

Rapid Normalization of Vitamin D Levels: A Meta-Analysis

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abstract

BACKGROUND: Vitamin D deficiency may represent a modifiable risk factor to improve outcome in severe illness. The efficacy of high-dose regimens in rapid normalization of vitamin D levels is uncertain.

METHODS: We conducted a systematic review of pediatric clinical trials administering high-dose vitamin D to evaluate 25-hydroxyvitamin D (25[OH]D) response and characteristics associated with final 25(OH)D levels by using Medline, Embase, and the Cochrane Central Register of Controlled Trials, including reference lists of systematic reviews and eligible publications. Uncontrolled and controlled trials reporting 25(OH)D levels after high-dose (≥ 1000 IU) ergocalciferol or cholecalciferol were selected. Two reviewers independently extracted and verified predefined data fields.

RESULTS: We identified 88 eligible full-text articles. Two of 6 studies that administered daily doses approximating the Institute of Medicine's Tolerable Upper Intake Level (1000–4000 IU) to vitamin D-deficient populations achieved group 25(OH)D levels >75 nmol/L within 1 month. Nine of 10 studies evaluating loading therapy ($>50\,000$ IU) achieved group 25(OH)D levels >75 nmol/L. In meta-regression, baseline 25(OH)D, regimen type, dose, age, and time factors were associated with final 25(OH)D levels. Adverse event analysis identified increased hypercalcemia risk with doses $>400\,000$ IU, but no increased hypercalcemia or hypercalciuria with loading doses $<400\,000$ IU (or 10 000 IU/kg). Few studies in adolescents evaluated loading dose regimens $>300\,000$ IU.

CONCLUSIONS: Rapid normalization of vitamin D levels is best achieved by using loading therapy that considers disease status, baseline 25(OH)D, and age (or weight). Loading doses $>300\,000$ IU should be avoided until trials are conducted to better evaluate risk and benefit.



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Dr McNally conceptualized and designed the study, carried out the initial analysis, drafted the initial manuscript, and revised the manuscript for important intellectual content; Mr Iliriani, Dr Pojsupap, and Ms O'Hearn designed the data collection instrument, determined study eligibility, acquired data, and revised the article critically for important intellectual content; Dr Sampson conceptualized and designed the search strategy, acquired data, drafted the initial manuscript, and revised the manuscript for important intellectual content; Drs McIntyre, Fergusson, and Menon conceptualized and designed the study, interpreted the data, and critically revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

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The evidence for vitamin D in calcium homeostasis, cardiovascular and respiratory health, inflammation, and innate immunity has led to questions about whether deficiency might represent a modifiable risk factor in the prevention of or recovery from acute and critical illness. A large body of observational literature from adult ICU and cardiovascular populations has documented high vitamin D deficiency (VDD) rates and association between blood 25-hydroxyvitamin D (25[OH]D) and organ dysfunction, health resource utilization, and mortality. More recently, pediatric observational studies have supported these findings in similar populations, including patients with asthma, ICU patients, and postsurgical patients with congenital heart disease.¹⁻⁵

Normalization of vitamin D status has the potential to speed recovery and improve outcomes in multiple acutely unwell pediatric populations. Most of the guidelines and clinical practice surrounding vitamin D dosing involves a daily intake of <1000 IU.^{6,7} Because these standard dosing strategies target healthy children and require months to restore normal levels, they are not applicable to the acute and critical care settings. Although other regimens that involve the administration of higher doses have been reported, there remains concern about both inadequate dosing and excessive doses leading to toxicity.^{8,9} In the adult ICU setting, pilot trials of loading dose therapy have been completed, with results from a large trial evaluating clinical benefit completed but unpublished.¹⁰⁻¹² No PICU studies have been completed.

To inform clinical practice and future trials, we performed a systematic review with the goal of identifying all published pediatric trials that reported on the administration of high-dose vitamin D (≥ 1000 IU). The objectives of this review were as follows: (1) to assess the ability of different dosing regimens to

normalize vitamin D status, (2) to determine study characteristics that influence post-study drug 25(OH)D levels, (3) to determine what high-dose regimens are associated with vitamin D-related adverse events, and (4) to use the findings to recommend a dosing regimen for clinical practice and future clinical trials in pediatric acute and critical care settings.

METHODS

Study objectives and protocol were determined a priori (PROSPERO protocol registration number: CRD42013006677) and reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.¹³

Eligibility Criteria

Studies were eligible for inclusion in the systematic review if they met all of the following criteria: (1) an uncontrolled, controlled, or randomized controlled trial (RCT) conducted in neonates, infants, children, or adolescents; (2) the study administered at least 1 dose of cholecalciferol (vitamin D₃) or ergocalciferol (vitamin D₂) ≥ 1000 IU; and (3) the study evaluated the effects of drug administration on 25(OH)D status. Studies were excluded if the study population was exclusively premature or of low birth weight, had a genetic problem related to vitamin D metabolism, or was pregnant. Furthermore, studies were excluded if they prescribed UV exposure, gave vitamin D as part of a food without precisely controlling quantity, or administered vitamin D with another vitamin or drug (without a control arm).

Identification of Studies

Medline (1946–2014; week 2, January 10th), Embase (1974–2014; week 3, January 17th), and the Cochrane Central Register of Controlled Trials (December 2013) were searched by using the Ovid

interface. The Medline search strategy was developed by a librarian experienced in systematic review searching (M.S.) and peer-reviewed by another librarian (Lorie Kloda, MLIS, PhD), using the PRESS (Peer Review of Electronic Search Strategies) standard.¹⁴ The Medline search was then adapted for the other databases. No date, language, or study design limits were applied. We searched conference abstracts from 2010 to 2013 through Scopus. The search strategies are presented in the Supplemental Information. The initial search was conducted on April 30, 2013, and updated on January 21, 2014. We also conducted a gray literature search by reviewing ongoing trials registered with clinicaltrials.gov, the citations of all eligible articles, and 24 systematic reviews of vitamin D in children.

