

Aunt Cathy's Guide:

## **Vitamin D: A Quick Review of Forms, Labs and Other Things People Have Asked Me About Recently**



**Aunt Cathy**

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I regularly get questions about some of the confusing aspects about nutrition information in the news. Vitamin D issues can be especially complex and crazy-making. But there is a new understanding of the international epidemic nature of vitamin D deficiency. Additionally, we have a rapidly-expanding understanding of its critical role in the functioning of over 200 tissues and its role as a factor in an ever increasing number of serious health problems (like cancer, heart disease, diabetes, arthritis, multiple sclerosis, lupus and more.) Health care professionals need to have this sorted out more now than ever.

[Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008 Apr;87(4):1080S-6S.  
Hypovitaminosis D among healthy children in the United States: a review of the current evidence. Arch Pediatr Adolesc Med. 2008 Jun;162(6):513-9. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med. 2008 Jun;162(6):505-12. Lots more references are in my other papers.]

This little paper evolved from a question emailed to me recently from a dietitian. As I was typing away with an answer, it occurred to me that other health professionals might find this information helpful as well. And so ... a new handout is born!

For more information about vitamin D or other nutrition issues, go to MeritCare's website ([www.meritcare.com](http://www.meritcare.com)) and type my name in the search box. Click on "Cathy Breedon's Handouts" and a list of topics will pop up, including these:

**"Vitamin D: It's Not Just for Bones Anymore!"** This is designed primarily for those who like to look at the issues in some depth. It contains lots of references and information about the many contributions of vitamin D to health, but it is a hefty 16 pages long, with the promise of more to come. Not for the faint of heart!

**“My Current Top Five Easy Ways to Improve Your Family’s Nutrition (subject to change at any moment! ☺)”** This paper addresses vitamin D as one of the Top Five issues, but in much less detail than the Vitamin D paper described above. It is designed for those who want just a cut-to-the-chase version of why this matters so much and what are we supposed to do about it. Vitamin D issues make up only 3 of the 10 pages, so it is short and sweet.

As always, my handouts are intended to provide some summarizing of interesting nutrition information in the news. They are not intended to take the place of the guidance and recommendations of an individual’s health care providers.

And of course everything is way more complicated than my descriptions suggest, but this is just an attempt at a nice simplified discussion trying to sort things out sufficiently to give direction in thinking about functional applications.

### **Here was the original inspiring question:**

What form of Vitamin D is absorbed the best? One of our Nurse Practitioners is wondering if it matters – capsule v gelcap, etc. Thank you! \*\*\*\*\* RD,LD

### **My rambling response:**

**She is probably mixing up the two areas of two big distinctions in the vitamin D world** (so what is NOT confusing about all this?!):

1. There are two major forms of vitamin D that come into the body as food or supplements:

**Cholecalciferol**

**Ergocalciferol**

2. There are two major forms of vitamin D floating around in the body:

**25-hydroxycholecalciferol (25-hydroxyD)**

**1, 25-dihydroxycholecalciferol (1,25-hydroxyD)**

Here’s a look at all four:

**1. Food and Supplement Vitamin D Sources Coming in from Outside**

**2. Forms of Vitamin D Floating Around in the Body**

<p><b><u>Ergocalciferol</u> Vitamin D-2</b> in plants and some supplements</p>	<p><b><u>25-hydroxycholecalciferol</u></b> <b>also called <u>Calcidiol</u></b>; a storage form of circulating non-activated vitamin D</p>
<p><b><u>Cholecalciferol</u> Vitamin D-3</b> in animal foods and some supplements. This is also the kind one makes in the skin from exposure to ultraviolet light.</p>	<p><b><u>1,25-dihydroxycholecalciferol</u></b> <b>also called <u>Calcitriol</u></b>; the active steroid hormonal form of vitamin D</p>

**1. The difference between the plant source vs animal source (ergocalciferol D2 vs cholecalciferol D3)**

The kind we make (out of 7-dehydrocholesterol in the skin + UV light) and the kind we use in the body is the chole type (because we are animals.) But we can make chole out of ergo so the questions are NOT about ABSORPTION (i.e. getting it into the body from out there in the intestinal lumen) but about whether the same number of mg or iu's of ergo is equal to the same amount of chole.

