studies
performed in human subjects and written in English.

Manuscripts generated by the PubMed search were
individually evaluated. Study designs that did not evaluate
oral vitamin D supplements in more than one vehicle were
excluded. Studies that used activated forms of vitamin D,
derivatives of vitamin D or cutaneous preparations of vita-
m D were also excluded.

In an effort to include all studies that assessed the
absorption of vitamin D using two vehicles, studies that
gave vitamin D to two or more groups were evaluated
to determine whether more than one vehicle was
administered. Three manuscripts contained adequate
information about the supplement vehicles to meet our
criteria and were included in this review. Eight studies did
not include information about the vehicles of the vitamin D
supplements; therefore, that information was requested
from the authors by email. Of these, seven authors replied.
As a result, one additional study that met our search
criteria was included in this review. A total of seven
were excluded: five were excluded because they used a
single vehicle; one was excluded because the authors did
not return our emails, and one more was excluded because
the author was unable to identify the vehicle that had
been used in the study (Fig. 1).

The results of each study were standardized and then
combined to produce a summary figure with standardized
units. Since most studies did not measure vitamin D
concentrations in the serum, we used 25(OH)D as a surro-

gate marker of bioavailability of vitamin D. Each study was
unique in the dosage of vitamin D administered and in the
duration of supplementation. The following equation was
used to calculate this standardized rate of change in mean
serum 25(OH)D in each study. The standardized unit was
calculated for each study using the total change in mean
serum 25(OH)D divided by the mean dose of vitamin D
administered per day multiplied by 100 IU (Eq. 1).

\[
\text{Change in } 25\text{(OH)D} \frac{(\text{nmol} \times 100 \text{ IU})}{\text{Mean daily dose}} \tag{1}
\]

Studies were categorized into three groups depending on
the vehicle of the supplement: oils (soybean or peanut),
powders (lactose- or cellulose-based), or ethanol. The mean
rate of change in mean serum 25(OH)D per 100 IU and
standard error for each vehicle was determined. All statis-
tical calculations were performed using SAS 9.2 (SAS
Institute, Cary, NC).

3 Results

3.1 Studies eligible for review

We identified 322 manuscripts that described a clinical or
randomized trial of vitamin D supplements. After careful
assessment, four manuscripts were found that evaluated the
absorption of vitamin D using more than one vehicle. Two
manuscripts evaluated the absorption of vitamin D from an
oil vehicle versus powder vehicles; one manuscript evaluated
a cellulose powder vehicle versus a lactose powder vehicle;
and another manuscript evaluated an ethanol vehicle versus an oil vehicle. The oil vehicles were administered as oil capsules, except in the Maalouf study which administered the oil as a liquid. The ethanol vehicle was also administered as a liquid. The powder vehicles, cellulose and lactose, were administered as pressed-powder tablets. Two of the studies (Heaney et al. [16] and Holvik et al. [15]) verified the contents of the supplements that were used. However, the other two (Maalouf et al. [17] and Saadi et al. [14]) reported only partial verification of the content of their supplements. The specific details of each comparison are discussed below and summarized in Table 1.

3.2 Vehicle comparison: oil versus cellulose or lactose

Saadi et al. [14] compared the mean change in serum 25(OH)D between a monthly 60 000 IU oil supplement (Pliva, East Hanover, NJ, see above) and a daily 2000 IU lactose tablet of vitamin D2. The vehicle of the lactose tablet, manufactured by Tishcon, Westbury, NY, was magnesium stearate. It acts both as an anti-adherent and as a filler. As an anti-adherent, it aids in the dissolution of the supplement tablet. Also, magnesium stearate adds bulk to the active ingredient to fill out the volume of the tablet and therefore serves as a filler as well. The subjects of this study had deficient mean 25(OH)D levels at baseline, the mean 25(OH)D for all the subjects was 19.3 ± 12.2 nmol/L and only one subject had a mean 25(OH)D greater than 50 nmol/L. Both groups increased 25(OH)D, but neither group reached sufficient mean serum 25(OH)D levels (oil = 39.2 ± 21.4 nmol/L and lactose = 41.7 ± 26.5 nmol/L) in the 3 month study. Saadi et al. found that the daily lactose tablet produced mean 25(OH)D levels 1.09 times the monthly supplement in the oil vehicle, but the difference was not statistically significant.