Unless otherwise noted, 2 of the study authors independently reviewed the citations sequentially through 3 sets of screening questions to determine eligibility (Supplemental Table 6). Level 1 screening was performed by using Mendeley (Mendeley Desktop, version 1.10.3), and those citations that could not be excluded were uploaded to DistillerSR (Evidence Partners, Inc, Ottawa, Canada) for level 2 and 3 screening. The full text of all potentially eligible citations was independently appraised by at least 2 of 3 reviewers (K.I., K.O., J.D.M.). Conflicts between reviewers were resolved through discussion, with a third author available to resolve disagreement (M.S.). The eligibility of articles not in English, French, or Spanish was determined by a single author after written translation or with the assistance of a translator.

Data Collection and Risk of Bias

Extraction of data from full text, with independent verification, was shared by four review authors (J.D.M., K.I., K.O., S.P.). Data were collected and

managed by using REDCap (Research Electronic Data Capture) hosted at the Children's Hospital of Eastern Ontario.¹⁵ Vitamin D or calcium data values that were only published graphically were extracted from figures by using Digitizeit software (<http://www.digitizeit.de/>; Germany). During the data collection process, 18 authors were contacted to clarify or request additional 25(OH)D study data, 5 of whom responded. Study quality was described by using the Cochrane risk of bias assessment tool.¹⁶

Data Analysis and Reporting

Summary statistics and data from eligible studies and independent arms were described as text, through tables and figures. Clinical heterogeneity between studies was assessed by using information on population (age, disease status, baseline vitamin D), dosing regimen (dose, frequency, form, route), and measurement features (time, assay type). Regimens were considered intermittent if they provided a vitamin D dose in excess of 40 000 IU as a single administration (or divided over 2 days) or were repeated with a frequency >1 month. Methodologic heterogeneity was evaluated by using information collected on study type (single arm, RCT, controlled non-randomized trial) and the Cochrane risk of bias tool. For specific dosing regimens, 25(OH)D response was presented using figures (Sigma plot, version 12.3) and the success of each dosing regimen was defined as achieving a group 25(OH)D average >75 nmol/L.

Given significant heterogeneity in post-25(OH)D administration levels, we performed random-effects meta-regression to evaluate the contributions of specific study-level population, dosing, and methodologic characteristics. This analysis included study arms reporting a group 25(OH)D level between 1 and 13 weeks after drug initiation and for which an accurate cumulative dose

could be calculated. An assessment of heterogeneity and meta-analysis was performed by using Comprehensive Meta-Analysis (version 2) with meta-regression performed using the PROC MIXED function in SAS (version 9.3; SAS Institute, Cary, NC). Analysis used group mean or median 25(OH)D levels and within-study variance with the use of provided or calculated SEs.^{17,18} For age, if the median or mean was not provided we used the midpoint of the age range as an approximation.¹⁹ Initially, single-variable random-effects meta-regression was performed and potentially significant variables were then tested in a multivariable meta-regression analysis. A potential interaction was sought between cumulative dose and age, and an interaction term was included in the regression analysis to control for and evaluate for how timing from a single or divided loading dose influences the 25(OH)D levels influenced the level. No new variables were to be added to the multivariable model once the ratio of variables to eligible 25(OH)D measurements exceeded 10:1. The final multivariate model was used to predict group 25(OH)D levels after 4 loading doses in 4 age groups of VDD children with disease (Table 5).

RESULTS

Search Strategy

Figure 1 shows the flow of studies through the identification and review process. A total of 2453 unique records were identified for screening. Of the 367 full-text citations that remained after initial screening, 256 articles describing clinical trials were identified. Of these, 88 full-text publications^{8,20-107} and 10 conference abstracts (Supplemental Table 7) met all population, dosing, and 25(OH)D outcome-related eligibility criteria. The flow of eligible articles and study arms is presented in Supplemental Figure 5. The 88 full-text articles reported on 96 eligible study populations and included 199

different arms. Of these 199 arms, 3 were ineligible due to UV exposure ($n = 2$) or administration of active vitamin D ($n = 1$). Of the remaining arms, 62 involved the administration of no vitamin D (eg, placebo) or a dose <1000 IU. Of the 134 high-dose arms, 22% ($n = 29$) and 78% ($n = 105$) were from uncontrolled and controlled studies, respectively.

Patient Populations

Tables 1 and 2 relevant clinical and methodologic characteristics of the eligible high-dose arms. Of the eligible high-dose study arms, 73% involved administration of vitamin D to healthy children (49%), children with rickets (16%), or pediatric populations with subclinical VDD (8%). Populations of children with "other" disease states (eg, HIV, arthritis, seizures) accounted for 19% of the study arms (Supplemental Table 8). As shown in Table 1, studies included children from all age ranges, with neonates being evaluated in 15% ($n = 20$) and adolescents in 50% ($n = 67$) of high-dose study arms. Vitamin D dosing regimens evaluating intermittent loading therapy accounted for 46% ($n = 62$) of the eligible study arms, with daily regimens representing 38% ($n = 51$). A minority of the eligible high-dose arms (14%; $n = 19$) described a dosing regimen that varied depending on factors including baseline 25(OH)D, weight, or age. The number of participants in each arm ranged from 5 to 233, with a median size of 27 (interquartile range: 13-40).