At the moment there is no official differentiation, and there have been some suggestions that chole may be superior in certain instances but in other situations they appear to be comparable. In a recent study of elderly people with vitamin D deficiency, the cholecalciferol and ergocalciferol forms were compared as agents to correct the deficiency. They found that cholecalciferol was almost twice as potent as ergocalciferol in raising serum 25(OH)D, when administered either by mouth or as an injection. The simple solution -- in my non-opinionated opinion :- ) -- is just get the “chole” type and quit worrying about that particular issue.

[Short and Long Term Variations in Serum Calcitrophic Hormones after a Single Very Large Dose of Ergocalciferol (Vitamin D2) or Cholecalciferol (Vitamin D3) in the Elderly. J Clin Endocrinol Metab. 2008 May 20.]

**Absorption is not usually a problem with vitamin D unless a person has a condition that makes one have significant fat malabsorption ...** like steatorrhea in Cystic Fibrosis, as a major example. Anything that makes people malabsorb fat will make them malabsorb the fat soluble vitamins (A, D, E and K) as well. To the best of my knowledge, tablets are fine, gel caps are fine, liquids are fine ... don't sweat

the small stuff. However, as always, remember that anything I think is true today can easily be found to be wrong tomorrow, so this is just my best guess as of the date on the top right corner of the handout.

In the world of renal disease and chemotherapy adjuncts, however, there are other specialized vitamin D analogs available and questions in the professional literature about the relative efficacy of various injectable forms of D2 vs D3, etc. This is beyond the scope of this brief discussion about the most typical nutrition-related issues encountered by health professionals.

## **2. The difference between two lab values:**

### **25-hydroxy D vs 1,25-dihydroxy D.**

**This is not about any food forms or any of that business in #1 above. It is about what one does with vitamin D in the body.**

The 25-hydroxy form is the non-activated-yet-but-stored-and-available-to-be-used form. (And that's just its nickname!) It is made in the liver from cholecalciferol (obtained from any source: food, supplement, skin production) by attaching a hydroxyl group (an OH group) at the #25 carbon of the molecule. **This form (25-hydroxycholecalciferol or 25-hydroxyD,) is the storage form that we ordinarily test to check for plain old "deficiency vs adequacy" in the person's body.** (I am using the simple letter D to stand for the word cholecalciferol in more and more of these descriptions because it is tedious to keep writing it out.)

**As you know, we health professional types need to begin a habit of regularly checking this in everybody because just counting up the amount we think people took in misses the boat in many circumstances.** I think an automatic 'standing orders' scenario would be very informative and helpful. I just found eight more people this week who were overtly deficient in spite of what "should have been enough" vitamin D. You can only know for sure by checking their blood.

When we need the active hormonal form (for one of the 200 different tissues with vitamin D receptors that are looking for it,) the 25-hydroxyD storage form is sent to the kidney and another hydroxyl group is attached there at the #1 carbon on the molecule. **The product ... the active hormonal form of vitamin D ... is 1,25-dihydroxycholecalciferol.**

This is not something one would ordinarily check as a blood test unless the person had some sort of potentially vitamin-D related symptoms in spite of a good intake of vitamin D. It would usually be done to identify people with kidney disease who have lost the ability to make the 1,25 vitamin D. There is also a much smaller group of people who have an inborn error of vitamin D metabolism that results in the same problem. While this is likely to be rare, I have found this situation to exist in five out of five people for whom I asked to have it checked.

I certainly check this when their symptoms are unusual, such as extremely severe or rapidly progressing MS (e.g. in a 10-year-old.) Another time I might ask to have it checked is if the person has vitamin D deficiency symptoms but it has already been shown that their blood 25-hydroxyD level is OK. In that situation I know it is not simple inadequacy that is contributing to any problems.

Additionally, there are certain genetic factors that impair the utilization of vitamin D. For example, there are “polymorphisms” (different forms) of vitamin D receptors found on some people’s cells that contribute to having vitamin D related problems in spite of a good vitamin D intake and normal ability to activate it to the active form. In other words, vitamin D hormone knocks on the door of a cell with a message but nobody answers the door. But this kind of metabolism problem is only a tiny part of the problem of vitamin D adequacy. Most folks just aren’t getting enough sun or enough vitamin D supplementation, so that is where we need to look first in order to identify problems and do some serious good.

## **So, a good order of thinking about this for a patient is:**

**First** Get a regular 25-hydroxy D level (for EVERYBODY!!!) and if it is low give them a therapeutic supplemental amount of vitamin D to get them up to normal and then figure out a maintenance dose to switch to once subsequent tests show that the low level has been corrected. Also, it is wise not to assume it has been corrected after some prescribed number of doses. We really need to check it.

