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Drug-vitamin D interactions: A systematic review of the literature

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Abstract

Extensive media coverage of the potential health benefits of vitamin D supplementation has translated into substantial increases in supplement sales over recent years. Yet, the potential for drug-vitamin D interactions is rarely considered. This systematic review of the literature was conducted to evaluate the extent to which drugs affect vitamin D status or supplementation alters drug effectiveness or toxicity in humans. Electronic databases were used to identify eligible peer-reviewed studies published through September 1, 2010. Study characteristics and findings were abstracted, and quality was assessed for each study. A total of 109 unique reports met the inclusion criteria. The majority of eligible studies were classified as Class C (non-randomized trials, case-control studies, or time series) or D (cross-sectional, trend, case report/series, or before-and-after studies). Only two Class C and three Class D studies were of positive quality. Insufficient evidence was available to determine whether lipase inhibitors, antimicrobial agents, antiepileptic drugs, highly active antiretroviral agents or H_2 receptor antagonists alter serum 25(OH)D concentrations. Atorvastatin appears to increase 25(OH)D concentrations, while concurrent vitamin D supplementation decreases concentrations of atorvastatin. Use of thiazide diuretics in combination with calcium and vitamin D supplements may cause hypercalcemia in the elderly, or those with compromised renal function or hyperparathyroidism. Larger studies with stronger study designs are needed to clarify potential drug-vitamin D interactions, especially for drugs metabolized by cytochrome P450 3A4 (CYP3A4). Health care providers should be aware of the potential for drug-vitamin D interactions.

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Keywords

vitamin D; drug-nutrient interactions

Introduction

Vitamin D, a steroid hormone precursor, is well known for its role in maintaining calcium homeostasis and normal bone structure. Recent evidence suggests that the vitamin may also play a role in a variety of other physiologic processes such as modulation of inflammatory pathways [1] and susceptibility to diabetes [2], cancer [3], and infectious [4] and cardiovascular [5] diseases. Extensive media coverage of the potential health benefits of vitamin D has translated into vitamin D supplement sales in the United States (US) increasing from $75 million in 2006 to $550 million in 2010 [6]. Supplemental vitamin D is available in doses that can be considered pharmacologic (≥400 IU) compared to the usual US dietary intake (approximately 160–200 IU/day [7]), and thus may interact with several types of prescription medications [8], potentially altering drug effectiveness or toxicity. Conversely, certain drugs may alter vitamin D metabolism and status.

Supplemental vitamin D is available in two forms, cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Vitamin D_3 is produced endogenously in the skin upon exposure to ultraviolet (UV) radiation, and is found in fortified foods and foods of animal origin such as fish, eggs, and liver. Vitamin D_2 is only available exogenously, primarily through consumption of plant foods, fortified foods and dietary supplements. The liver is the primary site for the initial hydroxylation reaction that converts both vitamin D_2 and D_3 to the main circulating form of vitamin D, 25-hydroxycholecalciferol (25(OH)D). This conversion occurs via hepatic 25-hydoxylases, which include the cytochrome P450 (CYP) enzymes 2R1, 3A4, and 27A1. The active steroid hormone form of vitamin D is 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$), which is formed from 25(OH)D at both the local tissue level and in the kidney by an additional hydroxylation of 25(OH)D via 1α-hydroxylase (CYP27B1) [9]. Catabolism of vitamin D metabolites occurs via 24-hydroxylase (CYP24A1). Vitamin D metabolism is depicted in Figure 1.

As a steroid hormone, $1,25(OH)_2D$ is involved in intracellular signaling through both rapid responses (initiation of membrane-associated signal transduction) and genomic responses (initiation/inhibition of transcription for genes containing a vitamin D response element) [10]. In the slower genomic responses, binding of $1,25(OH)_2D$ to the vitamin D receptor in the cytoplasm forms a heterodimer with the retinoid X receptor (RXR), which is then translocated into the nucleus where it binds to vitamin D receptor elements (VDRE) in the promoter region of certain genes and either activates or inhibits gene transcription (Figure 2). Gene expression profiling has shown that $1,25(OH)_2D$ enhances transcription of several phase 1 [11] and phase 2 [12] biotransformation enzymes, as well as p-glycoprotein (also known as multidrug resistant protein 1) [13], enzymes which are involved in drug bioavailability and metabolism.

The metabolically active $1,25(OH)_2D$ form is tightly regulated at the tissue level, and is present in circulation only in picomolar quantities, thus 25(OH)D is considered the more

clinically relevant metabolite for assessing overall vitamin D status. Although the Dietary Reference Intakes for Calcium and Vitamin D report issued in 2011 by the Institute of Medicine proposes ≥20 ng/mL as the definition of sufficiency based solely on requirements to prevent osteoporosis [14], it has been hypothesized that serum 25(OH)D concentrations of ≥30–32 ng/mL (75–80 nmol/L) are optimal in healthy populations [15–17].

Lower 25(OH)D levels are commonly reported in obese individuals compared to normal weight subjects. These findings have been attributed to sequestration of the fat-soluble vitamin D in adipose tissue, the major storage site for vitamin D [18]. At latitudes >40° (Minneapolis = 45° N), UV intensity is not strong enough to stimulate cholecalciferol synthesis in the skin during the winter months [19]. Several studies show that 25(OH)D concentrations are higher in men than women, although the reasons for these differences are not known [20]. In addition to low dietary/supplemental vitamin D intake and low UV exposure, other factors associated with suboptimal 25(OH)D levels include advanced age and darker skin pigmentation [20, 21].

