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What are the effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age? - A Cochrane Review summary with commentary

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Keywords: Children, Linear Growth, Supplementation, Vitamin D

The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review, "Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age"[1] by Huey et al.[a], under the direct supervision of Cochrane Developmental, Psychosocial and Learning Problems. This Cochrane Corner is produced in agreement with the Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation.

Background

Vitamin D deficiency is a common, global, public health concern that affects almost 50% of the population worldwide[2]. Vitamin D supplementation is already known as an effective treatment for vitamin D deficiency or insufficiency and, consequently, for regulation of skeletal homeostasis during infancy and childhood[1,3]. There are many protocols for vitamin D supplementation; however, the optimal supplementation for bone health and growth is still unclear[4,5]. This Cochrane Review[1] reviewed the evidence of the impact of oral vitamin D supplementation on linear growth and other health outcomes in infancy and childhood.

Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age

(Samantha L Huey, Nina Acharya, Ashley Silver, Risha Sheni, Elaine A Yu, Juan Pablo Peña-Rosas, Saurabh Mehta, 2020)

What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to investigate the impact of oral vitamin D supplementation on linear growth and other health outcomes in infants and children aged under five years of age.

The author declares no conflicts of interest.

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What was studied in the Cochrane Review?

The population addressed in this review was infants and children aged under five years of age, whose health status ranged from being healthy with no vitamin D deficiency to being vitamin D deficient; children who were born preterm or of low birth weight, or both, or who had other underlying medical conditions such as rickets, asthma, etc., were also included. The interventions studied were any intervention that assessed the impact of oral vitamin D supplementation. The comparisons were: (1) vitamin D supplementation versus placebo or no intervention, (2) higher-dose vitamin D supplementation versus lower-dose vitamin D supplementation, (3) vitamin D supplementation plus micronutrient(s) versus the same micronutrient(s) alone (i.e. without vitamin D), and (4) higher-dose vitamin D supplementation plus micronutrient(s) versus lower-dose vitamin D plus the same micronutrient(s). The primary outcomes of the review were linear growth, length/height-for-age z-score (L/HAZ), stunting, adverse effects relevant to excessive vitamin D intake (i.e. hypercalciuria, hypercalcemia, hyperphosphatemia, kidney stones).

Search methodology and up-to-dateness of the Cochrane Review?

The review authors searched for relevant randomized controlled trials (RCTs) and quasi-RCTs, including cluster-randomised and cross-over trials up to December 2019. They did not limit the searches by language, publication year, country, or region.

What are the main results of the Cochrane Review?

The review included 64 studies (169 reports, 10,854 participants) for the meta-analysis while a total of 75 studies (187 reports, 12,122 participants) were qualitatively analysed. The findings were as follows.

Comparison 1: vitamin D supplementation (at doses 200 to 2000 IU daily; or up to 300,000 IU bolus at enrolment) versus placebo or no intervention (31 studies)

- **Linear growth**: vitamin D supplementation may make little to no difference in linear growth (mean difference (MD) 0.66 cm, 95% confidence interval (CI) -0.37 to 1.68; 3 studies, 240 infants and children; low-certainty evidence), compared to placebo or no intervention.
- **L/HAZ**: vitamin D supplementation probably improves L/HAZ (MD 0.11 units, 95% CI 0.001 to 0.22; 1 study, 1258 infants and children; moderate-certainty evidence), compared to placebo or no intervention.
- **Stunting**: vitamin D supplementation probably makes little to no difference in stunting (risk ratio (RR) 0.90, 95% CI 0.80 to 1.01; 1 study, 1247 infants and children; moderate-certainty evidence), compared to placebo or no intervention.
- **Adverse events:**
  - **Hypercalciuria**: vitamin D supplementation probably makes little to no difference in developing hypercalciuria (RR 2.03, 95% CI 0.28 to 14.67; 2 studies, 68 infants and children; moderate-certainty evidence), compared to placebo or no intervention.
  - **Hypercalcemia**: it is uncertain whether vitamin D supplementation impacts the development of hypercalcemia (RR 0.82, 95% CI 0.35 to 1.90; 2 studies, 367 infants and children; very low-certainty evidence), compared to placebo or no intervention.
  - Hyperphosphataemia and kidney stones were not assessed in the included studies.

Comparison 2: higher-dose vitamin D supplementation (200 to 6000 IU daily; or up to 600,000 IU bolus at enrolment) versus lower-dose vitamin D supplementation (100 to 1000 IU daily; or up to 300,000 IU bolus at enrolment) (34 studies)

- **Linear growth**: higher-dose vitamin D supplementation may have little to no effect on linear growth (MD 1.00 cm, 95% CI -2.22 to 0.21; 5 studies, 283 infants and children; very low-certainty evidence), compared to lower-dose vitamin D supplementation, but the evidence is very uncertain.
- **L/HAZ**: higher-dose vitamin D supplementation may make little to no difference in L/HAZ (MD 0.40 units, 95% CI -0.06 to 0.0.86; 2 studies, 105 infants and children; low-certainty evidence), compared to lower-dose vitamin D supplementation.
- **Stunting**: no studies evaluated stunting.
- **Adverse events**:
  - **Hypercalciuria**: higher-dose vitamin D supplementation may make little to no difference in developing hypercalciuria (RR 1.16, 95% CI 1.00 to 1.35; 6 studies, 554 infants and children; low-certainty evidence), compared to lower-dose vitamin D supplementation.
  - **Hypercalcemia**: higher-dose vitamin D supplementation may make little to no difference in developing hypercalcemia (RR 1.39, 95% CI 0.89 to 2.18; 5 studies, 986 infants and children; low-certainty evidence), compared to lower-dose vitamin D supplementation.
  - Kidney stones and phosphatemia were not assessed in the included studies.