At least 1 measure of average post-study drug group absolute 25(OH)D (or change) was available from all but 1 of the high-dose study arms. Of the 134 high-dose arms, 35% ($n = 48$) and 76% ($n = 106$) measured 25(OH)D within 1 and 3 months of study drug initiation. Supplemental Tables 9-16 show relevant information on population, dosing regimen, and 25(OH)D response for each study arm that

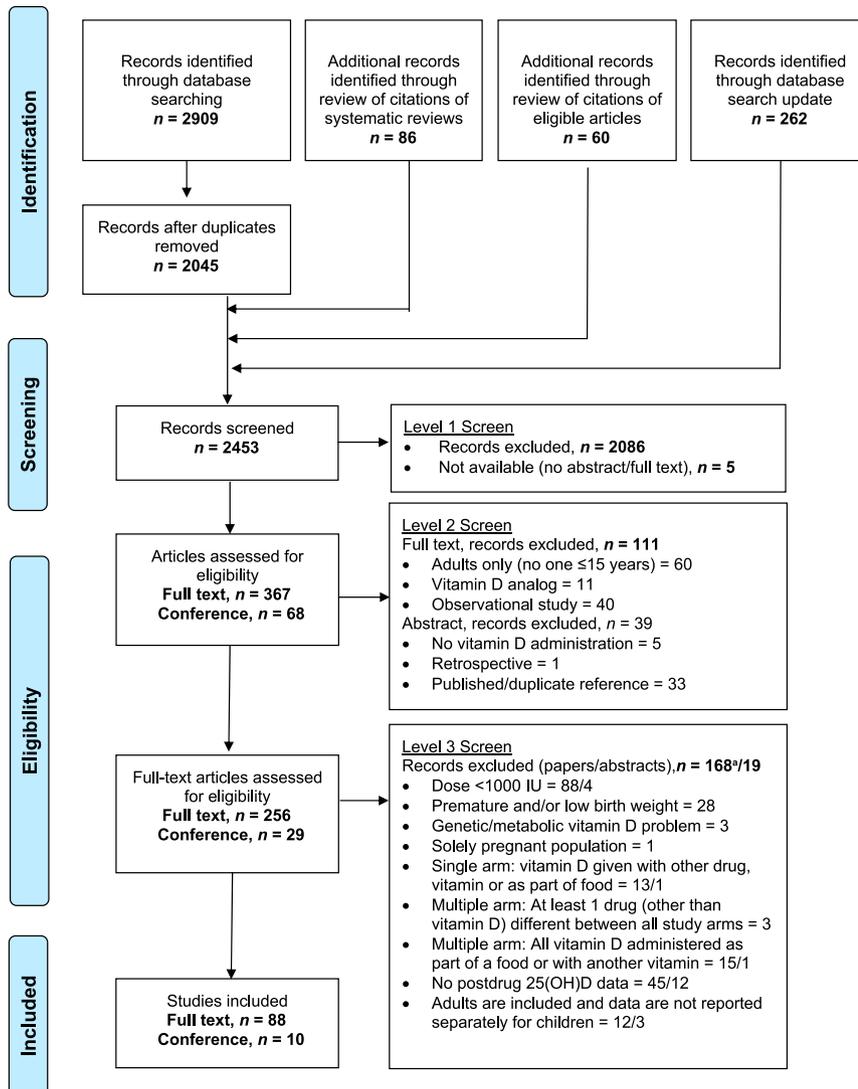


FIGURE 1 Flowchart of study selection based on inclusion and exclusion criteria. The stages of a systematic selection scheme include identification, screening, eligibility, and final included studies. ^aNumbers will not total 168 because studies could be excluded for multiple reasons.

reported 25(OH)D within 3 months of study drug initiation.^{8,20–90}

Evaluation of 25(OH)D Response by Dosing Regimen

Six independent treatment arms were identified that evaluated response to daily vitamin D between 1000 and 4000 IU in a group of children who were vitamin D deficient and reported 25(OH)D levels within the first month.^{42,50,75,79,84,108} As shown in Fig 2, none of the arms achieved a group 25(OH)D level >75 nmol/L with the first measurement, and 2 (33%) achieved this target within the

first month. A single weekly dosing regimen was identified that enrolled VDD children and performed blood work within 1 month; this study reported an increase in 25(OH)D from 22 to 143 nmol/L with 4 weekly doses of 60 000 IU. Ten independent study arms were identified that evaluated oral loading doses with VDD populations and measured 25(OH)D within 1 month (Fig 3).^{42,58,68,73,76,81,109,110} As shown in Fig 2, 9 (90%) achieved an average post-study drug group level >75 nmol/L, with 3 arms exceeding 200 nmol/L.^{42,68,76} Five additional

arms calculated 25(OH)D change after oral vitamin D loads and reported increases ranging from 45 to 73 nmol/L.^{56,72,77} All arms with >1 post-study drug measurement showed a decline between the first and subsequent measurements. Dosing regimens that reported multiple measurements during the first week after oral loading suggested that 25(OH)D peaks on day 3 and declines from days 3 to 7 by an average of 15% (Supplemental Figure 6).^{73,81}

Evaluation of Variable Loading Dose Regimens

Seven independent arms were identified that evaluated 25(OH)D response in vitamin D-deficient children by using a variable intramuscular dosing strategy (10 000 IU/kg).^{64,65,67,78,111} The single 10 000 IU/kg intramuscular dosing regimen that reported 25(OH)D within 1 month of therapy achieved a mean group level >75 nmol/L.¹¹¹ No published studies or conference abstracts evaluating 25(OH)D response within 1 month of a variable oral load were identified. One of the conference abstracts, Frizzell et al,¹¹² evaluated response to an age-based loading regimen (<3 years:150 000 IU; 3–12 years: 300 000 IU; >12 years: 600 000 IU) among 40 children; ~6 weeks after treatment, the group average increased from 27 to 93 nmol/L, with at least 1 participant exceeding 300 nmol/L.