The 25-hydroxylase CYP3A4, which converts ergo- and cholecalciferol to 25(OH)D, is also a phase I biotransformation enzyme for many drugs [22]. *In vitro* studies indicate that as many of half of all therapeutic drugs are metabolized by CYP3A4, while other drugs may inhibit or induce CYP3A4 activity (Table 1) [23]. CYP3A4 is active in the mucosal enterocytes in the intestines as well as hepatocytes [24, 25], therefore interactions between orally administered drugs and dietary/supplemental vitamin D intake may be more significant than for intravenously administered drugs or vitamin D synthesized as a result of UV exposure. The CYP3A4 gene also contains a vitamin D response element, and CYP3A4 expression is up-regulated in the presence of $1,25(OH)_2D$ [26, 27]. Thus, vitamin D may alter metabolism of drugs requiring CYP3A4 activation [13].

Other potential biologic mechanisms for drug-vitamin D interactions include: 1) altered absorption of the fat soluble vitamin D when taken concurrently with drugs that inhibit absorption or enhance elimination of dietary fat, and 2) exacerbation of risk of hypercalcemia when taken with calcium-sparing medications.

The purpose of this systematic review is to determine the extent to which drugs affect vitamin D status (by altering absorption, metabolism, or excretion of vitamin D), or the extent to which vitamin D alters drug absorption and metabolism, activity or toxicity. Specifically, the review will focus on human studies examining non-calcemic/bone mineralization drug-vitamin D interactions.

Methods

Study selection

A systematic literature search of electronic databases was conducted for articles published through September 1, 2010. Databases that yielded articles meeting the eligibility criteria were: BIOSIS Previews, CAB Abstracts, Cumulative Index of Nursing and Allied Health, Global Health, International Pharmaceutical Abstracts, and Medline.

A search strategy was initially performed using the Medical Subject Headings (MeSH) and keywords “vitamin D”, “cholecalciferol”, “ergocalciferol”, “drug interactions”. Based on articles identified during the initial search, the search terms “colestyramine”, “statin”, “antibiotics”, “cimetidine”, “anticonvulsants”, “glucocorticoids”, “cyclosporins”, “mineral oils”, “hormone replacement therapy”, “weight reduction”, “mineral oils”, “diuretics”, “thiazides”, “hydroxymethylglutaryl-CoA reductase inhibitors”, “histamine H2 antagonists”, “HIV protease inhibitors”, or “immunosuppressive agents” were added in subsequent searches. Additional references within identified primary research or review articles were also examined for eligibility.

Studies were included in the systematic review if they assessed vitamin D intake or concentrations and drug interactions in humans. Reports were excluded if the focus was on vitamin D analogues, osteoporosis or osteopenia treatment, or if vitamin D metabolism was altered as a consequence of the disease process rather than a treatment or an intervention. Animal or cell culture studies were also excluded. Case reports were included for most drug categories, however they were excluded for steroid and antiepileptic drugs because a considerable number of studies with stronger study designs were available for those drug categories.

Data abstraction and quality assessment

Using a standardized data abstraction form, two of the authors (K.R., J.H.R.) abstracted data for each trial. A third author (S.J.O.) reviewed the articles and abstraction forms for accuracy of the classification and quality rating. In cases where the third author disagreed with classification and/or rating assigned by the primary reviewer, the study was discussed among the authors until a consensus was reached. The following information was abstracted from each study: first author, year of publication, location of the study, study design, study population, sample size, duration of participant follow-up, drug dose and formulation, effect on 25(OH)D concentrations or drug level/activity, potential confounders evaluated in the study, and study limitations. If a study reported findings related to both 25(OH)D and $1,25(OH)_2D$ concentrations, only the data related to 25(OH)D were abstracted.

The American Dietetic Association Evidence Analysis classification system and quality criteria checklist [28] was used to assign class and quality ratings. The ADA system was chosen because it is oriented towards medical nutrition interventions and is designed to support translation to clinical practice guidelines. Study classification was based on study design, with randomized controlled trials being assigned a classification of A, cohort studies assigned a B classification, case-control and time series studies assigned a C classification, and cross-sectional, case series, case reports and before-and-after studies assigned a D classification. The quality criteria checklist includes questions in 10 categories relating to the reporting of the research methods and findings: a clear statement of the research question, potential for bias in selection of study participants, comparability of the study groups, methods for handling withdrawals, appropriateness of exposure assessment or the intervention, appropriateness of the outcome assessment, statistical analysis methods, whether the conclusions are supported by the data, and the potential for bias from the study’s funding or sponsorship. Studies that appeared to be free from selection bias, applied

appropriate randomization procedures, and had appropriate intervention methods/exposure assessment and outcome measurements received a positive rating. Studies that failed to meet the reporting requirements for six or more of the quality criteria categories received a negative rating. All other studies received a neutral rating.

Results

A total of 1225 reports were identified through the initial search process. Titles were reviewed for eligibility, and 912 manuscripts were excluded at this stage. Abstracts were obtained for the remaining 313 reports. After reviewing the abstracts, 109 unique reports met the full inclusion criteria (Figure 3).

Included studies are summarized in Supplementary Table 1 (available online). The majority of the studies were classified as Class C (non-randomized trials, case-control studies, or time series; n=30, 28%) or D (cross-sectional, trend, case reports/series, or before-and-after studies; n=69, 63%). Ten of the included studies were randomized controlled trials (RCT, Class A), of which eight were of neutral quality and two were rated as negative quality. None of the included studies were cohort studies (Class B). Only two of the Class C and three of the Class D studies were found to be of positive quality. All positive quality studies were published after 1996, likely reflecting increasing reporting standards for publication.

Drugs that interfere with vitamin D absorption

Bile Acid Sequestrants

The bile acid sequestrants, colestipol and cholestyramine, reduce cholesterol by binding bile acids in the gastrointestinal tract and preventing reabsorption of the bile acids. Bile acid sequestrants may also bind fat-soluble vitamins including vitamin D. As vitamin D metabolites are also present in the bile, increased bile acid excretion could reduce body stores of vitamin D.