Holvik et al. [15] compared the mean increase in serum 25(OH)D between groups given 400 IU of D3 in either a multivitamin tablet (Vitaplex ABCD, CederrothAS, Revetal, Norway) or a fish oil capsule (MollerCollet AS, Lysaker, Norway). The vehicle of the multivitamin tablet was micro-crystalline cellulose. The tablet also included other vitamins: ascorbic acid, nicotinamide, calcium-D-pantothenate, pyridoxine hydrochloride, riboflavin, thiamine mononitrate, and retinyl acetate. Other constituents included: magnesium stearate, hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, and silicon dioxide. Study subjects were healthy young adults deficient in mean serum 25(OH)D at baseline in both the multivitamin group (40.3 nmol/L (CI = 31.8,48.8)) and in the fish oil group (48.5 nmol/L (CI = 38.7,58.3)). Four weeks of supplementation were sufficient to increase the mean 25(OH)D to above 75 nmol/L in both groups. This resulted from a rapid increase of 8.0 and 9.0 nmol/L (cellulose and fish oil, respectively) per 100 IU/day of vitamin D administered. The fish oil supplement produced an increase in mean serum 25(OH)D that was 1.13 times as great as the increase produced by the multivitamin supplement, a result that was not statistically significant.

3.3 Vehicle comparison: lactose versus cellulose

The study by Heaney et al. [16] was designed to determine the serum 25(OH)D response to three levels of vitamin D supplementation: 1000, 5000, and 10 000 IU/day. The
1000 IU supplement was composed of cellulose, silica, and vegetable stearate supplied by Douglas Labs, Pittsburgh, PA, USA. Cellulose acts as a binder to bond the ingredients of the supplement together and serves as a filler as well. The other two supplements were lactose tablets supplied by Tishcon (see above). The mean baseline serum 25(OH)D in all three groups was close to sufficient (72.05 $\pm$ 16, 69.3 $\pm$ 16.7, and 65.6 $\pm$ 24.2 nmol/L, respectively) and all reached sufficient levels (84.1 $\pm$ 22.8, 161.2 $\pm$ 41.1, and 225.0 $\pm$ 66.9 nmol/L, respectively). The lactose press-powder tablet increased the mean serum 25(OH)D an average of 1.42 times as much as the cellulose tablet (results not statistically significant).

3.4 Vehicle comparison: oil versus ethanol

Maalouf et al. [17] compared the absorption of crystalline vitamin D$_3$ (Sigma, St. Louis, MO, USA) dissolved in pharmaceutical grade ethanol to the absorption of D$_3$ dissolved in Vigantoil, a medium-chain fatty acid supplement (Merck KGaA, Darmstadt, Germany). The purpose of this study was to determine whether high-dose vitamin D supplements were safe for subjects aged 10–17 years. This 8 wk study gave once weekly 14 000 IU supplements of D$_3$ for an average daily dose of 2000 IU. They found that the oil vehicle produced a 4.25 times greater increase in serum 25(OH)D levels than the ethanol vehicle. At baseline both groups had 25(OH)D serum levels >75 nmol/L, the oil group with mean 25(OH)D level of 92.5 $\pm$ 15 nmol/L and the ethanol group with a statistically higher 122.5 $\pm$ 30 nmol/L level. The final serum levels of the groups were similar with mean 25(OH)D of 135 $\pm$ 50 and 132.5 $\pm$ 47.5 nmol/L (oil and ethanol groups, respectively).

4 Discussion

This review synthesizes what is known regarding the bioavailability of the different vitamin D vehicles and identifies important areas for future research. The literature has not yet reached a conclusion about which vitamin D supplement vehicle yields the greatest increase in mean serum 25(OH)D per 1U of vitamin D administered. When the information from these study populations was combined, oil-soluble vehicles produced the greatest rate of change in mean serum 25(OH)D per 100 000 IU, followed by powder-based vehicles and vitamin D dissolved in ethanol (4.05, 2.75, 0.5 nmol/L per 100 IU/day, respectively, Fig. 2). However, there were discrepancies among the studies in the sample characteristics and the outcomes reported.

