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## Who Benefits from Calcium and Vitamin D Supplementation

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The use of calcium and vitamin D products in Oregon fee-for-service patients account for over 44,000 claims annually.<sup>1</sup> Suggestion of benefit for many common disorders, from depression to cancer, have led to increased utilization of both supplements. As with any supplement or medication, prudent use should be supported by evidence of benefit. Additionally, the financial implications of the high utilization of calcium and vitamin D requires justification. This newsletter will examine the evidence of benefits and harms associated with calcium and vitamin D products and offer suggestions for optimal use.

**Background** - Calcium is important for adequate bone formation with a suggested recommended daily allowance (RDA) of 700-1,300 mg daily, depending on age.<sup>2,3</sup> Calcium is prevalent in many foods and adequate RDAs may be met through diet alone. If supplementation is required, calcium supplements should be dosed based on elemental calcium. The National Osteoporosis Foundation endorses the Institute of Medicine (IOM) recommendations of 1,000 mg daily of calcium for men aged 51-70 years and 1,200 mg daily for men 71 years and older and for women 51 years and older.<sup>3</sup> The World Health Organization (WHO) recommends 1,500-2,000 mg of calcium daily for pregnant women.<sup>4</sup>

Vitamin D is needed for intestinal absorption of calcium and phosphorous.<sup>5</sup> Vitamin D is produced in the skin as vitamin D3 through exposure to sunlight; alternatively, vitamin D can be supplemented as vitamin D<sub>3</sub> (cholecalciferol), vitamin D<sub>2</sub> (ergocalciferol) or obtained through diet (oily fish, etc.).<sup>2</sup> Absorption of vitamin D can vary depending on several factors.<sup>2,4</sup> The U.S. Preventative Services Task Force (USPSTF) recommends against routine screening of asymptomatic adults, but other guidelines recommend screening individuals at high risk for vitamin D deficiency.<sup>5,7</sup> Low sun exposure, obesity, fat malabsorption syndromes, bariatric patients, nephrotic syndrome, certain medications and endocrine disorders increase the risk of vitamin D deficiency.<sup>5</sup> There is no consensus on optimal vitamin D levels and commonly used assays have high levels of variability.<sup>8</sup> The IOM recommends a serum 25-hydroxyvitamin D [25(OH)D] level of  $\geq 20$  ng/mL for adequate bone health.<sup>3</sup> However, the Endocrine Society, National Osteoporosis Foundation and International Osteoporosis Foundation suggest 25(OH)D levels of  $\geq 30$  ng/mL.<sup>5</sup> Recommended vitamin D intake via diet and/or supplementation is presented in Table 1.<sup>5</sup>

Table 1. Recommended Vitamin D Intake by Age<sup>\*5</sup>

Population			
1-70 years	$\geq 600$ IU	Over 70 years	$\geq 800$ IU
Risk of Deficiency			
0-1 years	400 – 1,000 IU	19-50 years	1,500 – 2,000 IU
1-18 years	600 - 1,000 IU	>50 years	1,500 – 2,000 IU
Pregnant or Lactating	600 - 2000 IU		
Vitamin D Deficient			
1-18 years	Treatment: 2,000 IU/day or 50,000 IU D <sub>2</sub> once weekly for 6 weeks Maintenance: 600 - 1,000 IU/day		
> 18 years	Treatment: 6,000 IU/day or 50,000 IU D <sub>2</sub> or D <sub>3</sub> once weekly for 8 weeks Maintenance: 1,500 - 2,000 IU/day		

\* Daily dose unless otherwise stated / IU - International Units

## CALCIUM

**Bone** - The benefits of calcium supplementation on bone health have recently been evaluated. A high-quality systematic review (n=26 trials) with meta-analysis found supportive evidence for the use of calcium supplementation in elderly women. There was a lower risk of total body fractures (any non-vertebral fractures) versus control groups (11% vs. 12%, respectively; relative risk [RR] 0.89; 95% CI, 0.81 to 0.96; P=0.004) and fewer vertebral fractures versus controls (1.3% vs. 1.5%, respectively; RR 0.86; 95% CI, 0.74 to 1.00; P=0.04) regardless of calcium dose.<sup>9</sup> No benefit was seen in hip or forearm fractures.

Calcium with vitamin D had similar results as calcium monotherapy. Studies of dietary calcium (milk powder and hydroxyapatite) had no effect on fracture rates.<sup>9</sup> A second systematic review (n=59 trials) of women under 70 years of age found bone mineral density (BMD) increased by 0.7-1.8% in the hip, lumbar spine, femoral neck, forearm and total body with calcium supplementation dosed 250-2,500 mg daily.<sup>5</sup> In contrast, anti-resorptive therapy (e.g., bisphosphonates) increased BMD by 6-9% over 3 years.<sup>5</sup>

**Pregnancy** - Calcium has been thought to lower the risk of pre-eclampsia, pre-term birth and blood pressure in pregnant women. A systematic review of 13 trials (n=15,730) found moderate evidence that calcium supplementation ( $\geq 1$  g/day) decreases the risk of pre-eclampsia during pregnancy (RR 0.45; 95% CI, 0.31 to 0.65), with an incidence rate of 65/1000 in controls (placebo or no treatment) compared to 29/1000 in women treated with calcium.<sup>10</sup> The greatest benefits were seen in women with diets low in calcium and women who had a high risk of pre-eclampsia. Calcium supplementation was also found to reduce the risk of hypertension in this population compared to placebo (RR 0.65; 95% CI, 0.53 to 0.81) as well as decrease the incidence of pre-term birth (79/1000 vs. 104/1000, respectively; RR 0.76; 95% CI, 0.60 to 0.97).<sup>10</sup> However, calcium supplementation did not reduce the occurrence of pre-term birth in women not at increased risk for pre-eclampsia.<sup>11</sup>

