

Aunt Cathy's Guide:

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



Aunt Cathy

Cathy Breedon PhD, RD, CSP, FADA
Prenatal/Pediatric Nutrition Specialist
Clinical Nutrition Specialist
MeritCare Medical Center, Fargo, ND
and UND School of Medicine

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, fibromyalgia, immune compromise 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) and type my name in the search box. Click on "Cathy Breedon's Handouts" and a list of topics will pop up, including:

"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.

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 and doing some good.

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><u>Ergocalciferol</u> Vitamin D-2 in plants and some supplements</p> | <p><u>25-hydroxycholecalciferol</u> also called Calcidiol; a storage form of circulating non-activated vitamin D</p> |
| <p><u>Cholecalciferol</u> Vitamin D-3</p> | <p><u>1,25-dihydroxycholecalciferol</u></p> |

| | |
|--|---|
| <p>in animal foods and some supplements. This is also the kind one makes in the skin from exposure to ultraviolet light.</p> | <p>also called Calcitriol; 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, but there have been reports that the chole form may be superior in certain instances especially. For example, 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. [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.]

Other studies have shown correction of vitamin D deficiency using ergocalciferol supplements, but they generally are not studied in terms of efficacy in comparison with using chole ... just whether or not they correct the deficiency. Since the ergocalciferol must be converted to cholecalciferol, the simple solution -- in my non-opinionated opinion ☺ -- is to just get the “chole” type and quit worrying about that particular issue. Very high-dose ergocalciferol is effective for correcting vitamin D deficiency in children and young adults with cystic fibrosis. J Cyst Fibros. 2009 May 14.

Absorption is not usually the major 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.

For other people, in some comparisons the gel caps and liquids have somewhat better absorption than solid tablets, and in general, taking the supplements daily appears to be more effective than weekly or monthly supplementation regimens.

Taking the vitamin D supplements with the largest meal of the day also appears to enhance absorption.

Taking vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. *J Bone Miner Res.* 2010 Feb 8. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. *Osteoporos Int.* 2008 May;19(5):663-71. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ.* 2009 Oct 1;339:b3692.

However, the biggest problems with supplementation regimens are that:

- 1) **the amount of vitamin D being supplemented is often far too low to correct deficiency, let alone bring about rapid correction of deficiency; and**
- 2) **people simply don't take them reliably.**

Because of the poor adherence to therapeutic or maintenance regimens, some other approaches are being tried. For example, a one-time dose of 300,000 iu has been shown to be effective in correcting severe deficiency without negative effects.

High-dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency. *Bone.* 2009 Oct;45(4):747-9. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary? *Best Pract Res Clin Rheumatol.* 2009 Dec;23(6):789-95.

I am including an abstract here of a very important recent report that evaluated randomized double blind studies and addressed the question of how much vitamin D supplementation was needed to achieve health targets for risk of falls, fractures, cardiovascular disease and colon cancer. It also addresses the issue of the safety of these levels. The authors are all very well known and respected researchers.

Benefit-risk assessment of vitamin D supplementation.

Osteoporos Int. 2009 Dec 3.

Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, **Willett WC.**

Current intake recommendations of 200 to 600 IU vitamin D per day may be insufficient for important disease outcomes reduced by vitamin D. INTRODUCTION: This study assessed the benefit of higher-dose and higher achieved 25-hydroxyvitamin D levels [25(OH)D] versus any associated risk.

METHODS AND RESULTS: Based on **double-blind randomized control trials (RCTs)**, eight for falls (n = 2426) and 12 for non-vertebral fractures (n = 42,279), there was a **significant dose-response relationship between higher-dose and higher achieved 25(OH)D and greater**

fall and fracture prevention. Optimal benefits were observed at the highest dose tested to date for 700 to 1000 IU vitamin D per day or mean 25(OH)D between 75 and 110 nmol/l (30-44 ng/ml).

Prospective cohort data on **cardiovascular health and colorectal cancer prevention** suggested increased benefits with the highest categories of 25(OH)D evaluated (median between 75 and 110 nmol/l).

In 25 RCTs, mean serum calcium levels were not related to oral vitamin D up to 100,000 IU per day or achieved 25(OH)D up to 643 nmol/l. Mean levels of 75 to 110 nmol/l were reached in most RCTs with 1,800 to 4,000 IU vitamin D per day without risk.

CONCLUSION: Our analysis suggests 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; further work is needed, including subject and environment factors, to better define the doses that will achieve optimal blood levels in the large majority of the population.

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 most 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!!!) --- ideally annually in the winter -- and if it is low give them a therapeutic supplemental amount of vitamin D to get them up to normal. 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 one might 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**.

This problem is much less common than the problem of simple inadequacy of vitamin D, but I have found four individuals with this as the unrecognized basis of some very severe symptoms. These people were not kidney patients. That tells me that the problem is likely more common than we think but generally unrecognized.

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, and contribution of adequate vitamin D in decreasing the risk of progression to kidney disease in people with diabetes.

[E.g.: Vitamin D and chronic kidney disease. *Ethn Dis.* 2009 Autumn;19(4 Suppl 5):S5-8-11. Vitamin D, proteinuria, diabetic nephropathy, and progression of CKD. *Clin J Am Soc Nephrol.* 2009 Sep;4(9):1523-8. 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 intake of 10,000 iu/day. It is WAY less toxic than most of us were taught. “Therapeutic” levels to correct deficiency are often something like 50,000 iu/week for 8 weeks, or as described earlier, a one-time dose of 300,000 iu.]

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) 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.