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REVIEW

Vitamin D Supplementation and Serum 25-Hydroxyvitamin D Response in Infants and Children: A Narrative Review

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Background: Vitamin D deficiency remains common among infants and young children, particularly in higher latitudes and among exclusively breast-fed infants. Although routine supplementation is widely recommended, variability in achieved serum 25-hydroxyvitamin D [25(OH)D] concentrations has been reported across pediatric populations. Understanding the consistency of biochemical response across diverse pediatric settings remains clinically relevant for both research and supplementation practice.

Objective: To summarize evidence from pediatric clinical studies utilizing a standardized vitamin D formulation and to assess the magnitude and consistency of serum 25(OH)D response across independent investigator-initiated studies.

Methods: Relevant studies were identified through company-supported research records and a supplementary PubMed search. Eligible publications were published between 2010 and 2020 and included infants or children ≤18 years receiving vitamin D supplementation with reported baseline and follow-up 25(OH)D concentrations. Studies were required to explicitly identify the study formulation and report serum 25(OH)D outcomes. A narrative synthesis approach was applied.

Results: Seven studies (Canada, Australia, Vietnam, and Mongolia; total n ≈ 3,800) met inclusion criteria. Supplementation doses ranged from 400 IU/day to 14,000 IU/week across study durations of 1–12 months. Mean baseline 25(OH)D concentrations (≈53 nmol/L) increased to ≈75 nmol/L (mean Δ ≈22 nmol/L). Daily supplementation at 400 IU achieved sufficiency in the majority of infants, while higher-dose regimens produced proportionally greater increases. No study reported clinically significant adverse events attributable to supplementation.

Conclusion: Vitamin D supplementation produced consistent and clinically meaningful increases in serum 25(OH)D concentrations across diverse pediatric populations. The approximately 20–25 nmol/L increase observed across the included studies was broadly consistent with published pediatric vitamin D supplementation literature. These findings support current supplementation practices while highlighting the reproducibility of biochemical response across independent pediatric research settings.

Keywords: vitamin D, 25-hydroxyvitamin D, infant, child, supplementation, bioavailability

Introduction

Vitamin D plays a central role in calcium homeostasis, skeletal mineralization, and immune regulation during development.[1] Despite longstanding awareness of its importance, vitamin D insufficiency remains common globally. Systematic reviews estimate that 40–60% of infants and young children fall below the 50 nmol/L 25-hydroxyvitamin D [25(OH)D] threshold recommended by international agencies.[2] At northern latitudes, seasonal ultraviolet limitation further constrains endogenous synthesis. Understanding the consistency of serum 25(OH)D response across pediatric populations remains clinically relevant because biochemical response may vary according to dose, formulation, adherence, baseline vitamin D status, and environmental factors.

Accordingly, professional bodies including the American Academy of Pediatrics (AAP), Health Canada, and the European Food Safety Authority (EFSA) recommend routine supplementation of 400 IU (10 µg) vitamin D_3 daily from birth through early childhood.[3–5]

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Nevertheless, variability in achieved serum 25(OH)D concentrations is frequently observed despite adherence to recommended dosing. Multiple factors contribute to this heterogeneity. Vitamin D_3 has demonstrated greater potency than vitamin D_2 in raising and maintaining circulating 25(OH)D concentrations.[6] Baseline vitamin-D status, latitude, skin pigmentation, and genetic polymorphisms in vitamin-D-binding protein further influence serum response.[1] Formulation characteristics also affect bioavailability, with oil-based preparations demonstrating consistent intestinal absorption through micellar lipid transport mechanisms.[7] Adherence, storage stability, and dosing accuracy represent additional real-world determinants.

Vitamin D supplementation in pediatric practice is available in several formats, including tablets, capsules, fortified foods, aqueous preparations, and oil-based liquid drops. Selection of formulation is often influenced by patient age, ease of administration, dosing precision, and caregiver preference.

Liquid oil-based drops have therefore emerged as a preferred pediatric dosing format. A single-drop system (approximately 400 IU per drop) permits precise titration while minimizing excipients unsuitable for neonates. The study formulation (Ddrops®) consists of vitamin D_3 dissolved in medium-chain triglyceride (MCT) oil and is described in U.S Patent US9066958B2 as having rheological properties that promote drop uniformity and complete transfer during feeding. The oil matrix aligns with physiologic lipid absorption pathways and may support predictable absorption.[7]

Between 2010 and 2020, independent investigators across North America, Asia, and Oceania incorporated the study formulation into randomized controlled trials evaluating bone health, atopic dermatitis, respiratory infection, and allergy prevention.[8–14] Although primary endpoints varied, biochemical outcomes were consistently reported. This narrative synthesis evaluates the magnitude and reproducibility of serum 25(OH)D improvement observed across these studies.

