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.

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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 D_3, dietary intake and intestinal absorption of D_3 and D_2, 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 supplement and the solubility of the supplement formulation contribute to its dissolution. The formulation of the supplement includes the active ingredients and the expedients, 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 influences 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 D_3) and ergocalciferol (vitamin D_2). 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 vitamin 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 surrogate 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).

$$\frac{\text{Change in 25(OH)D}\left(\frac{\text{nmol}}{L}\right)^{*}100\text{ IU}}{\text{Mean daily dose}\left(\frac{\text{IU}}{\text{day}}\right)} \quad (1)$$

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 statistical 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;

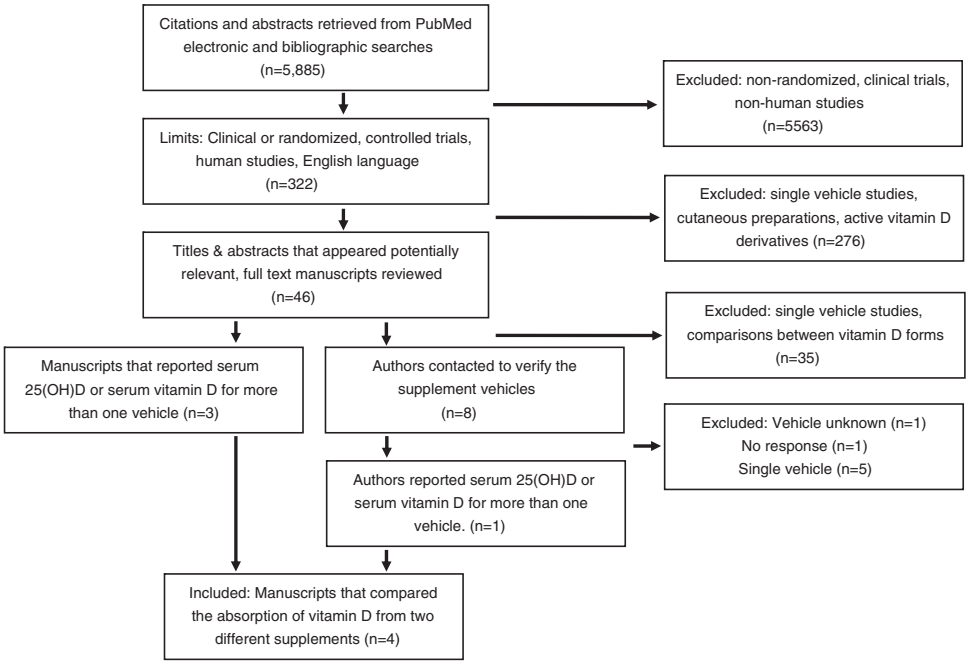

Figure 1. Flow diagram of the selection of manuscripts. PubMed search Mesh terms: cholecalciferol and ergocalciferol.

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 D_2. 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 D_3 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 microcrystalline 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, hydroxyproplymethylcellulose, 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

Table 1. Summary of reviewed studies

Author (year)	Study population (*n*, mean age, years ± SD)	Vitamin D form and total dose (IU)	Duration of study (days)	Dose (IU/ day)	Vehicles (source)	Change in 25(OH)D (nmol/L / day)	Total change/ mean daily dose*100 IU (nmol/L/100 IU/ day)[b)]	Comparison of the rate of absorption
Maalouf *et al.*, (2008) [17]	Healthy males and females $n = 25$, 13.7 ± 2.1	D_3 112 000	56	2000	Ethanol (Sigma)	0.179	0.50	Oil = 4.25 × Ethanol[a)]
					Oil, caplet (Merck KGaD)	0.759	2.13	
Holvik *et al.*, (2007) [15]	Healthy males and females $n = 55$, range = 19–48	D_3 11 200	28	400	Fish oil, caplet (MollerCollet)	1.286	9.00	Oil = 1.13 × Multivitamin
					Cellulose (Vitaplex)	1.143	8.00	
Saadi *et al.*, (2007) [14]	Healthy females $n = 88$, 23.8 ± 7.28	D_2 180 000	90	2000	Lactose, caplet (Tishcon)	0.246	1.11	Lactose = 1.09 × Oil
					Oil, caplet (Pliva)	0.224	1.01	
Heaney *et al.*, (2003) [16]	Healthy males $n = 67$, 38.7 ± 11.2	D_3 160 000	160	1000	Cellulose, tablet (Douglas)	0.750	1.20	Lactose = 1.84 × Cellulose
		D_3 800 000	160	5000	Lactose, caplet (Tishcon)	0.574	1.84	
		D_3 1 600 000	160	10 000	Lactose, caplet (Tishcon)	0.996	1.59	Lactose = 1.59 × Cellulose

a) The comparison between vehicles was significant in this study. b) Calculation from equation 1.

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 ± 16, 69.3 ± 16.7, and 65.6 ± 24.2 nmol/L, respectively) and all reached sufficient levels (84.1 ± 22.8, 161.2 ± 41.1, and 225.0 ± 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 ± 15 nmol/L and the ethanol group with a statistically higher 122.5 ± 30 nmol/L level. The final serum levels of the groups were similar with mean 25(OH)D of 135 ± 50 and 132.5 ± 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* IU 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

methods of the two studies that may or may not have affected the bioavailability of the supplements. The absorption of vitamin D in the Holvik study may have been influenced by its administration in a multivitamin tablet. However, it is not currently known whether this would increase or decrease the bioavailability of the vitamin D supplement. The Saadi study compared a daily dose of 2000 IU of vitamin D_2 to a monthly dose of 60 000 IU of vitamin D_2 which both produced a cumulative dose of 180 000 IU of vitamin D_2. Although the frequency of vitamin D dosing in the Saadi study was different in the two groups, Ish-Shalom *et al.* demonstrated that the frequency of vitamin D dosing did not influence the effect of the cumulative dose on serum 25(OH)D [18].

