The Effect of Oral Supplementation of Vitamin D₃ on Serum Levels of Vitamin D: A Review

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Abstract

Due to the strong interest in the role of vitamin D in health, we tried to find data to illustrate the relationship between oral supplementation and change in serum levels of vitamin D. We reviewed the literature of randomized, placebo-controlled trials of oral supplementation and serum levels of vitamin D through 2014. We found 25 informative studies which showed a significant dose-response between oral supplementation and serum levels of vitamin D with an r² of 0.61. These data are consistent with single studies and meta-analyses. In conclusion, the data show a consistent relationship that appears to be independent of multiple confounders.

Keywords: Ultraviolet radiation; Cholecalciferol; Serum levels

Introduction

Recently there has been a resurgence of interest in the role of vitamin D₃, or cholecalciferol, supplementation in disease prevention and health maintenance. Systematic reviews have recently been published with a focus on specific groups, such as those over 50 [1] or by body mass index [2]. Studies have been carried out on serum vitamin D levels to evaluate the role of supplementation on risk for multiple health conditions, ranging from bone health to cancer.

However, the benefits and risks of cholecalciferol supplementation are under debate after the publication of a 2010 Institute of Medicine Report that recommended supplementary and dietary reference levels for Vitamin D [3]. From an epidemiological perspective, cholecalciferol is unique, as it can be obtained not only through food and supplementation, but also from ultraviolet radiation, specifically UVB (280-320 nm) [4]. Thus, some groups have suggested that people increase time in the sun and forgo sunscreen in an effort to increase their serum 25-(OH)D levels [5]. However, because over exposure to UVB rays can also lead to an increase in skin cancer incidence, the health effects associated with UV exposure may be problematic.

Oral supplementation of Vitamin D₃ may be a safe alternative to UVB and should be easy to regulate to achieve optimum dosage [6]. Unfortunately, outside of single studies, there is little research that evaluates the dose-response relationship between oral intake of cholecalciferol and subsequent serum levels of vitamin D. Because of this knowledge gap, we conducted a literature review to gain perspective on current knowledge about the dose-response of serum vitamin D with supplementation.

Methods

We reviewed studies identified through a combination of personal archives and the National Library of Medicine database PubMed using the search terms “vitamin D supplementation,” “vitamin D serum” “randomized trials of vitamin D” and “25-(OH)D.” The earliest eligible study available was from 1991 and the most recent was from 2013. Studies were excluded for incomplete, or inaccessible data, leaving 36 studies that were included in this review. Of these 36 studies, 25 were analyzed (Table 1) and evaluated through graphical analysis (Figure 1), and 11 were listed separately (Table 2) because of irregular dose patterns, such as a one-time bolus intervention.