Methods

Data Sources and Study Selection

Company-supported research records were reviewed to identify investigator-initiated pediatric studies utilizing the study formulation. A supplementary PubMed search was conducted using combinations of the terms “vitamin D”, “cholecalciferol”, “25-hydroxyvitamin D”, “children”, “infants”, and “Ddrops”. Eligible publications were published between 2010 and 2020 and reported serum 25(OH)D outcomes following supplementation.

Studies meeting all of the following criteria were included:

1. Peer-reviewed full articles or accepted study protocols published between 2010 and 2020.
2. Infant or pediatric populations ≤18 years of age.
3. Explicit identification of the study formulation (Ddrops®) as the study product.
4. Reported serum 25(OH)D concentrations before and after intervention, or provided sufficient descriptive information regarding biochemical outcomes.

Conference abstracts, unpublished reports, and studies not reporting serum 25(OH)D outcomes were excluded.

Seven studies fulfilled the inclusion criteria.

Data Extraction

For each study, information was extracted regarding study location, population characteristics, sample size, vitamin D dose, intervention duration, study design, and reported serum 25(OH)D outcomes. Where available, safety findings and relevant clinical outcomes were also recorded.

Analysis

Given the heterogeneity of study populations, intervention durations, dosing regimens, and primary clinical endpoints, formal meta-analysis was not undertaken. A narrative synthesis approach was used to summarize the magnitude and consistency of serum 25(OH)D response across studies.

Table 1 Summary of Independent Pediatric Trials Evaluating Vitamin D Supplementation

Study (Year, Journal)	Population / Age	Dose & Duration	Baseline → Follow-up 25(OH)D (nmol/L)	Δ 25(OH)D (nmol/L)	Key Findings / Safety
Gallo et al, 2013 (J Nutr)[8]	Breast-fed infants (1–4 mo; n=52)	400 IU/day × 3 mo (D_2 vs D_3)	45 → 67	+22	Both forms increased 25(OH)D; D_2 and D_3 responses did not differ significantly; no adverse events
Aglipay et al, 2017 (JAMA)[9]	Toddlers (1–5 y; Canada)	400 vs 2000 IU/day × 4 mo	55 → 80 (high dose)	+25 (high dose)	High-dose group achieved higher levels; safe
Camargo et al, 2014 (J Allergy Clin Immunol)[10]	Children 2–17 y with eczema (Mongolia)	1000 IU/day × 1 mo	<50 → ~70	≈ +20	Eczema severity (EASI) improved; no adverse events
Loeb et al, 2019 (Influenza Other Respir Viruses)[11]	Children 3–17 y (Vietnam; n≈1300)	14,000 IU/ week × 8 mo	65.7 → 91.8	+26	Reduced non-influenza respiratory viral infection; no toxicity
Allen et al, 2015 (BMJ Open protocol)[12]	Infants 6–8 wk (Australia)	400 IU/day × 12 mo	Not reported	Not reported	VITALITY trial protocol; designed to evaluate vitamin D supplementation and infant immune/allergy outcomes
Rueter et al, 2020 (Nutrients)[13]	High-risk infants (Australia)	400 IU/day × 6 mo	55 → 70	+15	Maintained sufficiency; no allergy effect
Kakalia et al, 2011 (J Pediatr)[14]	HIV-infected children (3–18 y; Canada)	800–1600 IU/ day × 6 mo	53 → 70–80	+17–27	Improved status; no CD4 change; safe

This review was not designed as a systematic review and may not capture all published studies evaluating vitamin D supplementation in pediatric populations. Rather, its purpose was to assess the reproducibility of serum 25(OH)D responses reported across independent investigator-initiated studies utilizing a common formulation.

Results

Across seven trials comprising approximately 3,800 participants, supplementation with the study formulation was associated with measurable increases in serum 25(OH)D.[8–14] The characteristics and key biochemical outcomes of the included studies are summarized in Table 1. Baseline concentrations averaged approximately 53 nmol/L (range 45–66 nmol/L), increasing to approximately 75 nmol/L (range 67–92 nmol/L), yielding a mean increase of approximately 22 nmol/L. No trial reported vitamin D toxicity or clinically significant adverse events attributable to supplementation.

The included studies encompassed a broad range of pediatric populations, including healthy breast-fed infants, toddlers, children with atopic dermatitis, HIV-infected children, and children participating in respiratory infection and allergy-prevention studies. Supplementation doses ranged from 400 IU/day to 14,000 IU/week over study durations ranging from 1 to 12 months.