Comparison 3: vitamin D supplementation (50,000 IU vitamin D_2, monthly) plus micronutrient(s) (calcium, daily) versus the same micronutrient(s) (calcium, daily) alone (one study)

- Only one study (53 infants and children) compared this supplementation.

Comparison 4: higher-dose vitamin D supplementation (400 to 2000 IU daily, or up to 300,000 IU bolus at enrolment) plus micronutrient(s) versus lower-dose vitamin D supplementation (200 to 2000 IU daily, or up to 90,000 IU bolus at enrolment) plus the same micronutrient(s) (nine studies)

- **Linear growth**: higher-dose vitamin D supplementation plus micronutrient(s) may make little to no difference in

linear growth (MD 0.60 cm, 95% CI -3.33 to 4.53; 1 study, 25 infants and children; low-certainty evidence), compared to lower-dose vitamin D supplementation plus the same micronutrient(s).

- **L/HAZ**: no studies evaluated L/HAZ.
- **Stunting**: no studies evaluated stunting.
- **Adverse events**:
  - **Hypercalciuria**: higher-dose vitamin D supplementation plus micronutrient(s) may make little to no difference in developing hypercalciuria (RR 1.00, 95% CI 0.06 to 15.48; one study, 86 infants and children; low-certainty evidence), compared to lower-dose vitamin D supplementation plus the same micronutrient(s).
  - **Hypercalcemia**: higher-dose vitamin D supplementation plus micronutrient(s) probably makes little to no difference in developing hypercalcemia (RR 1.00, 95% CI 0.90, 1.11; 2 studies, 126 infants and children; moderate-certainty evidence), compared to the lower-dose vitamin D plus the same micronutrient(s).
  - Kidney stones and hyperphosphataemia were not assessed in the included studies.

What did the authors conclude?

The authors of the review concluded that oral vitamin D supplementation may lead to a slight increase in L/HAZ, but it may have little to no impact on linear growth, stunting, hypercalciuria, or hypercalcemia, compared with placebo or no intervention. Moreover, they found that higher-dose vitamin D supplementation may make little to no difference in linear growth, L/HAZ, hypercalciuria or hypercalcemia, compared with lower-dose vitamin D supplementation; no study assessed stunting. Lastly, they found that higher-dose vitamin D supplementation plus micronutrient(s) may make little to no difference in linear growth, hypercalciuria, or hypercalcemia, compared with lower-dose vitamin D supplementation plus the same micronutrient(s); no study assessed L/HAZ or stunting.

The authors of the review declared that there were several limiting factors in the included studies, such as small sample sizes, substantial heterogeneity within the population, and the contents of intervention, which reduced their ability to detect and confirm the certainty of evidence.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Vitamin D is important for bone health, muscular function, and all of which are related to optimal growth, and vitamin D deficiency has been associated with stunting and poor growth[6]. There are different vitamin D supplementation regimes to prevent vitamin D deficiency in infancy and childhood[1]. Many studies investigated the impacts of vitamin D supplementation in children. Vitamin D supplementation is already known to be an effective intervention in preventing rickets in early childhood. However, the evidence regarding the optimal doses and the impacts of oral vitamin D supplementation on growth faltering is still uncertain[4].

According to the results of this review[1], oral vitamin D supplementation may result in little to no difference in linear growth, stunting, hypercalciuria, or hypercalcemia, but probably leads to a slight increase in length-for-age z-score. However, the authors of the review could not be able to confirm the certainty of the evidence in terms of the impacts of vitamin D on the outcomes due to small sample sizes, substantial heterogeneity in the population and intervention parameters, and high risk of bias among the included studies. Moreover, oral vitamin D supplementation regimes were variable in range, quantity, frequency, and duration across studies.

The authors of the review[1] concluded that the current evidence does not support the recommendation of vitamin D supplementation for linear growth. The findings of the review may lead to implications for future researches to obtains more valuable data to find the optimal vitamin D supplementation programs in early childhood.

There is still a need to design studies investigating the effects of vitamin D supplementation in children, which use appropriate, valid, and reliable outcome measures related to growth, such as linear growth, L/HAZ, and stunting, with a longer period of supplementation and follow-up among large-scale populations to achieve more conclusive evidence.

From a rehabilitation point of view, vitamin D plays a significant role in calcium homeostasis, bone health, and neuromuscular function. There is a need to be aware of the effects of vitamin D on bone health and skeletal maturation, muscle function, as well as managing vitamin D deficiency as a potentially modifiable risk factor for musculoskeletal problems in children.

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