Three RCTs (Class A; two neutral quality [29, 30], one negative quality [31]), one time series (Class C, negative quality [32]), and one before-and-after study (Class D, negative quality[33]) evaluated the effect of bile acid sequestrants on vitamin D status. One of the RCTs reported a statistically significant decrease in serum 25(OH)D concentrations among children with familial hypercholesterolemia taking 8 g cholestyramine/day for one year compared to controls [30]. In contrast, the time series and before-and-after studies reported no significant change from baseline circulating 25(OH)D levels among children taking colestipol for 2–24 months [32, 33]. Similarly, two of the RCTs both reported no significant differences in circulating 25(OH)D concentrations between adults taking 24 g cholestyramine/day and a control group after 24 weeks [31] or 7–10 years [29]. Overall, these studies suggest that bile acid sequestrants do not alter vitamin D status.

Lipase inhibitors

Orlistat is used as a weight loss aid, and acts by binding the active sites of gastric and pancreatic lipases within the gastrointestinal tract to block absorption of dietary fats, and

thus calories [34]. As vitamin D is fat soluble, orlistat may also inhibit dietary and supplemental vitamin D absorption [35].

Two RCTs (Class A, both neutral quality [36, 37]) and one before-and-after study (Class D, negative quality [38]) met the inclusion criteria for this drug category. All three studies reported decreases in 25(OH)D concentrations among participants receiving orlistat. However, in the RCTs, the control groups also experienced a decrease in 25(OH)D concentrations suggesting that the decrease in dietary fat intake may be the reason for the decrease in 25(OH)D concentrations rather than the orlistat itself.

Vitamin D status should be monitored for individuals taking orlistat. If deficient, it would be prudent to recommend that these individuals take vitamin D supplements several hours prior to their orlistat dose to maximize vitamin D absorption.

Drugs that interfere with vitamin D metabolism

Statins

Statins lower serum cholesterol concentrations by inhibiting the rate-limiting enzyme in cholesterol synthesis, HMG Co-A reductase [39]. Vitamin D is derived from cholesterol, so by decreasing cholesterol synthesis, statins could also reduce vitamin D synthesis [40, 41]. Another potential mechanism for vitamin D-statin interactions is competition for CYP3A4 activity. Atorvastatin, lovastatin and simvastatin are primarily metabolized by CYP3A4 [42, 43]. Rosuvastatin and fluvastatin are primarily metabolized by CYP2C9 [43, 44]. Pitavastatin and pravastatin interact minimally with metabolizing enzymes, degrading in the stomach and excreted as parent compound [43, 44].

A total of five studies on statins and vitamin D status, including one RCT (Class A, negative quality [31]), one nonrandomized trial (Class C, neutral quality [45]) and two before-after studies (Class D, both negative quality [41], with data from one study published in two separate publications [46, 47]), and one cross-sectional study (Class D, neutral quality [48]) met the inclusion criteria. Three studies reported that atorvastatin therapy increased circulating 25(OH)D [45, 46, 48]. One study reported statistically significantly lower concentrations of atorvastatin and its metabolites among participants taking 800 IU/d supplemental vitamin D for 6 weeks compared to those who did not receive supplements ($p<0.05$) [45]. However, cholesterol levels were also lower during vitamin D supplementation despite lower atorvastatin concentrations. The two studies evaluating the effect of pravastatin therapy on 25(OH)D concentrations [31, 41] both reported no significant differences in 25(OH)D concentrations before and after treatment.

Although further study is needed, it appears that only the statins metabolized by CYP3A4 have the potential to interact with vitamin D supplementation. Clinicians should consider whether it is appropriate to ask patients to discontinue vitamin D supplementation while taking atorvastatin, lovastatin or simvastatin, or whether patients should be switched to a different statin in order to continue vitamin D supplementation.

Antimicrobials

Rifampin and isoniazid—Rifampin and isoniazid are used in treating tuberculosis (TB). The complex relationship between vitamin D and TB has long been recognized. Prior to the advent of antibiotics, sun exposure and vitamin D supplements formed the primary treatment for the disease [49]. Vitamin D is a modulator of macrophage activity and enhances the production of the antimicrobial protein cathelicidin [50]. Vitamin D deficiency has been associated with increased susceptibility to TB infection or reactivation of latent TB infections [51]. Treatment with rifampin and isoniazid may also alter vitamin D status, as CYP3A4 is induced by rifampin and inhibited by isoniazid [52].

Six small time series studies (Class C, all negative quality [53–58]), each with between 8 and 27 participants, have evaluated the association between rifampin, isoniazid and vitamin D status. Four studies reported that 25(OH)D decreased [53–56], one reported no change [57], and one reported increased 25(OH)D [58] after rifampin and/or isoniazid treatment. Several of the studies noted that the individuals with TB had below normal 25(OH)D concentrations pre-treatment [56, 57]. While some of the studies considered the season in which vitamin D status was assessed, few considered dietary or supplemental vitamin D intake, and none assessed UV exposure or stratified by race/skin tone. Thus, it is prudent to monitor 25(OH)D concentrations during rifampin and isoniazid treatment, however if vitamin D deficiency is noted, it may be due to decreased vitamin D exposure rather than a true drug-nutrient interaction.

Hydroxychloroquine—Hydroxychloroquine is used in the treatment of malaria, as well as autoimmune disorders such as systemic lupus erythematosus (SLE). Because individuals with autoimmune diseases often also have photosensitivity and avoid sun exposure, there has been concern that vitamin D deficiency might be common in this population.

One cross-sectional study with comparison group (Class D, neutral quality [59]) evaluated the prevalence and predictors of vitamin D deficiency (defined as serum 25(OH)D <10 ng/mL) among 92 adults with SLE. The researchers found that vitamin D deficiency is common among individuals with SLE (n=69, 75%), and individuals taking hydroxychloroquine had higher 25(OH)D concentrations compared to those who were not taking hydroxychloroquine, which the authors hypothesized may be due to a decreased rate of conversion of 25(OH)D to $1,25(OH)_2D$ [59].