For many people, getting the level during the winter is most likely to pick up any inadequacy issues. A level drawn any time of year will help identify problems for people who are not regularly in the sun even in the summer. This includes a large number of people, for a variety of reasons.

I continue to hear every week from a surprising number of health professionals (including dietitians, physicians, pharmacists and nurses) who have

had their levels checked after hearing me go on and on about the vitamin D deficiency problem. They had been startled to find that they were themselves vitamin D deficient. This is in spite of “eating right” and taking a multivitamin! What would be the likelihood of non–health-care-professionals also having this kind of problem?

**Second** If the person has good blood levels of 25-hydroxyD but still looks “suspicious” in terms of vitamin D-related conditions, then get a 1,25 D level to see if they have a metabolic defect in hydroxylation in the kidney or some other condition like kidney disease that is impairing production of the hormonal form. In that situation, one would utilize a special prescription form of supplemental vitamin D to get around the problem: the ready-to-go form of the active hormone 1,25-dihydroxyD which is usually ordered as **calcitriol**.

### **Here is an example to illustrate why I think doing this in the order described above is potentially useful:**

**1.** It was recently found in an observational study that **pre-dialysis kidney patients who start earlier on calcitriol supplementation may have improved survival and quality of life, etc.** (*Arch Intern Med.* 2008;168:397-403) compared with those who began to use it later. By early, they appeared to mean not waiting for severe deficiency symptoms to show up before providing it, or not waiting until the person had to go on dialysis because of kidney failure. This meshes nicely with another recent finding of an association between increased risk of death from all causes and low vitamin D status, including cardiovascular disease.

[E.g.: 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med.* 2008 Jun 9;168 (11):1174-80. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev.* 2008 May;17(5):1228-33. Vitamin D, cardiovascular disease, and survival in dialysis patients. *J Bone Miner Res.* 2007 Dec;22 Suppl 2:V95-9. Can vitamin D reduce total mortality? *Arch Intern Med.* 2007 Sep 10;167(16):1709-10, 1730-37. ]

Interestingly, in the pre-dialysis study described above, apparently plain old 25-hydroxy D levels were not regularly evaluated, so although calcitriol was shown to be helpful in many ways for preventing deficiency consequences, it may NOT have been a kidney-related hydroxylation problem that needed the earlier intervention. It may have been just the same old unrecognized common inadequacy of vitamin D intake that was the limiting factor for many of these folks.

For many people with serious kidney disease, foods like milk and salmon are restricted. As these are about the only reliable and rich sources of vitamin D in our

diet, simple inadequacy of vitamin D should not be an unexpected finding ... if we check for it. This possibility was not addressed in the study, but I think it has important implications for patient care:

**Although giving calcitriol (a significantly more expensive and prescription-only pharmacy product) was clearly associated with benefit in this situation, assuring vitamin D adequacy with generous plain old cheap vitamin D supplementation may have done the trick just as well for many of the people involved.**

This is another argument for a regular planned 25-hydroxy D level check for everybody. We could save the big guns (calcitriol) for those who really need it. Additionally, as described in the report below, there is evidence that even folks for whom calcitriol IS actually needed, there are other roles for 25-hydroxy vitamin D and therefore good reason to maintain that level in the safe and adequate range at the same time as providing ready-made calcitriol.

**Vitamin D in Health and Disease.** Clin J Am Soc Nephrol. 2008 Jun 4.

“Vitamin D functions in the body through both an endocrine mechanism (regulation of calcium absorption) and an autocrine mechanism (facilitation of gene expression). The former acts through circulating calcitriol, whereas the latter, which accounts for more than 80% of the metabolic utilization of the vitamin each day, produces, uses, and degrades calcitriol exclusively intracellularly.

In patients with end-stage kidney disease, the endocrine mechanism is effectively disabled; however, the autocrine mechanism is able to function normally so long as the patient has adequate serum levels of 25(OH)D, on which its function is absolutely dependent.