The studies we reviewed were chosen from available literature addressing vitamin D and met pre-determined criteria for involvement. These criteria included information as to the dose of oral supplementation of cholecalciferol (vitamin D₃) and serum levels of 25-(OH)D at baseline and post-intervention and included placebo groups for comparison (Tables 1 and 2). We found that many studies looked at the effect of vitamin D supplementation and dietary intake on disease outcome. Sixteen studies meeting our criteria evaluated...
<table>
<thead>
<tr>
<th>Study Number and Author</th>
<th>Location</th>
<th>Subjects [number, age, and sex]</th>
<th>Length of Study</th>
<th>Amount of Supplemental Vitamin D Given</th>
<th>Serum levels–Baseline and After [nmol/L]</th>
<th>Change in serum level [nmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biancuzzo RM et al. [7]</td>
<td>Boston, Massachusetts</td>
<td>34 healthy adults, 18-79</td>
<td>11 weeks</td>
<td>1000 IU/D</td>
<td>Baseline: 53.2 After: 83.9</td>
<td>30.7</td>
</tr>
<tr>
<td>Ng K et al. [9]</td>
<td>Boston, Massachusetts</td>
<td>328 African American, 30-80 years old</td>
<td>3 months</td>
<td>1000 IU/D 2000 IU/D 4000 IU/D</td>
<td>1000 Baseline: 40.4 1000 After: 74.1 2000 Baseline: 34.7 2000 After: 86.9 4000 Baseline: 39.2 4000 After: 114.6</td>
<td>1000: 26.9 2000: 48.2 4000: 75.6</td>
</tr>
<tr>
<td>Ala-Houhala MJ et al. [10]</td>
<td>Tampere, Finland</td>
<td>33 healthy hospital employees</td>
<td>4 weeks</td>
<td>800 IU/D</td>
<td>Baseline: 53.5 After: 73.7</td>
<td>20.2</td>
</tr>
<tr>
<td>Gepner AD et al. [12]</td>
<td>Madison, Wisconsin</td>
<td>114 healthy post-menopausal women mean age 63.9,</td>
<td>4 Months</td>
<td>2500 IU/D</td>
<td>Baseline: 78.1 After: 117.3</td>
<td>39.2</td>
</tr>
<tr>
<td>Holvik K et al. [13]</td>
<td>Oslo, Norway</td>
<td>55 subjects. Healthy adults, average age 28 years, 63.6% women</td>
<td>4 weeks</td>
<td>400 IU/D</td>
<td>Baseline: 44.3 After: 78.4</td>
<td>34.1</td>
</tr>
<tr>
<td>Toss G et al. [14]</td>
<td>Linköping, Sweden</td>
<td>45 subjects of which 32 were female, aged 55-84</td>
<td>1 Year</td>
<td>1600 IU/D</td>
<td>Baseline: 50.4 After: 84.2</td>
<td>33.8</td>
</tr>
<tr>
<td>Pfeifer M et al. [16]</td>
<td>Bad Pymont, Graz, Austria</td>
<td>114 healthy men and women, 70+ years</td>
<td>1 year</td>
<td>400 IU/D</td>
<td>Baseline: 55 After: 84</td>
<td>29</td>
</tr>
<tr>
<td>Holick M F et al. [17]</td>
<td>Boston, Massachusetts</td>
<td>68 healthy, different racial/ethnic groups, 18-84 years old</td>
<td>11 weeks</td>
<td>1000 IU/D</td>
<td>Baseline: 48.9 After: 72.1</td>
<td>23.2</td>
</tr>
<tr>
<td>Heany R P et al. [18]</td>
<td>Omaha, Nebraska</td>
<td>67 healthy men, average age 38.7</td>
<td>20 weeks</td>
<td>1,000, 5,000 or 10,000 IU/D</td>
<td>1000 baseline: 72.1 1000 after: 84.1 5000 Baseline: 69.3 5000 After: 161.2 10000 Baseline: 65.6 10000 After: 225.0</td>
<td>1000: 12 5000: 91.9 10000: 159.4</td>
</tr>
<tr>
<td>Trang H M et al. [19]</td>
<td>Toronto, Canada</td>
<td>72 subjects, mean age 38</td>
<td>14 days</td>
<td>4000 IU/D</td>
<td>Baseline: 41.3 After: 64.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Lips P et al. [20]</td>
<td>Amsterdam, Netherlands</td>
<td>2578 people, including 1916 women and 662 men, mean age 80, with no major health problems</td>
<td>3.5 years</td>
<td>4000 IU/D</td>
<td>Baseline: 23 After: 60</td>
<td>37</td>
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<tr>
<td>Chapuy MC et al. [21]</td>
<td>Lyon, France</td>
<td>142 Healthy, ambulatory women aged 84 ± 6 years</td>
<td>18 months</td>
<td>800 IU/D</td>
<td>Baseline: 39.9 After: 104.8</td>
<td>64.9</td>
</tr>
<tr>
<td>Dawson-Hughes B et al. [22]</td>
<td>Massachusetts</td>
<td>333 healthy, postmenopausal women, mean age 61.4</td>
<td>1 year</td>
<td>400 IU/D</td>
<td>Summer baseline: 81.6 Post summer: 97 Winter baseline: 60.6 Post winter: 92.3</td>
<td>Summer: 15.4 Winter: 31.5</td>
</tr>
<tr>
<td>Gallagher JC et al. [23]</td>
<td>Omaha, Nebraska</td>
<td>163 postmenopausal white females with vitamin D insufficiency, mean age 67, divided into 8 study groups of 20 or 21 participants</td>
<td>1 year</td>
<td>400, 800, 1600, 2400, 3200, 4000, or 4800 IU/D</td>
<td>400 Baseline: 37.8 400 After: 60.9 800 Baseline: 39.0 800 After: 74.4 1600 Baseline: 37.4 1600 After: 87.9 2400 Baseline: 38.2 2400 After: 95.8 3200 Baseline: 39.8 3200 After: 101.3 4000 Baseline: 37.2 4000 After: 105.8 4800 Baseline: 38.6 4800 After: 109.3</td>
<td>4000: 23.1 800: 35.4 1600: 50.5 2400: 57.6 3200: 61.5 4000: 68.6 4800: 70.7</td>
</tr>
</tbody>
</table>
Subjects came from Malmö, Sweden, mean age of 32

Al-Daghri NM et al. [25]
Riyadh, Kingdom of Saudi Arabia
92 total, 58 women, median age 56.6 and 34 men, median age 51.2. All had Diabetes Mellitus Type 2
18 Months 2000 IU/D Baseline: 32.2 After: 54.7 22.5

Harris SS et al. [26]
Boston, Massachusetts
69, Overweight or obese African Americans with prediabetes or diabetes
12 Weeks 4000 IU/D Baseline: 40 After: 81 41

