TITLE: Vitamin D Toxicity Associated with Different Vitamin D Dosing Regimens: Safety

DATE: 11 December 2014

RESEARCH QUESTION

What is the clinical evidence regarding toxicity associated with different vitamin D dosing regimens?

KEY FINDINGS

Three systematic reviews (including one meta-analysis), 24 randomized controlled trials (RCTs), and six non-randomized studies were identified containing clinical evidence regarding toxicity associated with different vitamin D dosing regimens.

METHODS

A focused search with main concepts appearing in title and focused subject headings was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 26, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults receiving vitamin D supplementation
Intervention	>600 IU of vitamin D
Comparator	None Placebo Various vitamin D doses
Outcomes	Safety (harms associated with toxicity)
Study Designs	Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies (safety only)

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs and non-randomized studies.

Three systematic reviews (including one meta-analysis), 24 RCTs, and six non-randomized studies were identified containing clinical evidence regarding toxicity associated with different vitamin D dosing regimens. No relevant health technology assessment reports were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Three systematic reviews (including one meta-analysis), 24 RCTs, and six non-randomized studies were identified containing clinical evidence regarding toxicity associated with different vitamin D dosing regimens.

Evidence on potential toxicity was identified for a variety of conditions including cystic fibrosis,[3,15] hypertension,[22] renal failure,[4,8] metabolic syndrome,[6] pregnancy,[7,10,11] obesity,[9] HIV,[16] critical illness,[17] chronic pancreatitis,[24] rheumatoid arthritis,[26] osteoporosis,[27] multiple sclerosis,[29] primary hyperparathyroidism,[30] and breast cancer.[33] In addition, evidence on potential vitamin D toxicity was identified for various populations including ethnic minorities[5,23,27] post-menopausal women,[14,20,25] community or nursing home dwelling seniors,[12,18,21,28] kidney stone formers,[31] and women of reproductive age.[32] The remaining trials were in varied[1,2] or healthy populations.[13,19]

Overall, toxicity symptoms and adverse events were not common. However, all but 11 studies[3,6,7,10,11,15,16,27,28,29,32] reported incidence of at least one occurrence of an undesirable outcome associated with vitamin D supplementation. The most commonly reported adverse outcomes were hypercalcemia[1,4,5,8,9,12,17,19,22,23,24,25,29,31,32] and hypercalciuria.[1,8,9,12,13,17,19,21,23,29,31] The most commonly reported renal outcome was nephrolithiasis.[1,2,19,30] Trials showing a negative effect of vitamin D supplementation on the above outcomes involved concomitant calcium treatment,[1,2,23,25,33] hydrochlorothiazide treatment,[22] or doses above 50000 IU.[13,19,21,31] Very limited evidence suggested an association between vitamin D supplementation and the occurrence of prostate cancer.[1] The only negative bone outcomes resulting from vitamin D supplementation were fractures and falls; the single trial[20] showing a negative effect with a mega-dose of 500000 IU. Gastrointestinal (GI) effects of vitamin D supplementation were

reported by a single review.[1] These GI outcomes were varied and mainly occurred in the context of concomitant calcium supplementation.[1]

Based on the identified evidence, vitamin D supplementation appears to be safe at doses below 50000 IU for most clinical populations. At doses above 50000 IU and with concomitant calcium or drug therapy, adverse effects relating to bone mineral homeostasis,[22,13,19,21,23,25,31,33] renal outcomes,[1,2,19] and skeletal outcomes[20] occurred in several trials. In general, the evidence suggests cause for caution when co-administering vitamin D and calcium[1,2,23,25,33] and when administering vitamin D doses in excess of 50000 IU.[13,19,20,21,31]

No evidence suggested negative effects of vitamin D supplementation on all-cause mortality,[1,2,8] tissue calcification,[8] cardiovascular outcomes,[1,6] hyperparathyroidism,[18,30,33] or hypervitaminosis D.[19,24]

Hypercalcemia and Hypercalciuria

Only one case of hypercalcemia was reported across eleven studies in the Agency for Healthcare Research and Quality (AHRQ) systematic review[1]. A post-hoc analysis of a RCT[22] reported a single occurrence of hypercalcemia and overall higher serum calcium in the group receiving concomitant hydrochlorothiazide and vitamin D supplementation compared to non-hydrochlorothiazide users receiving vitamin D supplementation. Two RCTs[23,25] investigating concomitant vitamin D and calcium therapy reported substantial rates of hypercalciuria and hypercalcemia, although they could not be attributed to vitamin D supplementation. One RCT[13] reported higher rates of hypercalcemia in the vitamin D group (50000 IU) compared to placebo. Three studies observed hypercalciuria in three,[19] six,[21] and 11[31] patients, respectively. Doses in these studies ranged from 3000 IU/d[19] to a single dose of 600000 IU.[21] One non-randomized study[33] reported a significant increase in serum calcium with concomitant vitamin D (10000 IU/d) and calcium (1000 mg/d) treatment for four months. No difference in the risk of hypercalcemia or elevated serum calcium between groups was observed in several RCTs,[4,5,6,8,9,12,17,18,19,24] and non-randomized studies.[29,30,31,32]

Renal Outcomes

Within the AHRQ systematic review[1] one trial reported an increased risk of renal stones with concomitant vitamin D and calcium supplementation. In addition, isolated vitamin D supplementation in two of the included RCTs was not associated with nephrolithiasis.[1] The identified meta-analysis[2] reported that concomitant vitamin D and calcium supplementation increased the risk of nephrolithiasis. One trial[12] reported similar elevations in serum creatinine between vitamin D and placebo groups. In another trial[29] renal impairment worsened in one patient; however, no incidence of nephrolithiasis occurred. One non-randomized study[30] reported stable creatinine in all patients and no new cases of nephrolithiasis during the vitamin D supplementation period.

