Vitamin D supplementation in clinical practice: a practical approach

Theocharis Koufakis MD, PhD
Internist
Research Associate
Division of Endocrinology and Metabolism - Diabetes Center,
1st Department of Internal Medicine
Medical School, Aristotle University
Thessaloniki, Greece
Disclosure statement

• I have no actual or potential conflict of interest in relation to this presentation
Introduction

• Another Vit D paradox...

• > 70,000 papers in Pubmed relative to Vit D

• However….no definite consensus regarding the optimal supplementation strategy, making clinical decisions difficult

• In terms of everyday practice, clinicians are required to select adequate recommendation from a variety of available guidelines
Introduction

• Most recommendations agree that Vit D can be given as a daily, weekly or monthly dose

• No clear indication that one dosing schedule should be preferred instead of the other

Cesareo et al, Nutrients, 2018
Aim of presentation

- To present the available evidence regarding potential differences of intermittent compared to daily supplementation strategies, in terms of:
  - Efficacy
  - Safety
  - Compliance
Which Vit D?

Comparison of vitamin D$_2$ and vitamin D$_3$ supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis$^{1-3}$

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>D3 Mean</th>
<th>D3 SD</th>
<th>Total</th>
<th>D2 Mean</th>
<th>D2 SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biancuzzo 2010-1 (7)</td>
<td>23.3</td>
<td>17.8</td>
<td>20</td>
<td>27</td>
<td>14.8</td>
<td>16</td>
<td>11.2%</td>
<td>-3.70 [-14.35, 6.95]</td>
</tr>
<tr>
<td>Biancuzzo 2010-2 (7)</td>
<td>32</td>
<td>25.3</td>
<td>18</td>
<td>26.5</td>
<td>18</td>
<td>17</td>
<td>9.9%</td>
<td>5.50 [8.99, 19.99]</td>
</tr>
<tr>
<td>Binkley 2011-1 (15)</td>
<td>23</td>
<td>33.8</td>
<td>16</td>
<td>15.3</td>
<td>16.5</td>
<td>16</td>
<td>8.6%</td>
<td>7.70 [10.73, 26.13]</td>
</tr>
<tr>
<td>Binkley 2011-2 (15)</td>
<td>22.3</td>
<td>18.3</td>
<td>15</td>
<td>9.14</td>
<td>13</td>
<td>16</td>
<td>10.9%</td>
<td>13.30 [1.69, 24.91]</td>
</tr>
<tr>
<td>Glendenning 2009 (16)</td>
<td>40</td>
<td>24.7</td>
<td>17</td>
<td>26</td>
<td>11.2</td>
<td>20</td>
<td>10.5%</td>
<td>14.00 [1.27, 26.73]</td>
</tr>
<tr>
<td>Heaney 2011 (17)</td>
<td>98.4</td>
<td>29.1</td>
<td>17</td>
<td>57.4</td>
<td>22</td>
<td>16</td>
<td>8.9%</td>
<td>41.00 [23.46, 58.54]</td>
</tr>
<tr>
<td>Holick 2008 (6)</td>
<td>23.3</td>
<td>17.8</td>
<td>20</td>
<td>24.8</td>
<td>8</td>
<td>16</td>
<td>11.8%</td>
<td>-1.50 [-10.23, 7.23]</td>
</tr>
<tr>
<td>Romagnoli 2008-1 (5)</td>
<td>70.2</td>
<td>20.8</td>
<td>8</td>
<td>25.5</td>
<td>16.9</td>
<td>8</td>
<td>8.6%</td>
<td>44.70 [26.13, 63.27]</td>
</tr>
<tr>
<td>Romagnoli 2008-2 (5)</td>
<td>65.4</td>
<td>30.3</td>
<td>8</td>
<td>23.1</td>
<td>13.8</td>
<td>8</td>
<td>7.2%</td>
<td>42.30 [19.23, 65.37]</td>
</tr>
<tr>
<td>Trang 1998 (4)</td>
<td>23.3</td>
<td>15.7</td>
<td>55</td>
<td>13.7</td>
<td>11.4</td>
<td>17</td>
<td>12.3%</td>
<td>9.60 [2.77, 16.43]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>194</td>
<td>150</td>
<td>100.0%</td>
<td>15.23</td>
<td>6.12</td>
<td>24.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{I}^2 = 162.74$, $\text{Chi}^2 = 47.10$, df = 9 ($P < 0.00001$); $I^2 = 81$

Test for overall effect: $Z = 3.28$ ($P = 0.001$)

D3 is more efficacious at raising 25(OH)D concentrations than is D2

The physiological background

• Is there a physiological background for intermittent Vit D supplementation?
Physiological Vit D synthesis follows an intermittent pattern, depending on the intermittent exposure to natural sunlight or access to Vit D rich food sources.
The physiological background

