

# D3 Liquid

## Vitamin D Liquid (cholecalciferol) 1000 IU Drops\*



Available in 1 fluid ounce (30 mL) and 2 fluid ounces (60 mL)

### Discussion

Vitamin D has numerous critical roles in human physiology and is imperative for supporting overall health from gestation to senescence. Vitamin D is unique because it can be synthesized in the skin. When 7-dehydrocholesterol reacts to sunlight, it is transported to the liver and converted into the metabolically active form 1 $\alpha$ ,25-dihydroxyvitamin D.<sup>1</sup> This process may be inefficient in those with darker skin tones and is dependent on sunlight intensity, which varies with latitude, season, and other factors.\*

Vitamin D insufficiency may occur more frequently in older adults, people with gastrointestinal (GI) issues that can impair vitamin D absorption, individuals with obesity or those who have undergone gastric bypass surgery, and those with limited sun exposure and extensive sunscreen use, which can limit vitamin D synthesis. Additionally, individuals consuming a low-cholesterol diet, those on medications that bind fats, or those with fat malabsorption issues are at risk for insufficiency as cholesterol is a precursor to vitamin D formation.\*<sup>2</sup>

According to the Dietary Guidelines for Americans and data from the National Health and Nutrition Examination Surveys (NHANES), vitamin D consumption falls short in many Americans' diets.<sup>3,4</sup> Most dietary vitamin D comes from fortified foods; however, food sources naturally containing vitamin D are limited to fatty fish, egg yolks, and small amounts in other animal source foods.<sup>2</sup> Therefore, assessing average intake levels of vitamin D is somewhat difficult.\*

Growing awareness of the functional role and health consequences associated with the lack of dietary vitamin D has prompted many healthcare practitioners to include a regular assessment of serum vitamin D as part of their standard order for lab work. Vitamin D levels below 20 ng/mL are considered deficient, and between 21 and 29 ng/mL are insufficient.\*<sup>2,5,6</sup>

The dose of vitamin D required to correct a deficiency and maintain a serum level above 30 ng/mL may be impacted by age, vitamin D status, and clinical circumstances. These factors also contribute to the wide variation in daily recommended intake levels. For example, the baseline recommended daily allowance for adults aged 19 to 50 set by the Institute of Medicine is 600 IU with an upper limit of 4,000 IU. Whereas the Endocrine Practice Guidelines Committee recommends an intake of 1,500 to 2,000 IU with an upper limit of 10,000 IU for individuals of this same age group *who are at risk for deficiency*, and daily dose recommendations ranging from 6,000 to 10,000 IU daily or 50,000 IU weekly to reach 30 ng/mL in those *who are deficient*.<sup>1,5</sup>

## Clinical Applications

- » Supports Bone Health\*
- » Supports Modulation of Immune Function\*
- » Supports Brain Health\*
- » Supports Musculoskeletal Comfort\*
- » Supports Cardiovascular Health\*
- » Supports Healthy Blood Sugar Metabolism\*
- » Supports Vitamin D Repletion\*

*D3 Liquid provides 1,000 IU of vitamin D per drop in a high-oleic sunflower carrier oil to facilitate biodistribution. Vitamin D is a crucial nutrient to support immune function, musculoskeletal comfort, healthy blood sugar metabolism, and cardiovascular, bone, and brain health. Liquid delivery allows for dose customization and may be preferable for those with digestive issues and pill fatigue.\**

A review comparing vitamin D intakes required to achieve a vitamin D level above 30 ng/mL suggests that an intake greater than 1,000 IU/d is needed in at least 50% of the population.<sup>7</sup> In a study comparing 1,000- to 2,000-IU doses of vitamin D for achieving adequate reference values in healthy subjects (N = 72) during the winter months, it was concluded that both doses helped to maintain sufficient serum D levels; however, the higher dose maintained the desired level for a longer period after discontinuation.\*<sup>8</sup>

### Immune Health

Vitamin D works as a modulator of immune function. Dietary deficiency and low vitamin D status have been linked to compromised immune system integrity and insufficient immune responses.<sup>9,10</sup> Vitamin D has multiple functions in immune cells, including increasing the antimicrobial activity of neutrophils, promoting apoptosis of immunoglobulin-producing B cells, suppressing T-cell proliferation, and differentiation of monocytes to macrophages, which increases their activity against pathogens and reduces the secretion of pro-inflammatory factors.\*<sup>11</sup>

In a randomized trial in young adults (N = 30), most of whom were vitamin D sufficient, placebo or supplemental vitamin D at 200 IU (low dose) or 4,000 IU (high dose) was given over a 28-day period during the winter. The low dose inhibited a decrease in serum D and interleukin-5, whereas the high dose increased serum D by 50%. The authors suggest this finding is of physiological importance regarding the maintenance of a sufficient D level to mediate immune system protection.\*<sup>11</sup>