Skeletal Outcomes

One RCT[14] reported no difference in the occurrence of falls between the vitamin D and placebo groups. Another RCT[20] reported an increased risk of fracture at three and nine months, and a higher rate of falls in the vitamin D supplementation group. No change in bone-specific alkaline phosphatase was reported for vitamin D and placebo groups in two other RCTs.[18,24]

General Morbidity and Serious Adverse Events

In the AHRQ systematic review[1] five included RCTs reported no adverse events for doses ranging between 200 IU/d to 120000 IU given biweekly for six weeks. Conversely, 11 RCTs in this systematic review[1] reported at least one adverse event for doses ranging between 400 to 5713 IU/d. Eleven studies reported zero adverse events or no difference in the incidence of adverse reactions or events between vitamin D and placebo groups.[3,6,7,10,11,15,16,27,28,29,32] Doses in these 11 studies ranged from 800 IU/d to a single 250000 IU dose.

Cancer

Observational evidence summarized in the AHRQ report[1] suggested an association between vitamin D intake and the occurrence of prostate cancer, and no association between vitamin D intake and incidence of other cancers.

Gastrointestinal Outcomes

Trial results summarized in the AHRQ review[1] reported incidence of gas, bloating, intestinal discomfort, constipation, nausea, diarrhea, vomiting, stomach ache, mouth irritation, and general GI symptoms. Concomitant calcium supplementation occurred in many of these included trials so the independent effect of vitamin D supplementation on GI symptoms is unclear.[1]

Other

Several occurrences of hepatic enzyme elevations were reported in an RCT, which included patients with rheumatoid arthritis.[26]

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses

1. Newberry SJ, Chung M, Shekelle PG, Suttorp Booth M, Liu JL, Ruelaz Maher A, et al. Vitamin D and calcium: a systematic review of health outcomes (update) [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2014 Sep. (Evidence Report/Technology Assessment Number 217). Report No.: 14-E004-EF. Contract No.: 290-2012-00006-I. [cited 2014 Dec 1]. Available from: http://effectivehealthcare.ahrq.gov/ehc/products/537/1953/vitamin-d-calcium-report-140902.pdf

2. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;1:CD007470.

3. Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. Cochrane Database Syst Rev. 2014;5:CD007298.
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Randomized Controlled Trials

Vitamin D Therapy (<50,000 IU)

4. Massart A, Debelle FD, Racape J, Gervy C, Husson C, Dhaene M, et al. Biochemical Parameters After Cholecalciferol Repletion in Hemodialysis: Results From the VitaDial Randomized Trial. Am J Kidney Dis. 2014 Nov;64(5):696-705.
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PubMed: PM24368437

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PubMed: PM24037880

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PubMed: PM23131462

11. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res [Internet]. 2011 Oct [cited 2014 Dec 1];26(10):2341-57. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3183324
PubMed: PM21706518

12. Lips P, Binkley N, Pfeifer M, Recker R, Samanta S, Cohn DA, et al. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am J Clin Nutr. 2010 Apr;91(4):985-91.
PubMed: PM20130093

Vitamin D Therapy (≥50,000 IU)

13. Zwart SR, Parsons H, Kimlin M, Innis SM, Locke JP, Smith SM. A 250 mug/week dose of vitamin D was as effective as a 50 mug/d dose in healthy adults, but a regimen of four weekly followed by monthly doses of 1250 mug raised the risk of hypercalciuria. Br J Nutr. 2013 Nov;110(10):1866-72.
PubMed: PM23595003

14. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. J Bone Miner Res. 2012 Jan;27(1):170-6.
PubMed: PM21956713

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PubMed: PM22933542

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Intramuscular Vitamin D

21. Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vitamin D deficient/insufficient elderly. Maturitas. 2012 Aug;72(4):332-8. PubMed: PM22613271

Concomitant Therapy

22. Chandler PD, Scott JB, Drake BF, Ng K, Forman JP, Chan AT, et al. Risk of hypercalcemia in blacks taking hydrochlorothiazide and vitamin D. Am J Med. 2014 Aug;127(8):772-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4127365 PubMed: PM24657333

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PubMed: PM21523344

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Non-Randomized Studies

Vitamin D Therapy (<50,000 IU)

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Concomitant Therapy

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PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

APPENDIX – FURTHER INFORMATION:

Systematic Reviews and Meta-analyses – Dosing Unspecified

34. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev. 2014;(6):CD007469.

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38. De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cocharane database Syst Rev. 2011;(2):CD008873.

Randomized Controlled Trials – Lead Poisoning

39. Groleau V, Herold RA, Schall JI, Wagner JL, Dougherty KA, Zemel BS, et al. Blood lead concentration is not altered by high-dose vitamin D supplementation in children and young adults with HIV. J Pediatr Gastroenterol Nutr [Internet]. 2013 Mar [cited 2014 Dec 1];56(3):316-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4132882 PubMed: PM23059649

Non-Randomized Studies

Dosing Unspecified

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Association between Serum 25(OH)D and Adverse Events

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Clinical Practice Guidelines – Uncertain Methodology

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Review Articles

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