Antiepileptic drugs

Physicians have long noted a higher incidence of osteopenia and osteporosis among patients on antiepileptic drugs (AEDs), however the mechanism by which this occurs is not entirely clear. Cell culture studies have shown that phenobarbital (PB), phenytoin (PHT), primidone (PRM), carbamazepine (CBZ), oxcarbazepine and felbamate induce CYP3A4 expression, whereas ethosuximide (ETHS), valproic acid (VPA), and lamotrigine (LTG) have no effect on CYP3A4 activity [60, 61]. PB and PHT have also been found to increase CYP24A expression [61, 62], which could result in decreased clearance of vitamin D metabolites and lower serum 25(OH)D levels.

In total, 46 studies have evaluated the effect of AEDs on vitamin D status, however most were small single-institution reports, and only 4 of these studies included more than 100 participants [63–66]. The majority of included studies were cross-sectional with (Class D; one positive quality [67], 17 neutral quality [63, 68–83], and 13 negative quality [64–66, 84–93]) or without a comparison group (Class D; three neutral quality [94–96], and two negative quality [97, 98]). The ten remaining studies were seven time series studies with (Class C; three neutral quality [99–101], two negative quality [102, 103]) or without comparison groups (Class C; two neutral quality [104, 105]), and three before-and-after studies (Class D; one positive quality [106], one neutral quality [107], and one negative quality [108]).

Study design limitations likely contributed to variation in the findings across the 46 studies. Most of the studies that compared AED users to non-AED users found AED use to be associated with lower serum 25(OH)D concentrations [63, 64, 66, 68–74, 76–78, 81, 84, 86, 88–90, 93, 99, 100, 102, 109], however two of these studies reported that the difference in 25(OH)D concentrations between AED users and controls occurred only in the winter months [76, 102]. Seven studies reported no significant differences in 25(OH)D concentrations between AED users and non-users [64, 65, 79, 80, 82, 85, 91, 101]. Most of the participants in these studies were ambulatory rather than institutionalized AED users, and two of the studies were conducted in lower latitude countries [82, 85]. Unexpectedly, one study reported that the individuals on AEDs had higher 25(OH)D concentrations compared to the controls [92], which the authors attributed to adequate sun exposure given that the study participants lived in Florida.

Many studies combined the data for individuals who were on a variety of different single or multidrug AED regimens, and did not adjust for dose or duration of AED use. Of the few studies that reported the effects of specific AEDs on 25(OH)D concentrations, no statistically significant differences in 25(OH)D concentrations were observed between those on the CYP3A4 inducing AEDs compared to normal controls [66], or within individuals over time [107]. One study reported no statistically significant difference in 25(OH)D concentrations among individuals on CYP3A4-inducing AEDs compared to those on other AEDs [96]. Overall, the literature suggests that the effect of AEDs on vitamin D status may only be evident among individuals with insufficient exposure to exogenous sources of vitamin D (diet, supplements or UV exposure).

Corticosteroids

Glucocorticoids, such as prednisone, hydrocortisone and dexamethasone, are used pharmacologically for a variety of clinical applications including adrenal replacement, immune suppression, and chemotherapy. However, osteoporosis is a well-known complication of corticosteroid therapy. Alterations in vitamin D metabolism have been investigated as a possible mechanism.

Two RCTs (Class A, both neutral quality [110, 111]), four time-series (Class C; three neutral quality [112–114], one positive quality [115]) and five cross-sectional studies (Class D; one negative [116], three neutral [117–119] and one positive quality [120]) have evaluated the effect of prednisone therapy on 25(OH)D concentrations. The majority found no difference in 25(OH)D concentrations in comparison to either pre-treatment concentrations or to a control

group [111–113, 116, 117, 119]. Lems et al [114] reported that 25(OH)D concentrations decreased after low dose prednisone treatment among healthy controls, which they attributed to seasonal effects given that the study concluded in the fall. In a study of 50 adult rheumatoid arthritits (RA) patients on low dose prednisone, Lund et al [118] also found that 25(OH)D concentrations were significantly lower than the laboratory's normal values, although none of the study participants were considered deficient. The decreased concentrations may be explained by the fact that the study participants were likely older than the subjects used to establish the laboratory norms. The authors also appropriately note that photosensitivity is a common complication of glucocorticoids and other RA treatments, and the study participants may have been more likely than the general population to avoid sun exposure.

Two studies of prednisolone, one RCT (Class A, neutral quality [121]) and one time-series (Class C, neutral quality [122]) both found no statistically significant differences in 25(OH)D concentrations pre- vs. post-treatment Six studies, all cross-sectional (Class D; one negative [123], five neutral quality [124–128]) did not specify the type of glucocorticoid that the participant received. One study comparing 31 adult RA patients on corticosteroids for at least six months (2.5–10 mg prednisone equivalents/day) to 38 healthy controls found that the corticosteroid users had significantly lower 25(OH)D concentrations compared to healthy controls [124]. Similarly, two studies of children and young adults found that individuals with low 25(OH)D concentrations had significantly higher lifetime cumulative glucocorticoid exposure compared to those with higher 25(OH)D concentrations [125, 126]. However, the remaining three studies, one in adults [123] and two in children [127, 128], found no significant differences in 25(OH)D concentrations between individuals receiving glucocorticoids and controls or laboratory normal values.

Overall, the studies evaluating the effect of glucocorticoids on vitamin D status suggest that 25(OH)D concentrations are not significantly affected by glucocorticoids, and that the observed association with osteoporosis/osteopenia may be related to drug effects on other parameters of bone metabolism [113]. Few of these studies considered potential differences in the glucocorticoid-vitamin D association by body composition, dietary or supplemental vitamin D intake, or UV exposure.