A meta-analysis of data from 25 randomized clinical trials concluded a significant overall protective effect on respiratory immune health in deficient individuals given a daily dose of 400 to 1,000 IU of vitamin D for up to 1 year.<sup>10</sup> Within that meta-analysis, 1 study assessed the correlation of vitamin D status to reducing the incidence of immune challenges in subjects (N = 223) with inflammatory bowel disease (IBD). Vitamin D supplemented at 500 IU/d during the winter and early spring months was found to have a protective effect on respiratory health, which correlated with improved vitamin D status.\*<sup>12</sup>

While there is a clear link between vitamin D and immune function, results from studies using vitamin D as a supplement to modulate immune function have been conflicting, and additional research is needed to validate the efficacy of this role.

\*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

### Musculoskeletal Comfort

Vitamin D is essential for developing muscle fibers and modulating healthy inflammatory processes, affecting muscle function. Insufficient vitamin D levels can adversely affect muscle strength and comfort.\*<sup>2,13,14</sup>

In a trial designed to assess the modulating effect of vitamin D on muscle cells after excessive exercise, male volunteers (N = 60) were subjected to exercise testing before and 3 months after supplementation. At a dose calculated based on body mass and baseline levels, vitamin D was found to be effective in restoring optimal serum D levels and significantly contributing to reduced post-exercise muscle damage markers compared with baseline.<sup>15</sup> Additionally, an in vitro analysis of the muscle cell migration dynamics from a similar study, in which subjects (N = 20) were given 4,000 IU of vitamin D for 6 weeks, suggests a role for vitamin D in human skeletal muscle regeneration, repair, and subsequent hypertrophy.\*<sup>16</sup>

In a randomized trial in which runners (N = 24) were supplemented with placebo or 2,000 IU of vitamin D daily for 3 weeks, significant differences were observed in pre- and post-intervention serum D levels. Results also indicated a decrease in post-exercise skeletal muscle biomarkers, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and myoglobin, suggesting a role for vitamin D supplementation in muscle recovery.\*<sup>17</sup>

Results from these trials challenge results from previous studies that did not suggest a benefit for vitamin D in easing musculoskeletal comfort; additional research is needed to elicit this role further.\*<sup>16,17</sup>

### Blood Sugar Metabolism

Vitamin D plays a role in blood sugar metabolism by stimulating insulin secretion via vitamin D receptors in pancreatic beta cells. It can also ease insulin resistance through its impact on muscles and liver receptors. Observational studies have linked low serum vitamin D status to an increased risk of insulin resistance. In a randomized trial of overweight, prediabetic African Americans (N = 89), 4,000 IU of vitamin D per day was correlated with a correction in insufficient serum D level and an increase in insulin sensitivity; however, an overall effect on risk for or improvement of glycemia was not observed.\*<sup>18</sup>

In a systematic review of 20 randomized clinical trials, short-term (~3 months) vitamin D supplementation in doses greater than 2,000 IU/d was found to increase serum vitamin D levels, which was correlated with reduced insulin resistance in subjects who were vitamin D deficient.<sup>19</sup> Additional research is needed to further define the role of vitamin D supplementation in blood sugar metabolism.\*

### Cardiovascular Health

Vitamin D is functional in regulating the renin-angiotensin system, which is important in controlling blood pressure. There is also evidence for a role for vitamin D in arterial elasticity, vascular function, hyperlipidemia, and left ventricular hypertrophy.\*<sup>20</sup>

In a double-blind, randomized clinical study, researchers assessed the differential effects of vitamin D supplementation in a high-risk cardiovascular disease group. Subjects (N = 70) with deficient serum vitamin D levels were randomized to receive 600, 2,000, or 4,000 IU/d of vitamin D or placebo for 16 weeks. Supplementation resulted in dose-dependent increases in serum vitamin D concentrations, with 2,000 or 4,000 IU/d reducing arterial stiffness, as measured by carotid-femoral pulse wave velocity, which was significantly reduced in the 4,000-IU/d group.\*<sup>21</sup>

In a randomized trial investigating the effects of vitamin D combined with calcium on blood pressure, older women (N = 148) were given either 800 IU of vitamin D with calcium or calcium alone. The subjects given vitamin D, in combination with calcium, demonstrated a more beneficial effect in reducing blood pressure. Although the results cannot be attributed to vitamin D alone, the researchers concluded that inadequate vitamin D could play a contributory role in the progression of hypertension and cardiovascular disease in older women.\*<sup>22</sup>