Factors Associated With Post-Study Drug 25(OH)D Levels

Significant heterogeneity in post-study drug 25(OH)D was evident, with group average levels ranging from 30 to 399 nmol/L, and a calculated *I*² value of 99. Single-variable random-effects meta-regression identified 8 variables as statistically significant, with 2 additional variables approaching significance (Table 3). Multivariate random-effects meta-regression performed by using data available from 102 independent arms

TABLE 1 Patient, Dosing, and Study Characteristics of High-Dose Study Arms

Study Characteristic	Vitamin D Dosing Regimen, <i>n</i>		
	Daily (<i>n</i> = 51)	Weekly (<i>n</i> = 19)	Intermittent (<i>n</i> = 64)
Age group ^a			
Neonates	12	1	7
Infants	7	2	14
Toddlers	17	4	28
School age	33	18	37
Adolescents	23	17	33
Diagnostic category			
Healthy	25	12	29
VDD (no rickets)	4	1	6
Rickets	3	0	19
Malabsorption	3	0	2
Renal disease	2	1	2
Other disease ^b	14	5	6
Dosing regimen			
Variable	4	2	13
Constant	47	17	51
1000–4000 IU	41	4	0
4000–10 000 IU	1	1	0
10 000–40 000 IU	2	6	0
40 000–1 000 000 IU	3	6	51
Enteral	51	19	49
Intramuscular	0	0	15
Vitamin D ₂ (ergocalciferol) ^c	12	3	9
Vitamin D ₃ (cholecalciferol)	35	16	49
Geography			
North America	23	5	2
Central/South America	0	0	2
Europe	15	1	12
East Asia	2	0	0
Rest of Asia	4	4	9
Africa	0	0	11
Australia/New Zealand	0	0	2
Middle East	7	9	26

^a Counts will exceed 134 because the population could include multiple age groups.

^b Supplemental Table 8 lists other diseases.

^c In 18 cases, vitamin D form was unclear.

identified 7 variables that were independently statistically significant in either the main effects or through an interaction (Table 4) (Table 5). The interaction term between age and cumulative dose determined that the 0.27-nmol/L increase in final group 25(OH)D per 1000 IU was reduced by 0.013 nmol/L for every 1-year increase in age. Similarly, the interaction term between dosing regimen and time showed that the group mean 25(OH)D gradually decreased after a loading dose by 5.6 nmol/L per week (confidence interval 95%[CI]: -7.7 to -3.48). Inclusion of the study type variable showed that nonrandomized controlled studies, but not uncontrolled studies, were associated with higher postdrug

25(OH)D levels. After including the variable for study design, no other measure of study methodologic quality from the Cochrane risk of bias tool was statistically significant. The exclusion of the obese or malabsorption studies did not significantly change any of the parameter estimates.

The final multivariate model was used to predict group 25(OH)D levels after 4 loading doses in 4 age groups of VDD children with disease. Regression analysis was also performed to model post-study drug 25(OH)D standard deviations (SDs). The SD was best predicted by the equation $SD = 0.42 \times \text{final } 25(\text{OH})\text{D}$ ($R^2 = 0.81$); no other variable significantly improved the model R^2 value.

Thresholds for Potentially Toxic Vitamin D Levels

Of the 88 eligible studies, 9 defined thresholds above which 25(OH)D was toxic or potentially toxic (range: 125–374 nmol/L).^{26,43,57,63,70,86,102,108,109} The most common definition was 250 nmol/L ($n = 6$) and another 2 used definitions of 374 and 375 nmol/L.

Adverse Event Analysis

There were 39 study arms that reported on high-dose (≥ 1000 IU) vitamin D regimens that provided hypercalcemia data within 3 months of drug initiation. Information on relevant population, dosing, and adverse events measurements is provided in Supplemental Tables 17 and 18. There were 23 study arms who received intermittent, weekly, or daily high-dose loading regimens. Significant heterogeneity in hypercalcemia rates was calculated ($I^2 = 61\%$; see Fig 4). Random-effects meta-analysis identified a statistically significant difference in hypercalcemia rates between accepted daily dosing (2.6%; CI: 1.1%–5.9%) and intermittent, weekly, and daily high-dose loading regimens (7.6%; CI: 4.1%–13.7%; $P = .041$). Further analysis identified higher hypercalcemia rates for the arms $\geq 400\,000$ IU (23.8%; CI: 16.3%–33.3%) when compared with doses $\leq 300\,000$ IU (4.2%; CI: 2.0%–8.8%; $P = .0001$). Subgroup analysis using 25(OH)D data revealed that hypercalcemia was more likely among studies with average group levels >200 nmol/L compared with those with levels <200 nmol/L (3.9% vs 19.6%; $P = .006$). Pooled hypercalcemia rates were similar for groups with levels <100 nmol/L and those with levels between 100 and 200 nmol/L. Further subgroup analysis by age was not possible due to the limited number of loading regimens administering doses $>300\,000$ IU. For hypercalciuria (29 study arms; Supplemental Tables 19–21),