Immunosuppressive agents

Immunosuppressive agents, such as cyclosporine and tacrolimus inhibit T-cell activation, and are used to decrease the risk of rejection of the transplanted tissue following solid organ and hematopoietic cell transplantation. Lower doses of these drugs are also used to treat autoimmune disorders. Osteoporosis is a common long-term side effect, especially among transplant patients who often receive both immunosuppressive agents and steroids.

Cyclosporine—Data from cell culture and animal models indicate that cyclosporine inhibits CYP27A1 [129–133] and decreases expression of the vitamin D receptor (VDR) and CYP24 [133], which would suggest that cyclosporine could alter circulating 25(OH)D concentrations. One RCT (Class A, neutral quality [134]) and five time series studies (Class C; one positive quality [135], one neutral quality [136], and three negative quality [137–139]) evaluated the effect of cyclosporine on vitamin D status. None of the studies reported significant

differences in 25(OH)D concentrations when comparing the effect of cyclosporine alone or in combination with prednisone.

Tacrolimus—Tacrolimus is metabolized by CYP3A4 and CYP3A5 [140], and thus may also be associated with altered 25(OH)D concentrations. One time series study (Class C, negative quality) evaluated the effect of tacrolimus on vitamin D status in individuals who had undergone renal transplantation [139]. Again, 25(OH)D concentrations were not significantly different than those of the healthy control group at any of the study time points.

While it does not appear that cyclosporine or tacrolimus alter vitamin D status, osteopenia and osteoporosis are common among this patient population. Thus, it is prudent to monitor vitamin D concentrations in individuals receiving these drugs, and provide supplements as needed to maintain adequate 25(OH)D concentrations. It is likely that the underlying disease state or factors associated with treatment may keep individuals from obtaining adequate vitamin D exposure from sunlight, diet or supplements, rather than a true effect of the immunosuppressant itself on vitamin D status.

Chemotherapeutic agents

A number of chemotherapeutic agents are metabolized by CYP3A4, including etoposide, epipodophyllotoxin, cyclosphosphamide, ifosfamide, vincristine, vinblastine, paclitasel, docetaxel, irinotecan, tamoxifen and imatinib [141], and thus may interact with vitamin D. However, few have been extensively studied with respect to their effect on vitamin D status to date.

Two time series studies (Class C; one neutral quality [142] and one negative quality [143]) and one cross-sectional study (Class D, neutral quality [144]) evaluated vitamin D status during chemotherapy. All three studies reported no significant changes in 25(OH)D concentrations during treatment of breast, ovarian, uterine, or colorectal cancers with a number of different chemotherapeutic agents (cisplatin, 5-fluorouracil, epirubicin, irinotecan, oxaliplatin, capecitabine, and several monoclonal antibodies). Given the small number of study participants in the studies to date, and the large number of different (often multi-agent) regimens used for cancer treatment, further research is needed. However, because of the high likelihood of vitamin D deficiency due to suboptimal dietary/supplemental intake and decreased UV exposure, vitamin D status should be monitored regularly for patients undergoing cancer treatment.

Highly active antiretroviral agents (HAART)

Highly active antiretroviral therapy (HAART) are a broad category of antiretroviral drugs that inhibit various stages of the human immunodeficiency virus (HIV) life-cycle, and include nucleoside reverse transcriptase inhibitors (NRTI), nucleotide reverse transcriptase inhibitors (NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and entry inhibitors [145]. *In vitro* studies have indicated that HAARTs are metabolized by CYP3A4, and can either induce or inhibit CYP3A4 activity [146], and thus drug-induced induction or inhibition of CYP3A4 could alter rates of 25(OH)D synthesis and degradation. Cozzolino et al [147] reported that conversion of vitamin D_3 to 25(OH)D and

$1,25(OH)_2D$, and degradation of the $1,25(OH)_2D$ metabolite was inhibited in human hepatocyte cell cultures exposed to PIs. However, evidence of HAART inhibiting vitamin D bioactivation in humans is currently limited, and inconclusive.

Three cross-sectional studies (Class D; two neutral quality [148, 149], one negative quality [150]) met the inclusion criteria for this drug category. The two Spanish studies reported lower serum 25(OH)D concentrations among individuals on HAART compared to those who were not on HAART [148, 150], but the difference was only statistically significant in one study [148]. The other study [149] reported that half of the 44 study participants on HAART had deficient 25(OH)D levels (< 34 ng/dL), but this study did not include a non-HAART comparison group.

Given the *in vitro* data suggesting that vitamin D status might be effected by HAART medications, vitamin D status should be monitored in individuals receiving HAART. Future research in this area should consider body composition changes as a potential covariate effecting vitamin D status. Lipodystrophy, a well described side effect of HAART characterized by alterations in adipose tissue deposition, may also contribute to alterations in circulating 25(OH)D concentrations.

Histamine H_2-receptor antagonists

The histamine H_2-receptor antagonist, cimetidine, inhibits gastric acid secretion by inhibiting histamine stimulation of the gastric parietal cells. However, animal data shows that cimetidine also inhibits CYP enzymes, including the 25-hydroxylases [151, 152]. One time series study (Class C, neutral quality) of nine adults with gastric ulcers found no significant change from baseline serum 25(OH)D concentrations while participants were taking cimetidine, yet serum 25(OH)D concentrations rose significantly once cimetidine was discontinued [153]. Without a placebo control or other similar studies published, this finding must be interpreted with caution. Ranitidine, another histamine H_2-receptor antagonist, has not been shown to interact with the CYP enzymes in animal models [154].