In contrast Khazai *et al.* found that in cystic fibrosis (CF) subjects with lipid malabsorption, a vitamin D supplement in a powder vehicle produced a greater increase in serum 25(OH)D levels than a vitamin D supplement in a lipid vehicle [25]. This study was not included in our analysis since it compared D2 absorption from an oil vehicle to D3 absorption from a powder vehicle. This finding contradicts the results from the studies in healthy subjects that compared lactose or cellulose powder vehicles to oil vehicles. It is noteworthy that in the Khazai study, the lactose tablets contained vitamin D_3 and the oil caplet contained D_2. Therefore, the difference between the intervention groups may have been due to the differences in the ability of these two vitamin D compounds to increase serum 25(OH)D rather than the vehicles.

The decreased absorption of oil-solubilized D_2 in the Khazai study may also be related to lipid malabsorption in the CF subjects. Supplements with oil-based vehicles may not be as well absorbed in subjects who require pancreatic enzyme replacement to maximize lipid-soluble vitamin absorption. Lark *et al.* [11] found that when an oil-solubilized D_2 supplement was administered to CF and normal subjects, the CF subjects demonstrated a 50% lower serum vitamin D_2 and 25(OH)D response than the normal

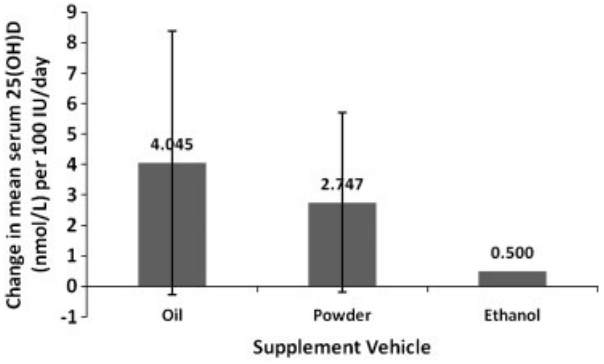

Figure 2. Comparison of three vitamin D vehicles on circulating 25-hydroxyvitamin D. Studies using oil-based vehicles ($n = 3$) showed the greatest mean rise in 25(OH)D compared with studies using lactose or cellulose powers ($n = 2$) or ethanol ($n = 1$) (Mean $\pm$ SD).

subjects. Vitamin A has also been found to be better absorbed in a water-miscible formulation than an oil-soluble formulation in subjects with intestinal malabsorption disorders [19]. Since both vitamin D and vitamin A are lipid-soluble vitamins, perhaps it should be expected that vitamin D supplements will produce higher 25(OH)D levels when administered in powder vehicles rather than in oil vehicles to patients with malabsorption disorders. Therefore, subjects with intestinal malabsorption may have unique responses to a vitamin supplement based on the vehicle in which it is administered.

In this review, individuals not affected by lipid malabsorption appear to be equally able to absorb vitamin D from both powder and oil vehicles. It may be that vitamin D absorption is dependent on micelle formation for absorption from oil vehicles and on protein transporters for absorption from powder vehicles. Recent evidence suggests that some sterol uptake is facilitated by protein transporters in the membrane of the enterocytes as well as by passive diffusion of micelles. It is not yet known if vitamin D is taken up in a protein dependent manner as well as by passive diffusion, but a protein transporter that recognizes sterols, including vitamin D, may explain why vitamin D is absorbed from both lipid and powder vehicles [20, 21]. Future research should determine if these lipid transport proteins may provide an additional mechanism for vitamin D absorption in both normal and in subjects with malabsorption. Perhaps, in subjects with malabsorption vitamin D absorption through micelle incorporation is impaired and the lipid transport proteins may be responsible for vitamin D absorption.

Another possible contributor to the variations in the bioavailability of the different vehicles among these papers may be the baseline 25(OH)D levels. In Saadi *et al.*'s [14] and Holvik *et al.*'s [15] studies, the mean serum 25(OH)D values were insufficient ($\leq$75 nmol/L). There is evidence that the rate of increase in serum 25(OH)D concentration in response to vitamin D supplements is dependent on the severity of baseline vitamin D deficiency. When serum 25(OH)D is less than 80–100 nmol/L, the rate of increase in 25(OH)D in response to D_3 supplementation is greater than when serum 25(OH)D exceeds 80–100 nmol/L [22]. Therefore, to accurately assess the contribution of vehicle to vitamin D bioavailability as assessed by serum 25(OH)D concentrations in future studies, it will be necessary to standardize the baseline vitamin D status of the sample, as well as, the form of the supplement (D_2 *versus* D_3).

Maalouf *et al.* [17] demonstrated that the rate of change of 25(OH)D may have been impacted by the baseline mean serum 25(OH)D level. This study compared ethanol as a vehicle to oil and found that ethanol was an inferior vehicle. However, the higher starting mean serum 25(OH)D level of the ethanol group may have limited the rate of increase in mean serum 25(OH)D in the ethanol group and underestimated the effectiveness of ethanol as a vehicle. Since both groups reached roughly the same final mean serum

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 D_3 supplements rather than D_2 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 D_2 and D_3. It is now time to take into consideration the multiple factors that impact the best strategy for vitamin D supplementation.

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