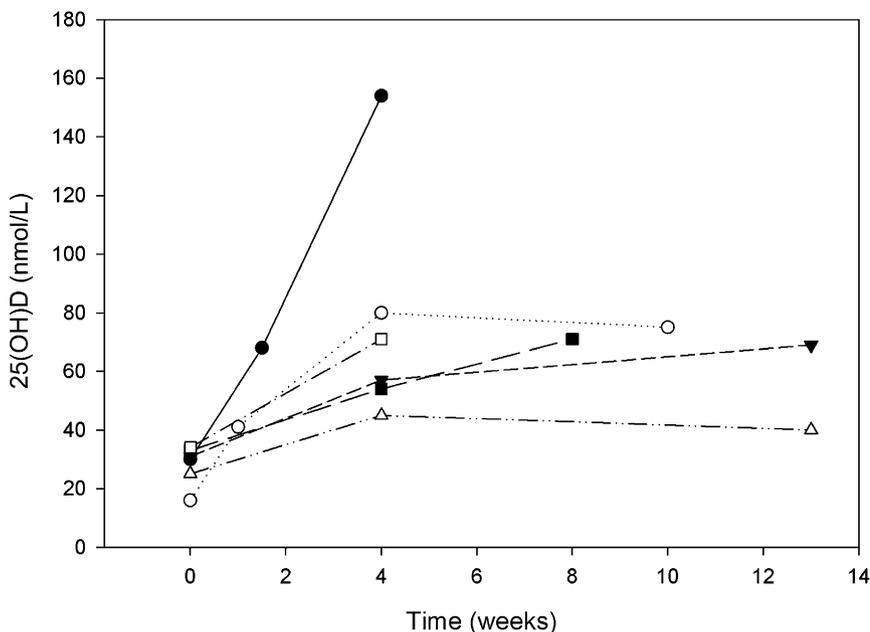
TABLE 2 Assessment of Study Design and Methodologic Quality

Study Characteristic	Vitamin D Dosing Regimen, <i>n</i>		
	Daily (<i>n</i> = 51)	Weekly (<i>n</i> = 19)	Intermittent (<i>n</i> = 64)
Year			
1970–1979	1	0	1
1980–1989	9	0	6
1990–1999	2	0	8
2000–2009	11	10	16
2010–2013	28	9	33
Study design			
Single arm	8	1	20
RCT/quasi-RCT ^a	36	15	37
Controlled, other	7	3	7
25(OH)D assay			
Immunoassay	37	18	47
LC-MS/MS	8	1	9
Unclear	6	0	4
25(OH)D measurement			
Within 3 months	41	10	51
Within 1 month	17	3	28
Randomized trial quality			
Low risk	15	1	8
Medium risk/unclear	20	14	28
High risk	1	0	1
Cochrane risk of bias ^b			
Generation adequate	26 (13)	8 (7)	26 (15)
Concealment adequate	17 (22)	7 (8)	13 (27)
Blinding adequate	19 (9)	8 (2)	12 (7)
Outcome report complete	33 (6)	15 (1)	45 (5)
Outcome not selective	26 (5)	7 (2)	24 (7)

LC-MS/MS, liquid chromatography–tandem mass spectrometry.

^a Only 1 study arm originated from a quasi-RCT.

^b Values represent the number of arms, whereas values in parentheses indicate unable to determine.

**FIGURE 2**

Short-term 25(OH)D response to high-dose daily vitamin D intake. Six study arms evaluated 25(OH)D response in VDD children within 1 month of initiating dosing that approximated the Institute of Medicine's daily Tolerable Upper Intake Level (1000–4000 IU). (●) Holst-Gemeiner, 1978⁴²; (○) Markestad, 1987⁸; (Δ) Leger, 1989⁵⁰; (▼) Vervel, 1997⁷⁵; (■) Dong, 2010⁵²; (□) Park, 2010.⁸⁴

13 distinct groups were identified that provided regimens corresponding to intermittent, weekly, or daily loading doses. Of these, 10 reported no episodes of hypercalciuria, and meta-analysis determined a pooled rate of 2.7% (CI: 0.8%–8.9%). Exclusion of the study by Shajari et al, who reported hypercalciuria in 28 of 30 children, reduced the pooled rate to 1.5% (CI: 0.5%–4.5%).⁶¹ Of note, the Shajari study was an RCT and the daily dosing arms reported hypercalciuria in 23 (200 IU/day) and 25 (400 IU/day) of the 30 children. Finally, our review did not identify any reported cases of nephrocalcinosis in the clinical trials that administered intermittent, weekly, or daily loading dose regimens.

DISCUSSION

The evaluation of daily vitamin D administration showed that a dosing strategy approximating the Institute of Medicine's Tolerable Upper Intake Level (1000–4000 IU) will not rapidly normalize vitamin D levels in deficient children. However, administration of a loading dose of >40 000 IU can rapidly elevate 25(OH)D concentrations. Our analysis also identified baseline 25(OH)D, age, cumulative dose, regimen type, disease status, time from loading dose, and study type as independent predictors of final 25(OH)D level. Adverse event analysis found no increased hypercalcemia or hypercalciuria risk with loading doses ≤300 000 IU, whereas a significant increase in hypercalcemia risk was observed with doses ≥400 000 IU.