Yiu et al. [27]
Hong Kong, China
100 type 2 DM patients with 25 [OH]D concentration <30 ng/mL
12 weeks 5000 IU/D Baseline: 54.9 After: 152.4 97.5

Pierrot-Deselligny C et al. [28]
Paris, France
156 Relapsing-remitting multiple sclerosis patients under first line immunomodulatory therapy and initial serum levels less than 100 nmol/L
29.1 Months 3010 IU/D Baseline: 49 After: 110 61

Garrett-Mayer E et al. [29]
Columbia, South Carolina
47 patients, 12 African American [mean age 63.2] and 35 White men [mean age 65.3] with early-stage low-risk prostate cancer
1 year 4000 IU/D Baseline: 91.6 After: 167.9 76.3

Bischoff-Ferrari HA et al. [30]
Zurich, Switzerland
173 patients with previous hip fracture age >65 [average age 84 years] 79% Women
1 year 800 IU/D or 2000 IU/D 800 Baseline: 31.5 After: 92.0 2000 Baseline: 34.1 After: 116.21 800: 60.6 2000: 82.2

Suzuki M et al. [31]
Tokyo, Japan
114 patients with Parkinson’s Disease, aged 45-85
1 year 1200 IU/D Baseline: 56.2 After: 104.1 47.9

Table 1: Randomized studies of daily vitamin D [IU/D] with change in serum level [nmol/L] over baseline.

<table>
<thead>
<tr>
<th>Study Number and Author</th>
<th>Location of Study</th>
<th>Subjects [number, age, and sex]</th>
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<th>Change in serum level [nmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matias PJ et al. [32]</td>
<td>Portugal</td>
<td>158 Hemodialysis Patients</td>
<td>6 months</td>
<td>50,000 IU/week [25(OH)D=15 ng/mL]</td>
<td>Baseline: 55.7 After: 104.8</td>
<td>49.1</td>
</tr>
<tr>
<td>Gowsami Ret al. [33]</td>
<td>New Delhi, India</td>
<td>173 Healthy Asian Indian females</td>
<td>6 Months</td>
<td>60,000 IU/week</td>
<td>Baseline: 57.9 After: 186.2</td>
<td>128.3</td>
</tr>
<tr>
<td>Alvarez JA et al. [34]</td>
<td>Atlanta, GA</td>
<td>46 patients with stage 2 &amp; 3 CKD 18-90 years</td>
<td>12 months</td>
<td>50,000 IU/week for 12 weeks 50,000 IU/every other week for 40 weeks</td>
<td>Baseline: 67.4 After: 116.6</td>
<td>49.2</td>
</tr>
<tr>
<td>Markmann Pet al. [35]</td>
<td>Odense, Denmark</td>
<td>52 Chronic Kidney Disease patients, male and female, mean age 71</td>
<td>8 Weeks</td>
<td>40,000 IU/week</td>
<td>Baseline: 23.8 After: 141.6</td>
<td>117.8</td>
</tr>
<tr>
<td>Armas LA et al. [36]</td>
<td>Omaha, Nebraska</td>
<td>Patients with Stage 5 Chronic Kidney Disease</td>
<td>15 Weeks</td>
<td>10,333 IU/week</td>
<td>Baseline: 33.2 After: 92.1</td>
<td>58.9</td>
</tr>
<tr>
<td>Lips Pet al. [37]</td>
<td>Subjects came from Mexico Washington, Indiana, Nebraska, Netherlands, Germany, and, Canada</td>
<td>226 men and women, mean age 78.5, who were vitamin D deficient</td>
<td>16 Weeks</td>
<td>8400 IU/week</td>
<td>Baseline: 34.7 After: 65.4</td>
<td>30.7</td>
</tr>
<tr>
<td>Tokmak Fet al. [38]</td>
<td>North Rhine-Westphalia, Germany</td>
<td>64 haemodialysis patients</td>
<td>9 months</td>
<td>20,000 IU/week</td>
<td>Baseline: 16.7 After: 79.5</td>
<td>62.8</td>
</tr>
<tr>
<td>Jakopin E et al. [39]</td>
<td>Slovenia</td>
<td>101 Hemodialysis patients [52 men, 49 women] Average age 63.3 years</td>
<td>24 months</td>
<td>40,000 IU/month</td>
<td>Baseline: 28.6 After: 54.9</td>
<td>26.3</td>
</tr>
<tr>
<td>Wilham MC et al. [40]</td>
<td>Dundee, United Kingdom</td>
<td>74 subjects with a history of myocardial infarction, average age 66 years</td>
<td>6 months</td>
<td>100,000 IU Bolus every two months</td>
<td>Baseline: 49 After: 62</td>
<td>13</td>
</tr>
<tr>
<td>Grossman RE et al. [41]</td>
<td>Atlanta, Georgia</td>
<td>30 Adults in the hospital for Cystic Fibrosis Pulmonary Exacerbation, mean age 24.9, both male and female, all Caucasian</td>
<td>12 Weeks</td>
<td>One time 250,000 IU Bolus</td>
<td>Baseline: 76.4 After: 91.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Tran Bet al. [42]</td>
<td>Australia</td>
<td>615 population-based, 60-84 years old</td>
<td>1 year</td>
<td>30,000 IU/month 60,000 IU/month</td>
<td>Baseline: 41.6 30,000 After: 63.9 60,000 Baseline: 41.7 60,000 After: 77.9</td>
<td>30,000: 22.3 60,000: 36.1</td>
</tr>
</tbody>
</table>