## VITAMIN D

**Bone** - Evidence suggests that vitamin D has limited benefit for fracture prevention. A Cochrane Review found vitamin D alone, compared to control (placebo, no intervention or calcium alone), does not prevent hip fractures (RR 1.12; 95% CI, 0.98 to 1.29) or new bone fractures (RR 1.03; 95% CI 0.96 to 1.11) in trials of predominately elderly women.<sup>12</sup> These results were supported by the USPSTF which found insufficient evidence to determine the benefits and harms of vitamin D<sub>3</sub> 400 IU or more and calcium 1000 mg or more. Doses of vitamin D<sub>3</sub> 400 IU or less and calcium 1000 mg or less were not found to be beneficial for primary prevention of fractures in postmenopausal women.<sup>7</sup>

**Falls** - There is evidence of fall prevention with vitamin D supplementation. Vitamin D doses of 400-1000 IU were found to decrease the number of falls compared to placebo (41.6% vs. 55.8%, respectively; RR 0.66; 95% CI, 0.50 to 0.88) in elderly women.<sup>13</sup> Limited evidence suggests an increased risk of falls with high doses (500,000 IU annually and >24,000 IU monthly) of vitamin D.<sup>14,15</sup> The USPSTF concluded that for patients 65 years and older at risk of falls, vitamin D supplementation may be beneficial for fall prevention.<sup>7,13</sup>

**Cancer** - Evidence from a systematic review and meta-analysis in primary and secondary prevention patients (n=50,623) that were cancer-free at study initiation found no benefit of vitamin D supplementation compared to placebo on cancer rates.<sup>16</sup> A modest 0.4% reduction in cancer-related mortality was found with vitamin D supplementation compared to controls (2.5% vs. 2.9%, respectively; RR 0.94; 95% CI, 0.91 to 0.98; p=0.002).<sup>16</sup>

**Mortality** - The evidence on the ability of vitamin D to reduce mortality has been inconsistent. The USPSTF found no significant effect of vitamin D on mortality compared to placebo (RR 0.83; 95% CI, 0.73 to 1.18).<sup>13</sup> This finding was substantiated by a second meta-analysis of high dose or intermittent dose vitamin D.<sup>17</sup> A Cochrane review found a 0.2% reduction in mortality with vitamin D supplementation, however, high levels of attrition cause concern over the reliability of the findings.<sup>18</sup>

Additional trial data found no beneficial effect of vitamin D for the following conditions: cystic fibrosis, pain scores, depression, systolic or diastolic blood pressure, asthma symptoms in children, and A1C in type 2 diabetes.<sup>18-26</sup> Outcomes related to pregnancy, such as pre-eclampsia and gestational diabetes were also not reduced by vitamin D supplementation.<sup>27,28</sup>

**Harms of Calcium and Vitamin D** - A recent retrospective review looked at emergency department (ED) visits related to dietary supplements.<sup>29</sup> Data was analyzed from 63 U.S. hospitals from 2004 to 2013. Deaths were not tracked

due to differences in reporting practices. Over 23,000 ED visits were identified. Of those, 32% were related to micronutrients. Calcium was associated with 3.4% (95% CI, 2.5% to 4.3%) of visits. In patients 65 years and older, iron, calcium and potassium accounted for one-third of all ED visits related to supplements. Visits due to calcium were primarily related to swallowing difficulties (combination of choking and pill-induced dysphagia or globus).<sup>29</sup>

A report by Canadian Agency for Drugs and Health Technologies in Health (CADTH) evaluated toxicities with vitamin D regimens.<sup>30</sup> Three systematic reviews, 24 randomized controlled trials (RCTs) and 6 non-randomized trials were evaluated. Hypercalcemia and hypercalciuria were the most commonly reported adverse events and nephrolithiasis was the most common kidney-related event. Combination therapy with calcium, hydrochlorothiazide or high dose vitamin D (>50,000 IU) were most notably associated with these adverse events. Reports of increased risk of prostate cancer and vitamin D supplementation have been reported but there is very limited evidence of this association.<sup>30</sup> Vitamin D regimens dosed less than 50,000 IU appear to be safe. Additional evidence found 25(OH)D levels greater than 50 ng/mL may be associated with a higher risk of mortality, cardiovascular disease, cancer and falls.<sup>7</sup> A second CADTH report found no link between combination calcium and vitamin D supplements and an increased risk of cardiovascular disease.<sup>31</sup>

**OHP Recommendations** - In March of 2016 the Oregon Health Plan (OHP) Pharmacy and Therapeutics Committee recommended vitamin D and calcium supplements be covered only for patients who are pregnant, have a nutrient deficiency, have a diagnosis of osteoporosis, or are 65 years of age or older and at increased risk for falls.<sup>32</sup> Evidence so far indicates these populations may benefit from supplementation with calcium and vitamin D. Additionally, it is recommended that patients receive a 90-day supply of these supplements to minimize the time and expense of multiple fills.

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