This systematic review identified 88 full-text publications that reported 25(OH)D levels after the prospective administration of high-dose vitamin D to ≥1 groups of children. Daily administration and loading dose therapy each accounted for ~40% of the eligible study arms. The rarity of loading dose arms originating from

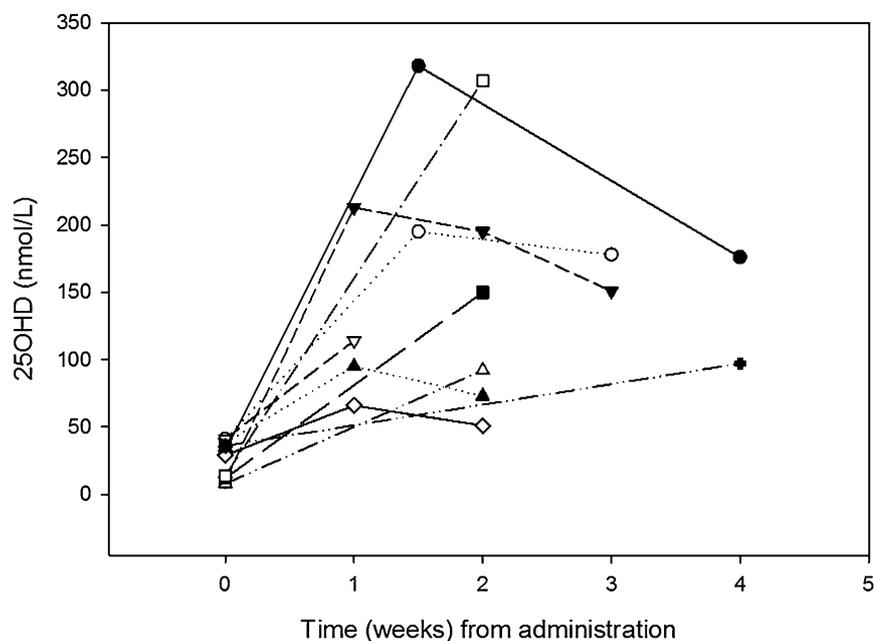


FIGURE 3 Short-term 25(OH)D response to vitamin D loading therapy. Ten study arms were identified that evaluated 25(OH)D response in VDD children within 1 month of administering a loading dose of vitamin D. (●) Holst-Gemeiner, 1978⁴²; (□) Zeghoud, 1994⁷⁶; (▼) Stogmann, 1985⁶⁸ (○) Raghuramulu, 1982⁵⁸; (■) Zeghoud, 1994⁷⁶; (v) Manaseki-Holland, 2012¹⁰⁹; (▲) Thacher, 2010⁷³; (△) Zeghoud, 1994⁷⁶; (◇) Thacher, 2006⁸¹; (Cross) Kari, 2013.¹¹⁰

TABLE 3 Single-Variable Meta-regression of Post-Study Drug 25(OH)D

	β	SE	95% CI
Population			
Pre-25(OH)D (per nmol/L)	0.58	0.22	0.15 to 1.01
Age (per year)	-2.66	0.79	-4.21 to -1.11
Diseased (versus healthy)	-14.5	9.4	-32.9 to 3.92
Regimen			
Cumulative dose (per 1000 IU)	0.12	0.019	0.083 to 0.16
Intramuscular versus enteral	-7.52	19.68	-46.03 to 30.99
Vitamin D ₃ versus vitamin D ₂	-9.68	13.86	-36.85 to 17.49
Single load versus placebo	61.08	11.26	39.01 to 83.15
Regular/repeat versus placebo	38.68	9.9	19.28 to 58.08
Loading dose versus other	36.88	10.01	17.26 to 56.5
25(OH)D measurement			
Time from initiation (in weeks)	-4.02	1.07	-6.12 to -1.92
Immunoassay versus LC/MS	4.98	12.15	-18.83 to 28.79
Study type			
Uncontrolled versus RCT	44.68	12.25	20.67 to 68.69
Non-randomized-controlled versus RCT	52.82	13.50	26.38 to 79.26
Study quality			
Overall assessment			
High versus low risk	21.84	9.97	2.30 to 41.38
Medium/unclear versus low	23.80	11.20	1.85 to 45.75
Components			
Allocation generation (adequate versus not)	-34.89	8.98	-52.49 to -17.29
Allocation concealment (adequate versus not)	-16.89	9.59	-35.69 to 1.91
Blinding (adequate versus not)	-15.88	9.69	-34.87 to 3.11
Outcome reporting (adequate versus not)	9.47	11.76	-13.58 to 32.50
Selective reporting (adequate versus not)	-1.16	9.31	-19.41 to 17.09

The β estimate provides the change (per 1 mmol/L) in post-study drug 25(OH)D for each variable. Study quality was determined by using the Cochrane risk of bias tool. LC/MS, liquid chromatography/mass spectrometry.

North America may explain why vitamin D position statements from Canadian and American pediatric societies make no mention of this therapy.^{6,113} Slightly more than 75% of the eligible study arms included healthy, VDD, or children with rickets or kidney disease. None of the studies were from acute or critical care settings, with the most relevant study being a pilot RCT that suggested long-term clinical benefit in stable outpatient congestive heart failure.⁶² Inspection of excluded studies did not identify any performed in the pediatric critical care setting, with the most relevant studies evaluating high-dose intake in pneumonia and severe asthma.¹¹⁴⁻¹¹⁶

The examination of post-study drug 25(OH)D levels from high-dose study arms revealed a wide range of final group levels. To remove some heterogeneity related to clinical and methodologic factors, we evaluated the short-term response to daily vitamin D approximating the Institute of Medicine's Tolerable Upper Intake Level (1000-4000 IU/day).⁷ Overall, the results strongly advise that this approach will not normalize levels (>75 nmol/L) in a time frame appropriate to potentially benefit acute and critically ill populations.^{42,50,75,79,84,108} These findings are important because they will inform future studies and help in the understanding of the results of published RCTs. For example, these findings might call into question the validity of the pediatric RCT by Choudhary and Gupta¹¹⁴ evaluating the effect of 5 days of vitamin D (1000-2000 IU/day) on recovery from pneumonia.