Table 2: Randomized studies of vitamin D [IU] that gave weekly, monthly or bolus supplementation [nmol/L].
healthy individuals [7-22]. Nine studies meeting our criteria evaluated individuals with disease included individuals with vitamin D deficiency [23,24], individuals with diabetes [25-27], relapsing multiple sclerosis patients [28], individuals with early stage prostate cancer [29], patients with previous hip fractures [30], and Parkinson Disease [31]. The number of studies that included the necessary information on serum levels pre- and post-supplementation were limited, and only a few addressed serum vitamin D levels exclusively in response to oral supplementation.

Although we wished to perform a meta-analysis, we found that the data were too heterogeneous for valid statistical evaluation. Some of the factors that contributed to the heterogeneity included varying geographical latitude, age, pre-existing medical conditions, dose size, and calcium supplementation, frequency of dose, follow-up time, and overall quality of the study. In addition, we found that several studies did not include crucial information, such as standard deviation or baseline levels, because vitamin D was not the primary focus of their research. Studies that were not placebo-controlled, randomized, or had an inadequate sample size (i.e., fewer than 20) were eliminated from our main analysis. It should be noted that seven of the studies gave weekly doses of cholecalciferol (Table 2) while three others administered one-time only bolus doses. These two groups were evaluated separately and not included in the daily dose results.

In order to determine the change in serum vitamin D per amount of oral supplementation, we subtracted the baseline serum level from the post-intervention serum level and correlated that with the amount of oral vitamin D given. This information was calculated by linear regression using change from baseline serum vitamin D and with duration included as both a quadratic and linear term using SAS 9.3 (Carr, NC).

Results

Analyses of the best available data show a clear trend. Figure 1, which shows the data from the twenty most reliable and homogeneous studies [7-26], exhibits a positive correlation between amounts of oral vitamin D administered and change in serum vitamin D levels. Figure 1 shows the change in vitamin D serum levels from the most rigorous studies that gave daily doses of cholecalciferol. These values are highly significantly correlated with a P-value<0.001 and an r² of 0.61. We did not analyze the data from Table 2 statistically because the data were too few for meaningful analysis.

Discussion

These results demonstrate the overall coherence of the more generalizable studies, all of which were double blind and had an adequate sample size. Interestingly, our simple model is quite robust. There is a relatively strong dose-response between the amount of supplement and the change in serum vitamin D status. Surprisingly, results did not change significantly when we restricted them to studies of healthy individuals or to studies with intervention of 6 months or more. From the large scatter noted in Figure 1, it is clear that a great deal more information needs to be evaluated regarding the appropriate dose of vitamin D3 to raise serum vitamin D to a specific level. In addition, there is a clear need for additional placebo-controlled, double-blind studies to be conducted on the effects of serum 25-(OH)D levels in response to oral supplementation. One of the main limitations to our research was the fact that there are actually few randomized studies of cholecalciferol supplementation. To be useful for study of the effect of cholecalciferol on health and disease outcomes as well as clinical utility, it is important to know how different doses of vitamin D change serum vitamin D. Thus more studies need to be conducted on the oral supplementation of cholecalciferol before the scientific community can understand the importance of vitamin D supplementation to health.

Limitations include the heterogeneous nature of the studies and the fact that our analysis did not take into account the climate zone in which a person lives, or the role of age, body mass index, activity and diet in determining serum levels of vitamin D. In addition, the linear regression and slope determined using Figure 1, do not account for the “plateau” of serum vitamin D levels at high concentrations (e.g., 23). However, as a beginning, our study provides a baseline from which we can develop a more precise evaluation. This is especially important in light of the aging US population, the recent increase in interest in the role of vitamin D in disease prevention and the urgent need to carefully understand the role of vitamin D in health—whether it is a symptom of poor health or a means to better health.

Acknowledgements

This work was supported by the National Cancer Institute at the National Institutes of Health (K05 CA131675 to M.B).

References