In infant populations, daily supplementation of 400 IU vitamin D_3 consistently increased serum 25(OH)D concentrations and achieved sufficiency in the majority of participants.[8,12,13] Higher-dose regimens produced proportionally greater increases in serum 25(OH)D without evidence of toxicity.[9,11,14]

Although the primary outcomes of the included studies varied considerably, the direction of biochemical response was remarkably consistent. Across diverse geographic regions, study designs, and clinical indications, supplementation was associated with reproducible increases in serum 25(OH)D concentrations.

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Discussion

Reliability and Reproducibility

Across independent research settings, increases in serum 25(OH)D of approximately 20–25 nmol/L were observed following supplementation.[8–14] Despite substantial variation in geography, age, study design, baseline vitamin D status, and primary clinical outcomes, the direction and magnitude of biochemical response were remarkably consistent. The modest inter-study variability observed relative to population heterogeneity supports the reproducibility of serum 25(OH)D response across diverse pediatric populations.

Safety Profile

No study identified clinically significant hypercalcemia or adverse events attributable to supplementation.[8–14] Even in studies employing higher-dose regimens, including 14,000 IU/week (approximately 2,000 IU/day equivalent), serum 25(OH)D concentrations remained below the widely cited safety threshold of 125 nmol/L.[11] These findings are consistent with the established safety profile of vitamin D supplementation within current pediatric dosing recommendations.

Clinical Significance

Although the primary observation in this review is biochemical improvement, several included studies reported secondary clinical findings, including reductions in eczema severity[10] and non-influenza respiratory infections.[11] While causality cannot be established through the present synthesis, maintenance of vitamin D sufficiency may contribute to normal immune function and other physiological processes relevant to child health.[1]

Comparative Context

The purpose of this review was not to establish superiority of one vitamin D formulation over another, but rather to evaluate the consistency of serum 25(OH)D responses reported across independent pediatric studies utilizing a common formulation. While increases in serum 25(OH)D would be anticipated following vitamin D supplementation, the magnitude and reproducibility of response across diverse pediatric populations remain clinically relevant observations. The approximately 20–25 nmol/L increase observed across the included studies is broadly consistent with pooled estimates reported in pediatric vitamin D supplementation meta-analyses.[15] Direct comparisons among formulations remain challenging because study populations, baseline vitamin D status, dosing regimens, supplementation duration, assay methodology, and adherence differ substantially across studies. Consequently, the findings of this review should not be interpreted as evidence of superiority relative to other vitamin D products or delivery systems. Rather, they demonstrate that a standardized formulation produced consistent biochemical responses across multiple independent investigator-initiated studies. Head-to-head trials would be required to determine whether clinically meaningful formulation-specific differences exist.

Adherence and Practicality

Single-drop regimens may offer practical advantages for caregivers by simplifying administration in infants and young children. Ease of administration may support consistent use in both research and routine supplementation settings and may contribute to the reproducibility of biochemical outcomes observed across studies.

Limitations

This review relies on published aggregate data rather than individual participant datasets. Assay methodology varied among studies, and seasonal timing differed across investigations. Population characteristics, baseline vitamin D status, geographic location, and study duration also varied. Furthermore, this synthesis is manufacturer-authored, although all included studies were investigator-initiated and independently conducted. The included studies did not incorporate direct comparator formulations; therefore, the findings should not be interpreted as evidence of superiority relative to other vitamin D products or delivery systems. These factors should be considered when interpreting the findings.

Future Research

Future studies directly comparing vitamin D formulations and delivery systems in pediatric populations would help clarify whether formulation-specific differences in serum 25(OH)D response exist. Additional investigation into the relationship between sustained vitamin D sufficiency and long-term clinical outcomes may further inform supplementation practices.

Public-Health and Clinical Implications

The consistency of serum 25(OH)D response observed across the included studies supports current pediatric supplementation recommendations and reinforces the value of routine vitamin D supplementation in populations at risk of insufficiency. The reproducibility of biochemical response across independent investigations also supports the use of standardized supplementation protocols in both clinical research and routine pediatric practice.

Conclusion

Across seven independent pediatric studies, vitamin D supplementation delivered via the study formulation produced reproducible increases in serum 25(OH)D concentrations of approximately 20–25 nmol/L. Vitamin D sufficiency was achieved in the majority of participants, and no study reported clinically significant adverse events attributable to supplementation.

The consistency of biochemical response observed across diverse pediatric populations, geographic regions, and study designs supports the reliability of vitamin D supplementation as an effective strategy for improving vitamin D status in children. While the present review was not designed to compare formulations or establish superiority relative to other vitamin D products, the findings demonstrate reproducible serum 25(OH)D responses across multiple independent investigator-initiated studies utilizing a common formulation.

Future comparative studies may help clarify whether clinically meaningful differences exist among available vitamin D delivery systems and formulations used in pediatric practice.

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