Conversely, there was convincing evidence that single or divided dose loading therapy is an effective means of rapidly increasing 25(OH)D levels. We also observed that numerous studies generated levels well in excess of the 75 nmol/L target. Multiple study arms administering loading doses of vitamin D achieved

TABLE 4 Multivariate Meta-Regression Predicting Post-Study Drug 25(OH)D

	Model 1		Model 2	
	β	(95% CI)	β	(95% CI)
Intercept	41.3	(24.0 to 58.6)	28.34	(12.2 to 44.4)
Baseline 25(OH)D	0.79	(0.54 to 1.05)	0.84	(0.62 to 1.06)
Age (per year)	-0.68	(-1.80 to 0.44)	-0.54	(-1.5 to 0.42)
Diseased (versus healthy)	-18.6	(-29.0 to -8.15)	-19.5	(-28.6 to -10.4)
Dose (per 1000 IU)	0.29	(0.22 to 0.36)	0.27	(0.21 to 0.34)
Loading dose (versus other)	32.6	(10.1 to 55.1)	43.8	(22.6 to 65.0)
Time from initiation (weeks)	-0.54	(-2.10 to 1.01)	0.02	(-1.37 to 1.41)
Cumulative dose \times age	-0.014	(-0.020 to -0.008)	-0.013	(-0.019 to -0.007)
Loading dose \times time (weeks)	-5.27	(-7.98 to -2.57)	-5.6	(-7.7 to -3.48)
Study type				
Uncontrolled (versus RCT)	—	—	-3.53	(-19.13 to 12.07)
Non-randomized-controlled (versus RCT)	—	—	34.95	(21.19 to 48.71)

Model 1 considered relevant population, dosing, and 25(OH)D measurement variables. Model 2 also considered study design and quality features. The β estimate represents the change (per 1 nmol/L) in post-study drug 25(OH)D levels.

TABLE 5 Predicted Final Group 25(OH)D Levels After Vitamin D Loading Therapy

Age Group	50 000 IU	150 000 IU	300 000 IU	600 000 IU
Infant (3 mo), nmol/L	86 (35)	112 (45)	152 (60)	232 (91)
Preschool age (2 y), nmol/L	83 (34)	108 (43)	144 (57)	217 (85)
School age (9 y), nmol/L	76 (29)	93 (34)	118 (43)	168 (61)
Adolescents (15 y), nmol/L	66 (24)	73 (27)	82 (31)	101 (40)

The predicted group 25(OH)D levels 1 week after 4 different loading doses of vitamin D are shown. The population was considered to be unhealthy and to have an average baseline 25(OH)D level of 30 nmol/L. Predicted SDs are shown in parentheses.

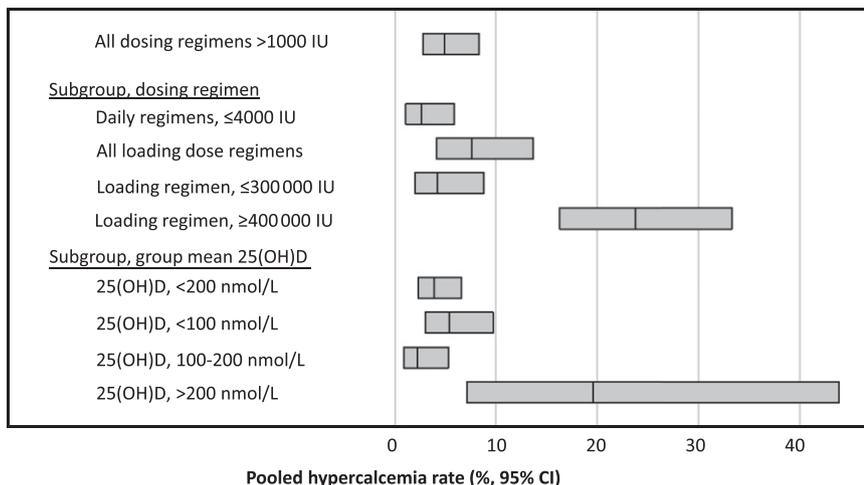
potentially toxic levels (group average of ≥ 200 nmol/L).^{42,68,76} Three of these administered doses in excess of 200 000 IU to neonates or infants, and the fourth evaluated 600 000 IU in toddlers and

preschool-aged children.⁵⁸ In contrast, the administration of 50 000 IU to a group of toddlers and preschool-aged children did not achieve levels of 75 nmol/L in more than half of the patients.⁸¹ These

results suggest that, with appropriate dose selection, single or divided loading regimens have the ability to rapidly normalize vitamin D status and may explain the positive benefits observed in clinical trials evaluating a loading dose in children with pneumonia and severe asthma.¹¹⁴⁻¹¹⁶

This study also sought to further explain heterogeneity in post-study drug 25(OH)D levels due to population, dosing, and methodologic characteristics. Single and multivariable random-effects meta-regression identified that baseline vitamin D status, cumulative dose, age, regimen type, healthy versus diseased status, and study type were significantly associated with post-25(OH)D level. Most important, we identified a statistically significant interaction between cumulative dose and population age, showing that the 25(OH)D response per dose declines as age increases. Although this observation is most likely related to the high correlation between age and weight, differences in developmental pharmacokinetics may contribute.¹¹⁷ Furthermore, our regression analysis identified lower post-study drug 25(OH)D levels in study arms originating from diseased populations, when compared with healthy children. There are multiple potential explanations, including differential compliance, malabsorption, increased losses (eg, capillary leak), and altered hepatic or end-organ metabolism.¹¹⁸⁻¹²²