Drug-vitamin D interactions that induce side effects

Thiazides

Thiazide diuretics are prescribed to reduce blood pressure, treat edema or fluid retention, treat diabetes insipidus, or prevent kidney stones in patients with hypercalciuria. Thiazides reduce the reabsorption of electrolytes from the renal tubules, increase the excretion of electrolytes and fluid, and reduce the excretion of calcium. The combination of thiazide diuretics (decreases urinary calcium excretion) and vitamin D supplementation (enhances intestinal calcium absorption) may theoretically cause or exacerbate hypercalcemia [155].

Excluding reports of patients with altered calcium metabolism due to idiopathic osteoporosis or hyperparathyroidism[156–159], three cases of hypercalcemia while on thiazides have been reported in two published manuscripts (Class D; one positive quality[160], one negative quality[161]), including: a 78 year old woman taking vitamin D_2 (50,000 IU/day), calcium carbonate (1.5 g elemental calcium/day) and hydrochlorothiazide (25 mg/day) [160]; an 87 year old woman taking vitamin D (dose not specified), calcium carbonate antacids (1.9 g

elemental calcium/day) along with hydrochlorothiazide (50 mg/day) [161]; and an 88 year old woman taking vitamin D (1000 IU/day) and calcium carbonate antacids (3.8 g elemental calcium/day) along with hydrochlorothiazide (50 mg/day) [161]. These cases were reversible after rehydration and withdrawing the calcium and vitamin D supplementation and the thiazide diuretic. Clinicians should be aware that the combination of thiazide diuretics and vitamin D supplementation may cause hypercalcemia, especially in at-risk individuals, such as the elderly, and individuals with compromised renal function or hyperparathyroidism.

Four additional reports evaluated the effect of thiazide diuretics on serum 25(OH)D concentrations, including one RCT (Class A, negative quality [162]), one non-randomized crossover trial (Class C, negative quality [163]), and one before-after study [164] and one cross-sectional study [165] (both Class D, negative quality). None of the studies reported significant alterations in 25(OH)D concentrations as a result of thiazide treatment.

Discussion

This systematic review found insufficient evidence to determine whether lipase inhibitors, antimicrobial agents, antiepileptic drugs, HAART or H_2 receptor antagonists alter serum 25(OH)D concentrations. Atorvastatin appears to increase 25(OH)D concentrations, while concurrent vitamin D supplementation decreases concentrations of atorvastatin. Use of thiazide diruetics in combination with calcium and vitamin D supplements may induce hypercalcemia in the elderly, or those with compromised renal function or hyperparathyroidism.

The area of drug-vitamin D interactions is a clear example of a situation where lack of evidence does not equate to “no harm”. The available research to date has primarily focused on drugs that are commonly associated with osteoporosis (suggesting a potential effect on vitamin D metabolism), or where case reports of adverse outcomes have been reported in the medical literature. Recent advances in understanding the mechanistic details of CYP3A4 mediated drug metabolism, and a growing appreciation of the role of vitamin D in CYP3A4 expression will likely lead to a systematic evaluation of potential interactions among drugs that are metabolized by CYP3A4, as well as those metabolized by CYP2R1, CYP27A, CYP27B and CYP24.

There is also a need for further research to understand the impact of drugs that inhibit CYP enzyme activity related to vitamin D status. For example, synthetic azole drugs, such as the antimicrobial agent ketoconazole and proton pump inhibitor omeprazole, have been shown to inhibit both CYP3A4 [166, 167] and CYP24 [168] *in vitro*, yet no studies to date have evaluated the effect of these drugs on human vitamin D status.

The currently available literature on drug-vitamin D interactions has a number of limitations, as reflected in the number of neutral and negative quality ratings assigned in this review. Much of the literature to date is based on small case-control studies, case studies, or secondary analyses of clinical data collected for other reasons. Many of the studies were hospital-based and lacked relevant comparison groups. Most studies failed to evaluate dietary or supplemental vitamin D intake and sun exposure, as potential effect modifiers.

And very few studies considered body weight or composition as a potential confounder effecting both vitamin D concentrations and drug response. The majority of studies also lacked statistical power to adjust for appropriate covariates or rule out false negative findings. For many of the studies where individuals taking a drug were found to have lower 25(OH)D levels than a non-drug comparison group, the lack of data collection on vitamin D intake and UV exposure makes it difficult to determine whether the observed vitamin D deficiency is due to insufficient intake or due to the drug itself.

Because vitamin D is highly hydrophobic and has several metabolites, serum vitamin D determinations are technically challenging. Methodology for assessing vitamin D status has improved significantly in recent years, and the older data reported in many of the studies included in this systematic review may not be accurate or comparable to more current data. Currently, high performance liquid chromatography (HPLC) or liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is considered the gold standard technique, although when performed by experienced users, radioimmunoassay (RIA) techniques correlate very closely with LC-MS/MS [169]. Commercially available testing kits have been found to produce highly variable results when performed by inexperienced users [170]. As a result of regional surveys revealing significant variation between laboratories, an international standardization group, the vitamin D External Quality Assessment Scheme (DEQAS), was started in 1989 [171]. In 2009, the US National Institute of Standards and Technology (NIST) developed a vitamin D standard (standard reference material 972, Vitamin D in Human Serum) with certified and reference values for 25(OH)D_2, 25(OH)D_3, and 3-epi-25(OH)D_3 [172]. Supplies of this standard quickly sold out, and NIST does not plan to continue producing this standard due to difficulties in formulating the product. A companion NIST product, SRM 2972, is a set of ethanol-based calibration solutions and has certified values for 25(OH)D_2 and 25(OH)D_3 which is currently available. NIST has also established a Vitamin D Metabolites Quality Assurance Program (VitDQAP, http://www.nist.gov/mml/analytical/vitdqap.cfm) in collaboration with the National Institutes of Health (NIH) Office of Dietary Supplements (ODS).