For this reason, calcitriol and its analogs do not constitute adequate replacement in managing vitamin D needs of such patients. **Optimal serum 25(OH)D levels are greater than 32 ng/mL (80 nmol/L). The consequences of low 25(OH)D status include increased risk of various chronic diseases, ranging from hypertension to diabetes to cancer.**

The safest and most economical way to ensure adequate vitamin D status is to use oral dosing of native vitamin D. (Both daily and intermittent regimens work well.) Serum 25(OH)D can be expected to rise by about 1 ng/mL (2.5 nmol/L) for every 100 IU of additional vitamin D each day. Recent data indicate that cholecalciferol (vitamin D3) is substantially more potent than ergocalciferol (vitamin D2) and that the safe upper intake level for vitamin D3 is 10,000 IU/d.”

The levels described as “normal” in many research studies set the level of insufficiency and deficiency at significantly lower levels than what appears to be needed for optimal health benefit. This accounts for some of the confusing research outcomes. For example, a study finding no benefit of supplemental vitamin D on some outcome in a population would not be surprising if only low levels of supplementation were tested. In most cases, blood levels were most often not evaluated to determine the success of the supplementation for achieving “adequacy.” Additionally, the ranges perceived to be “normal” were often set too low so that true comparisons of adequacy vs inadequacy did not take place...only gradations of inadequacy.

In fact, one of my old books actually had two sets of “normal values” to evaluate vitamin D adequacy. The cut-off to use in winter was much lower because it was “average” and “expected” to have a much lower level during those months. It is a classic illustration that just because something is average or expected does not mean it is good or safe. Live and learn ...

Here’s another report with some information about what serum vitamin D levels might be better indicators of adequacy:

**Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes.**

Adv Exp Med Biol. 2008;624:55-71.

**“Recent evidence suggests that higher vitamin D intakes beyond current recommendations may be associated with better health outcomes.** In this chapter, evidence is summarized from different studies that evaluate threshold levels for serum 25(OH)D levels in relation to bone mineral density (BMD), lower extremity function, dental health, risk of falls, admission to nursing home, fractures, cancer prevention and incident hypertension. **For all endpoints, the most advantageous serum levels for 25(OH)D appeared to be at least 75 nmol/l (30 ng/ml) and for cancer prevention, desirable 25(OH)D levels are between 90-120 nmol/l (36-48 ng/ml). An intake of no less than 1000 IU (25 mcg) of vitamin D3 (cholecalciferol) per day for all adults may bring at least 50% of the population up to 75 nmol/l. Thus, higher doses of vitamin D are needed to bring most individuals into the desired range.** While estimates suggest that 2000 IU vitamin D3 per day may successfully and safely achieve this goal, the implications of 2000 IU or higher doses for the total adult population need to be addressed in future studies.”

**2. The risk of injury from overdose in an individual is much higher if the active hormone form is given instead of just a precursor form.** This is analogous to the

higher potential for injury from giving high dose retinol (an active hormonal form of vitamin A primarily in liver and some supplements) compared with high doses of the pre-cursor form of vitamin A, the orange pigment beta-carotene in fruits, vegetables and some supplements. [Remember that the upper level of safety of “regular” vitamin D is now described as a chronic (and non-therapeutic level) intake of 10,000 iu/day. It is WAY less toxic than most of us were taught. “Therapeutic” levels are often something like 50,000 iu/week for 8 weeks.]

**3. Regularly monitoring 1,25-dihydroxyD levels would be a reasonable plan for folks with kidney disease so we can catch them when production just starts to decrease.** That way we can intervene BEFORE they suffer the multiple severe consequences associated with inadequacy of this vital steroid hormone. I would also like to see a one-time-only 1,25-dihydroxy D level for people with autoimmune diseases like MS, arthritis, lupus, diabetes, etc., for reasons beyond the scope of this paper. (Details are available in the other handouts listed earlier.)

**For additional information on these and other topics you can go to MeritCare’s website ([www.meritcare.com](http://www.meritcare.com)) and find other articles in the “Aunt Cathy’s Guide to Nutrition” series.**

Just type Cathy Breedon in the “search box” and a page comes up where you can click “Cathy Breedon’s Handouts.”

**-General nutrition for health**

(“Top Five Easy Ways to Improve Your Family’s Nutrition”)

**-Specific health problems**

(such as diabetes, celiac disease, cancer, multiple sclerosis, hemochromatosis, epidermolysis bullosa, and others.)

**-Pregnancy and infant nutrition**

**-Summaries providing much more detail about specific nutrients**

(such as iron, magnesium, vitamin D, vitamin K, B-vitamins, and different kinds of fat and oil.)