• Does the bioavailability of the molecule justify intermittent dosing?
• A single large dose will clearly elevate serum calcidiol

Armas et al, J Clin Endocrinol Metab, 2004

• Degree and duration of elevation?
• Is the response linearly related to dose?
30 healthy subjects received a single oral dose of 100,000 IU D3 (baseline 27.1 ng/ml)

Mean concentrations had fallen below the desirable 32.1 ng/ml at day 70

Serum concentrations declined linearly thereafter

Peak at day 7

This study recommends 100,000 IU every 2 months as a safe, efficient and cost-effective supplementation strategy
Pharmacokinetics of daily versus monthly vitamin D₃ supplementation in non-lactating women

Michael E MEEKINS, PharmD¹, Sara S OBERHELMAN, MD², Bernard R LEE, PharmD³, Brian M GARDNER, PharmD⁴, Stephen S CHA, Ph.D⁵, Ravinder J SINGH, Ph.D⁶, John M PETTIFOR, M.B.,B.Ch., Ph.D⁷, Phillip R FISCHER, MD⁸, and Tom D THACHER, MD²

No differences in mean 25(OH)D concentrations between groups on days 0 and 28 (p=.14 and p=.28, respectively)

The daily group had 11 more days detectable serum D3 than the single-dose group (p<.001)

No difference was observed in D3 AUC₂₈ between groups (p=.49)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>150,000 IU Once n = 19</th>
<th>5,000 IU Daily n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>26.11 (21 – 35)</td>
<td>25.8 (21 – 35)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.1 (50.4 – 96.1)</td>
<td>63.4 (50.8 – 93.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.4 (154.4 – 174.9)</td>
<td>166.9 (155.1 – 177)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 (19 – 23.4)</td>
<td>22.8 (18.6 – 33.5)</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>75.8 (56 – 112)</td>
<td>72.8 (49 – 103)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>111.8 (95 – 138)</td>
<td>115.9 (93 – 146)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66.3 (50 – 80)</td>
<td>65.5 (45 – 88)</td>
</tr>
<tr>
<td>Race: White</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>Asian</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Area Under the Curve: the amount of a therapeutic agent that is present in the circulation in a determined time period
Circulating vitamin D, the parent compound, likely plays an important physiological role, not originally thought to be important.

Weekly or longer interval dosing will result in large fluctuations in circulating vitamin D but stable concentrations of 25(OH)D.

Daily doses of vitamin D result in stable circulating concentrations of both compounds.
Intermittent vs daily supplementation
Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents

V. Chel · H. A. H. Wijnhoven · J. H. Smit · M. Ooms · P. Lips

338 individuals in 10 nursing homes. Mean age 84 y and baseline concentrations 25 mmol/L

They received oral D3 600IU/d, 4200 IU/w or 18000IU/m for 4 months

Daily administration was significantly more effective than weekly and monthly (p<.01 between groups)

The study can be criticized for presenting a high dropout rate (18.3% died or withdrew)

The compliance calculation could be questionable, as only random samples of the returned medications were counted
64 participants, Vit D deficient (<20 ng/ml). Prospective, controlled, randomized, multicenter clinical trial

Group A: 1000 IU/d
Group B: 7000 IU/week 3 months
Group C: 30000 IU/month

All treatment regimens demonstrated similar efficacy in increasing 25OHD levels

25OHD levels were restored above 20 ng/ml in all groups
Monthly supplementation produced a more rapid increase in 25(OH)D serum concentrations.

The cut-off value of 20 ng/mL in 25(OH)D3 was reached 24h after the intake of vitamin D3, while 14 days were needed after the daily supplementation ($p=0.02$).

Increases in 25(OH)D3 serum concentrations from baseline were similar after day 25 between the 2 groups and until the end of the study.

60 participants, Vit D deficient (10-20 ng/ml).
Comparison of two regimens of vitamin D supplementation for vitamin D-deficient neonates

Mehrdad Shakiba¹, MD, Ali Pahloosye¹, MD, Mehrdad Mirouiaei¹, MD, Zia Islami¹, MD

Bolus 30000 IU (n=34) or 400 IU/d (n=48)
Intermittent vs daily supplementation
Effects of Three-Monthly Oral 150,000 IU Cholecalciferol Supplementation on Falls, Mobility, and Muscle Strength in Older Postmenopausal Women: A Randomized Controlled Trial

Paul Glendenning,1,2,3 Kun Zhu,1,4 Charles Inderjeeth,1,5 Peter Howat,6 Joshua R Lewis,1,4 and Richard L Prince1,4

686 women > 70y, Baseline serum 25(OH)D 65.8±22.7 nmol/L

Group A: 1500000 IU every 3m
Group B: Placebo
Duration 9 m

Increased mobility and physical performance following supplementation?