Given the increasing prevalence of vitamin D supplementation in the general population, continued evaluation of potential drug-vitamin D interactions is warranted. Larger studies with stronger study designs are needed to clarify potential drug-vitamin D interactions. Future research in this area should address the limitations identified in this review, specifically with prospective data collection including assessment of vitamin D exposure and potential confounding factors such as body weight/composition and seasonality/UV exposure. Future studies should also use standardized vitamin D assay methodologies in a laboratory that participates in external quality assessment protocols specific to vitamin D. Until further research is available, health care professionals should be aware of the potential for drug-vitamin D interactions, assess their clients' use of dietary supplements, and monitor serum 25(OH)D concentrations where indicated with the ultimate goal of achieving adequate serum 25(OH)D concentrations while optimizing drug efficacy and minimizing drug toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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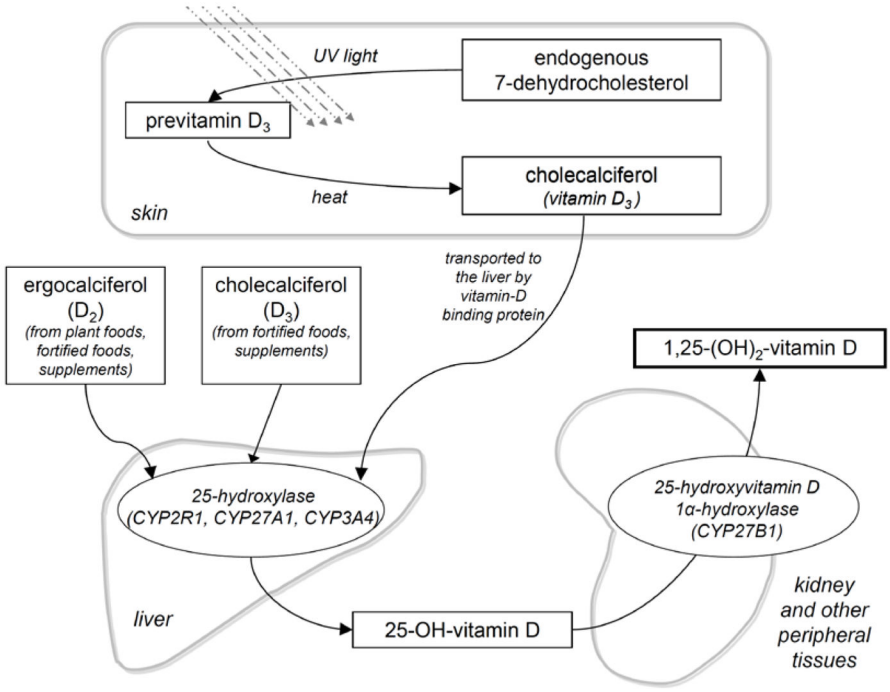

Figure 1. Vitamin D metabolism

Ovals denote metabolic enzymes, rectangles denote substrates.

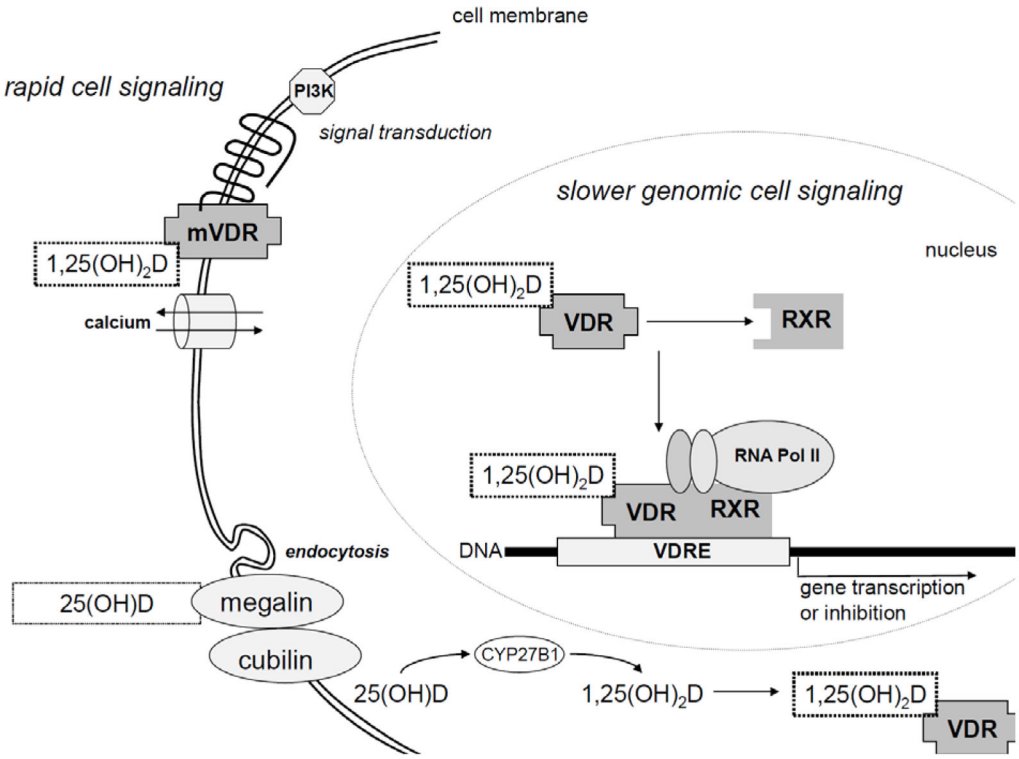

Figure 2. Vitamin D intracellular signaling pathways

As a steroid hormone, $1,25(OH)_2D$ is involved in intracellular signaling through both rapid responses (initiation of membrane-associated signal transduction as a result of $1,25(OH)_2D$ binding to membrane-bound vitamin D receptors (mVDR)) and genomic responses (initiation/inhibition of transcription for genes containing a vitamin D response element (VDRE)). In the slower genomic responses, vitamin D metabolites can enter the cell either as 25(OH)D (through carrier-mediated endocytosis with megalin or cubilin as the primary carriers, and subsequent intracellular conversion to $1,25(OH)_2D$), or directly as the active $1,25(OH)_2D$. Binding of $1,25(OH)_2D$ to the vitamin D receptor (VDR) in the cytoplasm forms a heterodimer with the retinoid X receptor (RXR), which is then translocated into the nucleus where it binds to VDREs in the promoter region of certain genes and either activates or inhibits gene transcription in complex with RNA polymerase (RNA Pol).