The Saadi and Holvik studies [14, 15] compared oil-based to powder-based vehicles and indicated that oil and powder vehicles have similar bioavailabilities in normal subjects, since the differences did not reach statistical significance for either vehicle. Further, there were differences in the
According to studies by Ish-Shalom et al. [18] and Holvik et al. [15], in cystic fibrosis (CF) subjects, the mean serum 25(OH)D values in the ethanol group were significantly lower than in the oil group. This suggests that ethanol may be an inferior vehicle for vitamin D supplements, compared to oil or powder vehicles, for individuals with CF.

In contrast, Khazai et al. [14] found that in healthy subjects, 25(OH)D levels were similar between the oil and powder vehicles. However, in subjects with CF, the mean serum 25(OH)D values were lower in the ethanol group compared to both the oil and powder groups. This indicates that the vehicle used for vitamin D supplementation can influence serum 25(OH)D levels, even in healthy individuals.

These findings highlight the importance of considering the vehicle when choosing a vitamin D supplement. Ethanol may not be the best vehicle for vitamin D supplementation in certain populations, such as those with CF, whereas oil or powder vehicles may be more effective.

In conclusion, the vehicle used for vitamin D supplementation can significantly affect serum 25(OH)D levels. Future research should consider the vehicle used in supplementation studies to ensure accurate assessment of the effectiveness of vitamin D supplements.
25(OH)D levels, the rate of change in serum 25(OH)D in the ethanol group was less than the oil group. It may be that at higher serum concentrations of 25(OH)D, a greater amount of ingested vitamin D is either stored in adipose tissue to be released later, as suggested by Heaney et al. [22], or lost through increased excretion of vitamin D metabolites, decreased binding to vitamin D binding proteins, and urinary excretion.

As the prevalence of vitamin D insufficiency in developed countries has come to the awareness of the public, there has been an increased public and scientific interest in vitamin D repletion strategies. Research has focused on increasing the amount of vitamin D available from food sources through fortification of common foods. It has been shown that vitamin D fortification of cheese, bread, and orange juice are able to produce increases in serum 25(OH)D levels similar to vitamin D supplements [23–25]. There has also been an increase in the availability of over the counter vitamin D supplements. In the United States the most common vehicles of vitamin D supplements are cellulose in a tablet followed by oil in a softgel. Although some vitamin D supplements contain potential allergens (lactose, gluten, etc.), many of the vitamin D supplements available over the counter are suitable for individuals with allergies. This review demonstrates the need for additional research into the contribution of the vehicle of vitamin D supplements.

The strength of our review is our comprehensive search of the literature for studies which purposely or inadvertently compared two or more vehicles on the bioavailability of vitamin D from supplements. Recently, several manuscripts have compared the advantages of using D3 supplements rather than D2 supplements [12, 26–28], but only two studies purposefully evaluated the impact of the supplement vehicle on absorption [15, 17]. This review found several more articles that also compared two or more supplement vehicles. These were included in this summary to expand the current knowledge of the bioavailability of the various vitamin D vehicles.

The limitations of our study result from the limited number of studies which directly evaluated this issue. This study was affected by the heterogeneity of the patient populations in the studies reviewed, the lack of serum vitamin D data and the use of 25(OH)D as a surrogate marker of absorption.

Future studies suggested in this review are important for designing public health strategies for addressing the prevalence of vitamin D deficiency [29]. Specifically we must address the unique supplementation needs of vulnerable populations with increased risk for vitamin D deficiency, such as individuals with malabsorption disorders, renal dysfunction, and hepatic diseases. As a society, we are also facing continued increases in chronic diseases, such as autoimmune diseases, cancer, cardiovascular disease, and diabetes. Since vitamin D may have a role in the development and prevention of these conditions, it is important to offer more precision in making recommendations for supplementation strategies. Understanding the impact of the vehicle on an individual’s response to vitamin D supplementation is important at a time when a large percentage of the population has been found to be vitamin D deficient and needs effective supplemental vitamin D.

In conclusion, future studies must be designed to directly compare the bioavailability of the different vehicles of vitamin D supplements. These studies should directly examine the absorption of vitamin D in addition to the rise in 25(OH)D in response to vitamin D supplement vehicles. Studies should also examine whether specific subpopulations (i.e. individuals with malabsorption disorders, excess adiposity, or previous vitamin D deficiency) respond uniquely to different vitamin D vehicles. In recent years, the focus on vitamin D absorption has been on the comparison between D2 and D3. It is now time to take into consideration the multiple factors that impact the best strategy for vitamin D supplementation.


The authors have declared no conflict of interest.

5 References


