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.

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Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults receiving vitamin D supplementation</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>&gt;600 IU of vitamin D</td>
</tr>
<tr>
<td>Comparator</td>
<td>None, Placebo, Various vitamin D doses</td>
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<tr>
<td>Outcomes</td>
<td>Safety (harms associated with toxicity)</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies (safety only)</td>
</tr>
</tbody>
</table>

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, hypertension, renal failure, metabolic syndrome, pregnancy, obesity, HIV, critical illness, chronic pancreatitis, rheumatoid arthritis, osteoporosis, multiple sclerosis, primary hyperparathyroidism, and breast cancer. In addition, evidence on potential vitamin D toxicity was identified for various populations including ethnic minorities, post-menopausal women, community or nursing home dwelling seniors, kidney stone formers, and women of reproductive age. The remaining trials were in varied or healthy populations.

Overall, toxicity symptoms and adverse events were not common. However, all but 11 studies reported incidence of at least one occurrence of an undesirable outcome associated with vitamin D supplementation. The most commonly reported adverse outcomes were hypercalcemia and hypercalciuria. The most commonly reported renal outcome was nephrolithiasis. Trials showing a negative effect of vitamin D supplementation on the above outcomes involved concomitant calcium treatment, hydrochlorothiazide treatment, or doses above 50000 IU. Very limited evidence suggested an association between vitamin D supplementation and the occurrence of prostate cancer. The only negative bone outcomes resulting from vitamin D supplementation were fractures and falls; the single trial 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, renal outcomes,1,2,19 and skeletal outcomes20 occurred in several trials. In general, the evidence suggests cause for caution when co-administering vitamin D and calcium1,2,23,25,33 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 RCT22 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 RCTs23,25 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 RCT13 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 1131 patients, respectively. Doses in these studies ranged from 3000 IU/d19 to a single dose of 600000 IU.21 One non-randomized study33 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 review1 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-analysis2 reported that concomitant vitamin D and calcium supplementation increased the risk of nephrolithiasis. One trial12 reported similar elevations in serum creatinine between vitamin D and placebo groups. In another trial29 renal impairment worsened in one patient; however, no incidence of nephrolithiasis occurred. One non-randomized study30 reported stable creatinine in all patients and no new cases of nephrolithiasis during the vitamin D supplementation period.
**Skeletal Outcomes**

One RCT\textsuperscript{14} reported no difference in the occurrence of falls between the vitamin D and placebo groups. Another RCT\textsuperscript{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.\textsuperscript{18,24}

**General Morbidity and Serious Adverse Events**

In the AHRQ systematic review\textsuperscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{1}

**Other**

Several occurrences of hepatic enzyme elevations were reported in an RCT, which included patients with rheumatoid arthritis.\textsuperscript{26}
Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


Randomized Controlled Trials

Vitamin D Therapy (<50,000 IU)


**Vitamin D Therapy (≥50,000 IU)**


**Intramuscular Vitamin D**


**Concomitant Therapy**


Non-Randomized Studies

Vitamin D Therapy (<50,000 IU)


Vitamin D Therapy (≥50,000 IU)


Concomitant Therapy

APPENDIX – FURTHER INFORMATION:

Systematic Reviews and Meta-analyses – Dosing Unspecified


Randomized Controlled Trials – Lead Poisoning


Non-Randomized Studies

Dosing Unspecified


Association between Serum 25(OH)D and Adverse Events

42. Zittermann A, Kuhn J, Dreier J, Knabbe C, Gummert JF, Borgermann J. Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery. Eur Heart J. 2013 May;34(18):1358-64.

PubMed: PM23315905

Clinical Practice Guidelines – Uncertain Methodology


Review Articles

PubMed: PM23250508

PubMed: PM23094916

PubMed: PM22414585

PubMed: PM20567854

Additional References