Direct effects on bone cells / altered enzymatic activity?

**Faller** Vitamin D 28.5%; Placebo 25.7%  
CR 1.06 (95% CI 0.75, 1.49)

**Multiple faller** Vitamin D 7.4%; Placebo 4.8%  
CR 1.35 (95% CI 0.70, 2.59)
Safety and Efficacy of Weekly 30,000 IU Vitamin D Supplementation as a Slower Loading Dose Administration Compared to a Daily Maintenance Schedule in Deficient Patients: A Randomized, Controlled Clinical Trial

66 Vit D deficient participants [baseline 25(OH)D < 20 ng/ml]

Group A: 30000 IU/w 12 weeks
Group B: 1000 IU/d 90 d
Group C (control): 30000 IU/m 12 weeks

No relevant change in mean serum Ca levels between groups

2 cases of hypercalcemia (one in each group) not exceeding the 110% of UNL

Both subjects were receiving Ca supplementation
Frail patients

• There is data regarding Vit D deficient, but otherwise healthy individuals

• What about the safety profile of intermittent doses in vulnerable group of patients?
Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation

Guillaume Jean¹, Jean-Claude Souberbielle² and Charles Chazot¹

107, Vit D deficient HD patients

100000 IU/m for 15 months

In the present study, administration of a monthly cholecalciferol dose of 100 000 IU during a 15-month period appeared to be a simple, inexpensive and efficient strategy to correct vitamin D insufficiency in ~90% of the HD patients and did not result in any evident mineral metabolism toxicity. The most significant consequences were a decrease in the levels of PTH and bone markers and an increase in the serum 1,25(OH)₂D level.
88 studies on Vit D supplementation in children and adolescents

A loading dose of > 40000 IU can rapidly elevate 25(OH)D concentrations

No increased hypercalcemia or hypercalcuria risk with loading doses ≤ 300000 IU

Significant increase in hypercalcemia risk with doses ≥ 400000 IU
10933 participants in 25 studies were analyzed. Stratification of safety analysis did not reveal any statistical increase in risk of adverse events with bolus, daily or weekly supplementation.
Intermittent vs daily supplementation
A phase IV, two-armed, randomized, cross-over study comparing compliance with once-a-month administration of vitamin D3 to compliance with daily administration of a fixed-dose combination of vitamin D3 and calcium during two 6-month periods

O. Bruyère¹ • R. Deroisy² • N. Dardenne¹ • E. Cavalier³ • M. Coffiner⁴ • S. Da Silva⁴ • S. De Niet⁴ • J.-Y. Reginster¹

99 individuals > 50 yo

<table>
<thead>
<tr>
<th>Reason</th>
<th>VD group</th>
<th>VDCa group</th>
<th>Fisher exact test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste</td>
<td>2 (3.0)</td>
<td>3 (18.8)</td>
<td>0.030</td>
</tr>
<tr>
<td>Ease of use</td>
<td>17 (34.0)</td>
<td>10 (62.4)</td>
<td></td>
</tr>
<tr>
<td>Frequency of use</td>
<td>21 (42.0)</td>
<td>3 (18.8)</td>
<td></td>
</tr>
<tr>
<td>No adverse events</td>
<td>7 (14.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment reputation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (6.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50 (76.5)</td>
<td>16 (23.5)</td>
<td></td>
</tr>
</tbody>
</table>

Group A: 25000 IU/w
Group B: 800 IU + 1000 mg Ca/d

After 6 months the groups were reserved

For both periods, the compliance was higher in the VD group (100%) than in the VDCa group (96.2% and 91.7%, periods 1 & 2)

56.8% preferred the VD treatment
18.2% preferred the VDCa
25% neither treatment was preferred
Skeletal and hormonal responses to vitamin D supplementation during sunlight deprivation in Antarctic expeditioners

S. Iuliano-Burns • J. Ayton • S. Hillam • G. Jones • K. King • S. Macleod • E. Seeman

110 healthy adults working in Antarctica for 12 months

Group A: 50000 IU/m
Group B: 50000 IU every 2m
Group C: 50000 IU single dose pre-departure

Compliance rate > 99% for all groups

A previous study using daily doses in healthy adults who spent winter in Antarctica demonstrated poor compliance

Smith et al, Am J Clin Nutr, 2009
Conclusions (1)

• Limitations of available evidence

• Small number of subjects included

• Heterogeneity in study designs (e.g. dosing) and explored outcomes
Conclusions (2)

• Intermittent dosing seems to be equally effective and safe compared to daily schemes

• No safety issues were observed even in studies that included frail groups of individuals

• Intermittent schemes produce a more rapid increase in serum 25(OH)D concentrations

• Intermittent regimens probably present higher compliance rates compared to daily ones
Thank you for your attention