

# The Importance of a Balanced Approach to Vitamin D Supplementation

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**Abstract** *Complementary and alternative medicine prides itself on nuance and a systems approach, rather than the straight pharmacological model of “fix it with a single molecule.” However, the recent approach to the profoundly important pro-hormone, vitamin D, has often left nuance behind in favor of the single-bullet pharmacological model. In contrast, a comprehensive review of peer-reviewed literature on vitamin D, and its fat-soluble companion, vitamin A, shows that a balanced systems approach is necessary. Both vitamin A and vitamin D share a secondary receptor, and thus balance, enhance and inhibit each other the way a tightly choreographed system always will. Optimal levels of either nutrient need to be determined on a case-by-case basis, with regular testing of vitamin D levels to determine how much supplementation is necessary.*

## Introduction

Vitamin D is part of a nutritional foursome of fat soluble nutrients: it works in the body with vitamin A, vitamin K, and vitamin E. While low doses (1,000-2,000 IU daily) have been shown to be safe and effective, high doses are sometimes recommended and regarded as safe when they are not necessarily so.<sup>1-4</sup> According to vitamin D expert Robert P. Heaney, PhD, a daily oral intake of 2200 IU of vitamin D may be necessary to achieve optimal levels of vitamin D.<sup>5</sup> His recommendation is echoed by Heike Bischoff-Ferrari, PhD, whose review with Andrew Shao, PhD, senior vice president of scientific and regulatory affairs, Council for Responsible Nutrition (CRN), in the July 2010 issue of *Osteoporosis International* concludes that 1,000 IU a day will bring 50% of the population to optimal levels.<sup>6</sup>

On the other hand, Shao, Bischoff-Ferrari and colleagues also concluded that “mean serum 25(OH)D levels of about 75 to 110

nmol/L provide optimal benefits for all investigated endpoints without increasing health risks. These levels can be best obtained with oral doses in the range of 1,800 to 4,000 IU vitamin D per day.” Unfortunately, that range is a wide one and may not take into account the fact that fat stores can build up silently until they are completely full and then spill into the blood at toxic levels that can take many months to reverse.<sup>7</sup>

Vitamin D can help us fight infections and lower the risk of multiple sclerosis, diabetes, heart disease, cancer (colon, breast, skin and prostate), osteoporosis, dental caries, lupus and rheumatoid arthritis, and depression.<sup>8-21</sup> There are over 47,000 peer review studies on vitamin D, stretching all the way back to 1922, with the most recent entries on its powerful role in lupus, fractures and breast cancer.<sup>22-25</sup> And yet, despite vitamin D’s promise, scientists still don’t know what optimal levels may truly be.<sup>26-28</sup>

### Vitamin D Synergy with A, E and K

Vitamin D is part of an ancient complex molecular script. It does not work alone. In fact, vitamins A, D, K and E work together, and the newest research shows that these lipid-based molecules are all powerful antioxidant nutrients which are intricately bound through shared receptors. They balance and enhance each other, and as a group, profoundly influence genes, immunity, inflammation and the healthy balance of lipids in our body.<sup>29</sup> Vitamin K enhances vitamin D's impact on bone, and protects against kidney damage from excess D. The top vitamin K expert in this country, Sara Booth, PhD, of Tufts University, speculates that K may also work through the ancient (steroid) retinoid X receptor (RXR), just like D and A. Finally, vitamin E seems to play a role as well, working together with vitamins A and D.<sup>30</sup>

Modest, regular doses of vitamin D can slowly and safely bring us to optimal levels—even in northern latitudes.<sup>31</sup> However, regular monitoring with blood tests is crucial, due to genetic variation.<sup>32,33</sup> Higher doses of vitamin D being recommended today have never been proven safe, especially long-term, and toxicity can occur when fat stores become saturated and excess vitamin D spills into the blood; this can take many months to reverse.<sup>1-4</sup> High dose vitamin D may increase fracture risk in elderly women. Women age 70 years or older who received a single annual high dose of vitamin D (500,000 IU of cholecalciferol) had a higher rate of falls and fractures compared to women who received placebo, according to a study published in *The Journal of the American Medical Association*.<sup>34</sup>

Vitamin D levels have dropped from an average of 30 ng/ml between 1988-1994 to 24 ng/ml between 2001-2004.<sup>35,36</sup> Half of Americans may be lacking optimal amounts of vitamin D, which have been set at about 80 nmol/L (or 32 ng/mL)—what vitamin D expert Robert Heaney calls the “canonical” number, based on optimal intestinal calcium absorption.<sup>6</sup> There is also a widespread vitamin A deficiency, since 50% of individuals may not be able to effectively con-

vert carotenes to vitamin A, and the richest dietary sources of vitamin A (full fat milk, butter, eggs and liver) are often avoided by many individuals worried about weight or cholesterol.<sup>37-39</sup> As an important aside, there is also a vitamin K deficiency—not severe enough to impair clotting, for which tiny amounts are required, but a subtle deficiency that impacts vitamin D's functions.<sup>40,41</sup>

Vitamin A is necessary for optimal mucosal immunity—and is a key nutrient in balancing the newly discovered pro-inflammatory cytokine, IL-17.<sup>42-49</sup> Carotenes are not an adequate or safe substitute for vitamin A in supplements, even though they've long been recommended as a substitute. New research shows they are not efficiently converted to vitamin A in as many as 50% of individuals,<sup>38</sup> and they can create cleavage products that form free radicals, interrupt vitamin A's protective function, and perhaps raise risk of cancer.<sup>37,39</sup>

