Review: In children and adults, vitamin D_3 supplementation reduces risk for acute respiratory tract infection

Martineau AR, Jolliffe DA, Hooper RL, et al. ***Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.*** *BMJ. 2017; 356:i6583.*

Clinical impact ratings: GIM ★★★★★★☆ ID ★★★★★★☆ PM ★★★★★★☆

Questions

Does vitamin D supplementation reduce risk for acute respiratory tract infection (ARTI)? Do effects differ in participant subgroups?

Review scope

Included studies compared oral vitamin D_3 supplementation with placebo, had research ethics approval, and prospectively collected data on ARTIs as a prespecified efficacy outcome. Long-term follow-up reports of primary randomized controlled trials (RCTs) were excluded. Primary outcome was ARTI. Other outcomes included upper ARTI, lower ARTI, ARTI-related hospitalization or emergency department visit, mortality, serious adverse events, and vitamin D–related adverse reactions (hypercalcemia or renal stones). PROSPERO International Prospective Register of Systematic Reviews CRD42014013953.

Review methods

MEDLINE, EMBASE/Excerpta Medica, Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and ISRCTN registry, all to Dec 2015; and reference lists were searched for double-blind RCTs. 25 RCTs (n = 11 321, duration 7 wk to 1.5 y, [n = 10 933 with primary outcome data; 50% women; age ≤ 1 y 51%, 1.1 to < 16 y 10%, ≥ 16 y 39%]) met the inclusion criteria. Individual patient data were obtained for all RCTs. 12 RCTs administered vitamin D_3 in daily doses (7.5 to 100 µg), 3 in weekly doses (35 to 500 µg), 7 as bolus doses (0.75 to 5.0 mg) given once or every 1 to 3 months, and 3 used both daily (10 to 100 µg) and bolus (2.4 to 2.5 mg) doses. All RCTs had adequate allocation concealment and blinded participants, study personnel, and outcome assessors; 23 RCTs had adequate follow-up rates.

Main results

The main results of 1-step individual patient data meta-analysis are in the Table. In prespecified subgroup analyses, effect of vitamin D supplementation for ARTIs differed by baseline serum 25-hydroxyvitamin D level (< 25 nmol/L, 41% receiving vitamin D_3 had ARTI vs 55% receiving placebo, P = 0.002; ≥ 25 nmol/L, 59% vs 63%, P = 0.15; $P_{interaction}$ = 0.01) and dosing regimen (bolus dose ≥ 30 000 IU, 36.4% vs 35.7%, P = 0.67; no bolus dose, 45% vs 50%, P < 0.001; $P_{interaction}$ = 0.05) but not by age, body mass index, daily dose equivalents, asthma or chronic obstructive pulmonary disease status, or influenza vaccination status.

Conclusion

In children and adults, vitamin D_3 supplementation reduces risk for acute respiratory tract infection.

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For correspondence: Professor A.R. Martineau, Queen Mary University of London, London, England, UK. E-mail a.martineau@qmul.ac.uk.

Oral vitamin D_3 supplementation vs placebo*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Vitamin D_3	Placebo		
Any ARTI	25 (10 933)	39%	42%	7.3% (2 to 12)†	33 (20 to 101)
Upper ARTI	19 (7019)	49%	50%	3.6% (−1 to 9)†	NS
Lower ARTI	9 (6698)	15.9%	16.5%	3.4% (−8 to 15)†	NS
ARTI-related hospitalization or emergency department visit	11 (7872)	1.0%	1.2%	17% (−27 to 46)†	NS
Serious adverse event	25 (11 224)	3.9%	4.0%	1.9% (−19 to 19)†	NS
Renal stones‡	14 (3841)	0.09%	0.23%	60% (−86 to 91)	NS
				RRI (CI)	NNH
All-cause mortality	25 (11 224)	1.2%	0.9%	39% (−15 to 124)†	NS
Hypercalcemia‡	14 (3850)	0.57%	0.52%	9.8% (−52 to 154)	NS

**ARTI = acute respiratory tract infection; other abbreviations defined in Glossary. Unless stated otherwise, weighted event rates, RRR, RRI, NNT, and CI calculated from placebo event rate and adjusted odds ratio for 1-step individual patient data meta-analysis in article using a random-effects model.*

†Adjusted for age, sex, and study duration.

‡Weighted event rates, RRR, RRI, and CI calculated from vitamin D_3 and placebo group event rates.

Commentary

For almost 100 years we have known that vitamin D can prevent bone disease. Its use in other circumstances is controversial. 2 respected groups concluded that convincing evidence does not exist for benefits of screening asymptomatic adults or for prescribing supplements to prevent other diseases (1, 2). After reviewing much of the same evidence, the Endocrine Society recommended screening for, and treating, vitamin D deficiency in a sizable proportion of the population (3). The disagreements may be due to differing interpretations of existing data and their quality.

The meta-analysis by Martineau and colleagues helps to clarify 1 narrow question and has several strengths. It combined individual patient data from 25 high-quality RCTs and so was able to look at effects in important subgroups. Although most participants were infants and children, the effect was consistent across all age groups and greatest in those with the lowest baseline levels of 25-hydroxyvitamin D, lending biological credibility to the findings. Adverse event rates were low and similar in treated and placebo groups. Martineau and colleagues suggested that unpublished studies were unlikely to change their results. However, time frames for follow-up and definitions of ARTI varied across RCTs, and treatment effects were small.

Several large, long-term RCTs evaluating the effect of vitamin D supplementation for other outcomes are ongoing (4); some results may become available soon and could prompt updates (and perhaps better agreement) of guidelines. In the meantime, because the benefit of vitamin D supplementation was mainly seen in the 5% of participants known to have very low levels of 25-hydroxyvitamin D, this review may provide some justification for screening high-risk persons (e.g., those with dark skin, low sun exposure).

Henry S. Sacks, PhD, MD
Icahn School of Medicine at Mount Sinai
New York, New York, USA

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