A systematic review and meta-analysis analyzed data from 41 randomized trials to assess the effect of vitamin D supplementation on serum lipid profiles. A beneficial effect was concluded for serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride reduction but not for high-density lipoprotein cholesterol, suggesting supplementation was useful in individuals with vitamin D insufficiency who are also at a high cardiovascular disease risk. Improvements in total cholesterol and triglycerides were more pronounced in subjects with vitamin D deficiency at baseline.<sup>23</sup> Although

it is clear that vitamin D status is correlated with cardiometabolic risk factors, additional research is needed to further assess the impact of vitamin D supplementation on cardiovascular health.\*

### Bone Health

The role of vitamin D in skeletal health and bone density is well-established. Vitamin D is intricately involved in calcium homeostasis. If calcium levels are low, parathyroid hormone (PTH) is secreted. The PTH stimulates vitamin D to balance serum calcium levels by increasing dietary calcium absorption, increasing reabsorption of calcium filtered by the kidney, and mobilizing calcium from bone when dietary levels are insufficient, putting bone health at risk. Vitamin D and PTH also regulate the homeostasis of serum phosphorus, which is involved in bone and teeth formation.\*<sup>24</sup>

Research indicates that vitamin D deficiency coexists with low bone mineral density, and vitamin D insufficiency is a common risk factor for osteoporosis associated with increased bone remodeling and low bone mass.<sup>25</sup> A pooled analysis evaluating 11 randomized, double-blind, placebo-controlled trials concluded that vitamin D supplementation (>800 IU daily), with or without calcium, was favorable in maintaining hip and nonvertebral bone integrity in individuals aged 65 and older.\*<sup>26</sup>

### Brain Health

Vitamin D supports brain health by regulating growth factors for neural and glial cells and neurotransmitter synthesis, including acetylcholine, dopamine, and GABA. Research has linked these biochemical effects and vitamin D insufficiency to the onset and progression of neurological conditions.<sup>1</sup> Additionally, higher vitamin D status has been suggested to benefit brain health.\*<sup>27</sup>

In a randomized trial in adult subjects (N = 48) with reported migraines, researchers investigated the potential role of supplemental vitamin D in reducing the frequency of migraines. Participants in the test group were given 4,000 IU of vitamin D for a 24-week treatment period and reported a reduction in migraine days when compared with those receiving placebo.<sup>28</sup> A similar trial in which subjects (N = 80) were given either 2,000 IU of placebo for 12 weeks resulted in fewer migraine attacks of less duration and severity in addition to significant improvements in inflammatory markers associated with migraines.\*<sup>29</sup>

Analysis of prospective data from the UK Biobank used to examine the association between serum vitamin D concentrations and neuroimaging outcomes revealed a link between low vitamin D status and the risk of dementia and stroke.<sup>27</sup> Additionally, results from animal, in vitro, and observational studies have suggested an association between vitamin D and cognition improvement in those at risk for decline. In a randomized clinical trial assessing the effect of vitamin D supplementation on cognitive function in subjects (N = 30) with type 2 diabetes, participants received either a weekly vitamin D dose of 50,000 IU or a comparator of 5,000 IU for 3 months. Upon comparison, there were no significant cognitive findings, but improvement in several cognitive function test parameters was observed for both dose groups. The authors suggested further research is warranted with a larger subject pool, a placebo group, and the inclusion of only participants with serum D levels below 20 ng/mL.\*<sup>30</sup>

**D3 Liquid** provides 1,000 IU of vitamin D (as cholecalciferol) per drop to support vitamin D repletion. Some practitioners prefer a liquid oil delivery system for easy dose customization, no pills to swallow for patients with pill fatigue, and the potential for enhanced bioavailability. Although limited studies have compared the bioavailability of different delivery systems for vitamin D, some evidence suggests that oil produces a greater serum vitamin D level response when compared with powder or ethanol as a delivery vehicle.<sup>31</sup> However, a post hoc analysis of an observational study suggested that tablets with 1,600 IU of vitamin D were equally efficient as 1,500 IU of liquid at raising serum levels.<sup>32</sup> Further exploration is needed to validate under which conditions liquid is preferred as a vitamin D delivery system for enhanced bioavailability.\*

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## D3 Liquid Supplement Facts

Serving Size: 1 Drop (about 0.0394 mL)

	Amount Per Serving	%Daily Value
Vitamin D3 (cholecalciferol)	25 mcg (1000 IU)	125%

**Other Ingredients:** High-oleic sunflower oil.

**DIRECTIONS:** Shake well before using. Take one drop, one to five times daily (plain or in liquid), or as directed by your healthcare professional.

**STORAGE:** Refrigerate after opening.

**FORMULATED TO EXCLUDE:** Wheat, gluten, corn, yeast, soy, dairy products, fish, shellfish, peanuts, tree nuts, egg, sesame, ingredients derived from genetically modified organisms (GMOs), artificial colors, and artificial sweeteners.

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