Overview

1. Vitamin D is important in maintaining calcium balance and bone health. Its natural form is Vitamin D3.
2. D3 dosing affects relevant bone health markers (e.g., serum calcium, 25(OH)D3 and PTH) and endpoints (lumbar spine bone-mineral density (BMDLS)).

Objectives

1. To explore the effect of combined D3 plus calcium supplementation (D3CA) on bone-health endpoints (i.e., serum PTH, BMDLS).
2. To evaluate D3 dose and 25(OH)D3 threshold recommendations for reaching target BMDLS or PTH levels and compare to Institute of Medicine (IOM) recommendations (400-600 IU/d; 40-50 nmol/L; 25(OH)D3).

Background

Vitamin D3 dosing affects relevant bone health markers (e.g., serum calcium, 25(OH)D3), which maintain bone health by facilitating the absorption of calcium (Ca) from the gut and kidneys (calcitriol = 1.25(OH)2D3) (Fig. 1).

Methods

Methods (a)

Population-Level Simulations

- Serum calcium, serum PTH, and BMDLS responses to 1 year of D3 (800, 1000, 2000 IU/d) with or without calcium (0, 300, 1000 mg/d)
- Serum calcium response to 1 year of D3 supplementation (400, 800, 2000 IU/d) over a range of calcium baselines (50-110 pmol/L)
- Explore D3 dose and 25(OH)D3 threshold recommendations for reaching BMDLS and PTH targets after 1 year of D3 with or without 1000 mg/d calcium supplementation (25(OH)D3 BL = 30 nmol/L)
- Software: R, mrgsolve [1]

Methods (b)

Modifying calcitriol ODE & AOH0 taken from Peterson & Riggs [3]

- Power model chosen due to mathematical parameter non-identifiability with more complex models (i.e., optimized parameter)
-Calcitrol self-inhibition implemented by parameterizing γ as an inverse function of AOH0
-A gamma parameter, relevant to sigmoidal inhibition, was re-estimated to describe BMDLS response in Vitamin D3 with or without calcium supplementation

Results: Meta-Analysis Data Search & Integrated Model Structure

Table 1: Summary of bone-marker and BMD studies used to fit (F) or validate (V) the integrated Vitamin D3-MSPM

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Study Type</th>
<th>Study Design</th>
<th>Baseline Calcium (mg/d)</th>
<th>Baseline 25(OH)D3 (nmol/L)</th>
<th>D3 Dose (IU/d)</th>
<th>D3CA Dose (IU/d)</th>
<th>Study Duration (y)</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Study 1</td>
<td>Source 1</td>
<td>Observational</td>
<td>Cross-sectional</td>
<td>300</td>
<td>20</td>
<td>800, 1000, 2000</td>
<td>800, 1000, 2000</td>
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<td>Notes 1</td>
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<tr>
<td>Study 2</td>
<td>Source 2</td>
<td>Interventional</td>
<td>Randomized controlled trial</td>
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<td>40</td>
<td>800, 1000, 2000</td>
<td>800, 1000, 2000</td>
<td>1</td>
<td>Notes 2</td>
</tr>
</tbody>
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Conclusions

- A power model as a function of 25(OH)D3 concentration described the conversion of 25(OH)D3 to calcitriol and its apparent self-inhibition
- External predictive checks indicated model performance for predicting bone health marker responses to Vitamin D3 with or without calcium
- Vitamin D3 with calcium administration is more effective than Vitamin D3 alone at raising BMDLS and decreasing PTH levels
- Calcium administration is more potent at increasing BMDLS/PTH for 25(OH)D3 > 70 nmol/L because of the non-linear D3 clearer
- Model simulations (25(OH)D3 BL = 30 nmol/L) indicated necessary 25(OH)D3 levels somewhat higher than those recommended by the IOM (40-50 nmol/L) for raising BMDLS > 5%
- BMDLS 1.5-2.0: 25(OH)D3 80-100 nmol/L without 1000 mg/d calcium; 1000-1100 IU/d D3
- Vitamin D3 dose and 25(OH)D3 threshold recommendations with 1000 mg/d calcium decreased relative to Vitamin D3 supplementation alone for BMDLS increases > 5%

Reference