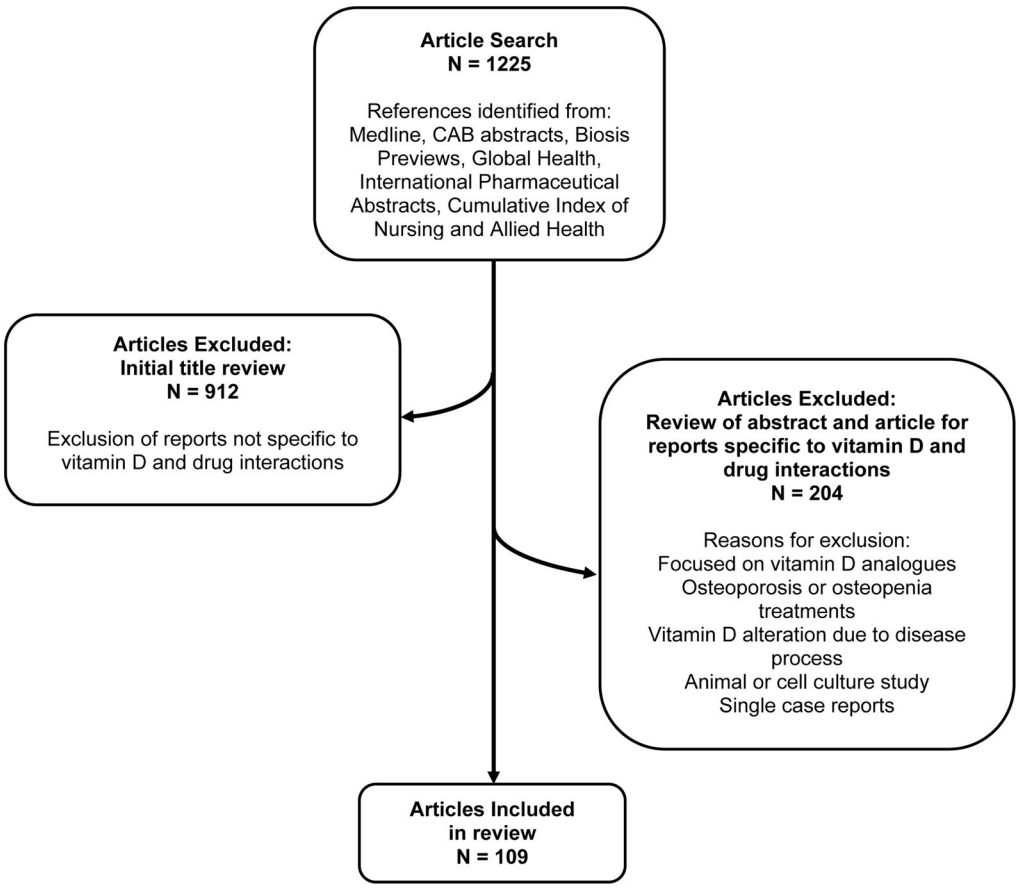

Figure 3.
Flow chart of manuscript identification and inclusion

Table 1

Examples of drugs that are activated by, inhibit or induce CYP3A4

Substrate for CYP3A4 [23, 173]	**Inhibits CYP3A4** [23, 173, 174]	**Induces CYP3A4** [23, 166, 167, 173]
Analgesics:	Antidiabetics:	Anticonvulsants
Acetaminphen	Rosiglitazone *	Carbamazepine †
Celecoxib	Antidepressants:	Phenobarbital
Codeine	Fluoxetine *	Phenytoin †
Fentanyl	Antifungal agents:	Primidone
Antimicrobial agents:	Clotrimazole	Antimicrobial agents:
Dapsone	Itraconazole	Erythromycin
Sulfamethoxazole	Ketoconazole	Quinine †
Calcium-channel blockers:	Antimicrobial agents:	Rifampin †
Nifedipine	Clarithromycin	Diuretics:
Chemotherapeutic agents:	Doxycycline	Spironolactone †
Cyclophosphamide	Erythromycin	Chemotherapeutic agents:
Docetaxel	Isoniazid *	Cyclophosphamide †
Etoposide	Primaquine	Ifosfamide †
Ifosfamide	Tetracycline	Paclitaxel
Paclitaxel	Antihypertensives:	Glucocorticoids:
Vinblastine	Amlodipine *	Dexamethasone
Vinorelbine	Dihydralazine	Vitamins:
Erectile dysfunction:	Diltiazem *	1,25$(OH)_2$D (calcitriol)
Sildenafil	Nicardipine	
Gastrointestinal motility:	Verapamil *	
Cisapride	Chemotherapeutic agents:	
Immunosuppressive agents:	Irinotecan	
Cyclosporine A	Tamoxifen *	
Sirolimus	Erectile dysfunction:	
Tacrolimus	Tadalafil *	
	Immunosuppressive agents:	
	Cyclosporine A *	
	Proton-pump inhibitors:	
	Omeprazole	
	Statins:	
	Atorvastatin	

* Indicates drugs that are reversible inhibitors of CYP3A4

† indicates drugs that are able to induce their own metabolism