Together, these findings suggest that rapid normalization of vitamin D status may require consideration of age (or weight), baseline 25(OH)D level, and disease status. Prediction of 25(OH)D levels by using the multivariate model suggested that 50 000 IU is appropriate in young infants, whereas doses in the 300 000 to 600 000 IU range may be required in adolescents. Because weight-based dosing represents the standard of care in pediatric medicine, these findings might be approximated to

**FIGURE 4**

Forest plot of hypercalcemia rates by dosing regimen. Random-effects meta-analysis was used to calculate pooled hypercalcemia rates and 95% CIs for all high-dose vitamin D regimens (≥ 1000 IU) and regimen subgroups. Point estimates are shown as the vertical lines in the boxes, and 95% CIs are represented by the edge of the boxes. The y-axis describes the various subgroup analyses.

10 000 IU/kg. A review of published variable high-dose regimens identified 7 independent pediatric populations with 25(OH)D measurements after the administration of 10 000 IU/kg intramuscular vitamin D. These studies suggest that intramuscular dosing might rapidly normalize vitamin D status, although the lack of measurements within the first month and paucity of enteral studies prevent definitive conclusions. Nevertheless, results from the intramuscular studies are relevant because many acute and hospitalized patients suffer significant malabsorption and/or are not able to take food and medication enterally.^{123,124} The need for pediatric studies evaluating 10 000 IU/kg using the enteral route is reinforced by evidence from adult studies that show significant differences in short-term response between enteral and intramuscular routes.^{125,126}

The current review also examined whether high-dose loading regimens were associated with vitamin D-related adverse events and toxicity. Vitamin D toxicity is characterized by hypercalcemia and hypercalciuria with the classic symptoms (eg, abdominal pain, anorexia, constipation, polyuria) directly attributable to these abnormalities. Presently, there is no accepted 25(OH)D threshold that identifies increased adverse event risk. The lack of certainty is emphasized by our finding that 90% of studies did not use or cite a specific threshold. For the few that did report a threshold, 250 nmol/L was the most common value.^{26,43,57,63,70,86,102,108,109}

A review of these articles identified that the more recent trials did not select thresholds on the basis of known toxicity, but the idea that supraphysiologic levels (not achievable with sun exposure or healthy diets) are unlikely to be of benefit.^{41,86,127,128} Our analysis supports a 200 to 250 nmol/L threshold because dosing regimens

with averages >200 nmol/L were associated with increased hypercalcemia risk.

To better inform selection of dosing regimens, we also sought to understand whether there was a cumulative loading dose associated with increased hypercalcemia and hypercalciuria. Our evaluation did not identify increased risk of hypercalcemia with loading doses $\leq 300\,000$ IU (4%) but did find a significantly higher risk for doses $\geq 400\,000$ IU. In addition, our review identified only 3 cases of hypercalciuria among the 878 study participants who received intermittent, weekly, or daily loading regimens (after exclusion of Shajari et al⁶¹). Furthermore, none of the eligible clinical trials reported a case of nephrocalcinosis with loading dose therapy. Together, these findings are consistent with the nephrocalcinosis literature, in which most cases potentially associated with vitamin D occurred in children with rare genetic disorders^{129–135} or after the intake of doses >600 000 IU in healthy children.^{132,136,137} On the basis of these findings, we would suggest age- or weight-based loading doses not exceeding 400 000 IU or 25(OH)D levels of 200 nmol/L. Of note, the increased hypercalcemia risk shown with doses $\geq 400\,000$ IU is largely driven by multiple studies in young children and only 1 study that administered 1.8 million IU to older children. Consequentially, our findings should not be interpreted to state that doses in the 400 000 to 600 000 IU range are toxic in adolescents. In fact, multiple adult studies, including pilot trials in the critical care setting, have not identified significant adverse events with loading dosing to adults in this range.^{10–12,138–141}

Although this systematic review summarizes a large body of literature and provides valuable information, a number of limitations must be acknowledged. First,

accurate information on a number of potentially relevant characteristics was not available, including race, UV exposure, diet, compliance, and blood collection techniques.^{108,142} Second, study size was often small, with the associated random error in the determination of group 25(OH)D levels potentially negatively influencing our ability to quantify associations. Third, there were relatively few studies compared with the number of potentially relevant characteristics and interactions. For example, due to the absence of appropriate 25(OH)D measurements after intramuscular administration, no conclusions can be made about the rapidity at which this regimen achieves peak 25(OH)D levels. Furthermore, to accommodate the discrepancy between potentially relevant factors and study number, we had to combine patient groups into broad categories (eg, diseased versus healthy). Because regression results generated by using patient- and study-level variables are not always consistent, our results and recommendations will need to be affirmed through future clinical studies. Finally, our adverse event analysis was limited by lack of reporting in close to half of the studies for measures of hypercalcemia and hypercalciuria. In addition, the lack of studies with loading doses $\geq 400\,000$ IU to older children and adolescents prevents a more definitive statement of risk and benefit.

CONCLUSIONS

This systematic review provides valuable information on the ability of different dosing regimens to rapidly restore vitamin D levels. Our study findings indicate that age- or weight-based loading therapy of 10 000 IU/kg (maximum: 400 000 IU) would be most appropriate. Given the absence of studies administering this dose enterally, and no studies in critically ill children, this dose along with vitamin

D-related adverse events including hypercalcemia and hypercalciuria should be evaluated in prospective RCTs before widespread use.

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