### Vitamin D and A Crosstalk

Vitamin A and vitamin D balance, enhance, and contain each other through the RXR. That is called crosstalk. Crosstalk is a fundamental mechanism hard-wired into our biology, by which molecules dock at the same receptor and initiate a cascade of responses in the body. Crosstalk between vitamin A and vitamin D is written into our biology, and if we look at studies on these two fat soluble nutrients with crosstalk in mind, we begin to understand how synergy between the two has been misinterpreted as interference.<sup>50</sup>

Understanding crosstalk is the key to correct supplementation. Receptors for vitamin A and vitamin D are found in every cell. They were even found in human sperm in 2006.<sup>51</sup> RXR regulates lipid balance and it also crosstalks with other hugely important steroid receptors—such as thyroid, glucocorticoid, estrogen, progesterone, and testosterone. Though vitamin A binds to its own retinoic acid receptor and vitamin D binds to its own vitamin D receptor, they then bind to RXR. Because they share a receptor, if we supplement either vitamin D or vita-

min A in an unbalanced fashion, we create a functional deficiency of the one not supplemented. In other words, even if our levels at baseline are adequate, adding just one to the exclusion of the other may create the equivalent of a deficiency.

The crosstalk between vitamins A and D has a profound impact on our health. Key crosstalk effects include:

*Effects on the liver:* Animal research shows that high levels of vitamin D lower vitamin A reserves in the liver.<sup>52-54</sup>

*Possible prevention of cancer:* Retinoic acid can help leukemia cells turn non-cancerous, and this effect is enhanced by the hormone form of vitamin D (calcitriol). And a synthetic vitamin D derivative along with a retinoid inhibits prostate cancer cells *in vitro*.<sup>55-61</sup>

*Lower risk of heart disease:* Low blood levels of vitamin D, vitamin A and carotenoids are all correlated with greater risk of heart disease.<sup>62-66</sup>

*Protection of bone:* This is a key area of confusion and contention. Does vitamin A increase risk of fracture? A 2009 study from the *American Journal of Clinical Nutrition*, reviewing 75,747 women from the Women's Health Initiative, found no association between vitamin A intake and the risk of fracture in postmenopausal women.<sup>67</sup> However, a modest increase was found among women having the highest intake of both vitamin A and retinol and low intakes of vitamin D ( $\leq 11$  micrograms/day). This makes sense given the fact that vitamin D was already low in some individuals, and that high vitamin A likely created a further "functional" deficiency. That may be why the highest rate of osteoporosis is found in northern Europe, where sunlight (vitamin D) is limited and vitamin A intake is high (through oily fish).<sup>68</sup>

Other recent research suggests balance is the key. A study of 3,113 postmenopausal women living at higher latitudes in England found that vitamin A from cod liver oil supplements (which also contain vitamin D) did not impair bone health. Yet high vitamin A from food led to increased resorption of bone. "Retinol from supplements and food

have different effects," noted the researchers, "which may in part be due to whether the source of retinol also provides vitamin D."<sup>69</sup>

This argues for a balance of both nutrients, not a fear of either one. Strong bone requires constant remodeling, and vitamin D and vitamin A must be in balance to optimize this process.<sup>70-72</sup>

In adults as well as children, vitamin A and vitamin D have been found to be deficient in type-1 diabetes.<sup>73</sup> In fact, the January 2009 issue of *Diabetes* asks if "a combination of vitamins A and D, in safe pharmacologically formulated doses...might be of benefit in the treatment of those at increased risk for type-1 diabetes."<sup>74</sup>

Vitamin D helps dampen autoimmune responses and decrease pro-inflammatory T cell cytokines. Similarly, vitamin A increases regulatory T-cells that help dampen hypersensitivity reactions.<sup>75-79</sup>

Though vitamin D does increase immune function and stimulate antimicrobial peptides, vitamin A is essential for the immune function of the very mucosal tissues that form the greater part of our immune system (the gut lining). According to Michael Ash, DO, ND, "Tolerance in immunity defines health. An intolerant immune system will lead to an unhealthy person and the gut is where many people lose tolerance. Vitamin A is a missing piece of the puzzle of mucosal immunology."<sup>80</sup>

## Conclusion

Rather than a pharmacological model (one nutrient isolated from others), we need a nutritional model that takes into account the diet and lifestyle with which we originally evolved, and the way our receptors respond to these nutrients. Studies can be inconsistent if they isolate a single factor, without taking into account the tight synergy among nutrients. For instance, research shows a positive impact on bone mineral density when both vitamin D and calcium are supplemented together—and none with vitamin D alone. One could wrongly conclude that vitamin D did not impact bone.

Both vitamin A and vitamin D are far

more than vitamins, with profound effects on every tissue in the body, and they dance together. Through the RXR receptor, they are linked to our most potent steroid hormones. They are involved in regulation of everything from bone to the brain, the kidney to the immune system, the heart to the pancreas. Adequate levels are crucial to health, and many of us are not getting enough of either, given our modern lifestyles and diet.

### Competing Interests

The author is the founder of and consultant to Allergy Research Group, a company which sells two vitamin D formulations.

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