KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Vitamin D Imbalance - Part Two

In the absence of a 25(OH)D reference range based on ethnicity or a biological vitamin D activity reference range that we talked about on the last slide, we can use markers such as PTH and calcitriol to help us clarify when low 25(OH)D is pathological versus when it is just normal physiology, and here is how that works.

PTH values and vitamin D

PTH Value (pg/mL)	Comment
10-65	"Normal"
37	Danes on western diet
30	Inuit on western diet
22	Inuit on traditional diet
<30	Optimal for vitamin D status

The PTH reference range at most labs is 10 to 65 pg/mL, but studies that have looked at various populations have found that normal, average PTH is 37 pg/mL in Danes who are following a Western diet, 30 pg/mL in Inuit following a Western diet, and only 22 pg/mL in Inuit who are following a traditional diet. A meta-analysis of the suppressive effects of vitamin D supplementation on PTH found the greatest effect with baseline levels of PTH over 49. In that case, vitamin D supplementation suppressed PTH by 21 pg/mL. When PTH was between 38 and 49, vitamin D supplementation suppressed PTH by 17 pg/mL, and then when PTH levels were between 6 and 38, vitamin D supplementation only dropped PTH by 2 pg/mL. This suggests that a PTH level above 30 pg/mL would corroborate concerns about low 25(OH)D levels in proportion to its upward divergence from 30.

Put a different way, if you see a 25(OH)D level that is low-normal, let's say 32 or even slightly below the lab range such as 27 or 26, and you test PTH and it's below 30, then that would suggest that this patient is not actually vitamin D deficient from a biological perspective and that supplementation, diet, and lifestyle change aren't required. However, if you see a low or borderline-low level of 25(OH)D, and you test PTH and it's above 30, then that would suggest that they are biologically deficient. The higher the PTH is above 30, the more biologically deficient they are.

Note that people on an industrialized diet get a majority of their vitamin D from cutaneous production. This means that serum vitamin D level is primarily a measurement of sun exposure and supplementation, not food sources. Dietary vitamin D contributes only 10 to 20 percent of vitamin D status in most people, and we'll talk about how to increase this percentage later. Only a few foods such as cold-water fatty fish or shellfish are rich in vitamin D, whereas the vitamin D content of the vast majority of other foods is small, or even zero. In the absence of effective food fortification programs, dietary vitamin D intake does not exceed 3 to 5 mg per day for most people. This is particularly true for patients with Crohn's disease, ulcerative colitis, celiac disease, or other conditions that cause fat malabsorption, since vitamin D is a fat-soluble vitamin.

Studies with inflammatory bowel disease patients demonstrate that vitamin D status is linked to sun exposure, and dietary supplementation is inadequate to raise serum levels. Cutaneous synthesis of vitamin D is the most bioavailable source for those with fat malabsorption caused by inflammatory diseases.

So far, we've been mainly discussing the low end of the 25(OH)D range and the effects of vitamin D deficiency, but what about vitamin D toxicity? The hallmark of vitamin D intoxication is hypercalcemia, which is due to intestinal calcium hyperabsorption and calcium resorption from bone. Excess vitamin D also causes hyperphosphatemia. Hypercalcemia and hyperphosphatemia cause mineralization of various soft tissues, including the kidneys, heart, aorta and other blood vessels, and cutaneous tissue, and this can lead to kidney stones and increased risk of cardiovascular disease, among other problems. Vitamin D-intoxicated patients suffer from headache, nausea, vomiting, diarrhea, anorexia, weight loss, polyuria, and polydipsia, and excess vitamin D intake has also been shown to contribute to several documented deaths.

Is the 25(OH)D reference range too broad?

Both the serum level of 25(OH)D and the safe upper limit for the intake of vitamin D are highly controversial. The conventional idea is that 25(OH)D levels above 125 ng/mL are potentially toxic and

that the toxicity threshold for oral vitamin D intake is somewhere between 10,000 to 40,000 IU per day. However, the Institute of Medicine has argued that 25(OH)D levels above 50 ng/mL when a patient is taking supplements may be cause for concern. This is based on several observational findings indicating the values above this level are associated with a higher risk of all-cause mortality and specific types of cancer. There is evidence for a U-shaped association of circulating 25(OH)D levels with allergy risk, indicating a high risk at both circulating 25(OH)D levels below 10 mg/dL and above 54 mg/dL. One study found that people taking 400 IU of vitamin D plus 1,000 mg of calcium per day had 17 percent higher risk of kidney stones, but of course, that is unclear whether it was the supplemental calcium, vitamin D, or a combination of both that caused that.

We should note that these studies don't prove causality. It's possible that high 25(OH)D levels may occur as a result of low 1,25(OH)2D levels, which could indicate deficient vitamin D actions at the cellular level. In other words, it is possible that increased mortality and disease are caused by a deficiency of active 1,25(OH)2D even though 25(OH)D levels are elevated.

Status of serum markers in vitamin D deficiency and toxicity

Vitamin D status	25(OH)D	1,25(OH)2D	PTH	Calcium	Phosphorus
Toxicity	High	Low, normal, or high	Low or normal	Normal or high	Normal or high
Deficiency	Low	Low, normal, or high	>30	Low or normal	Low or normal

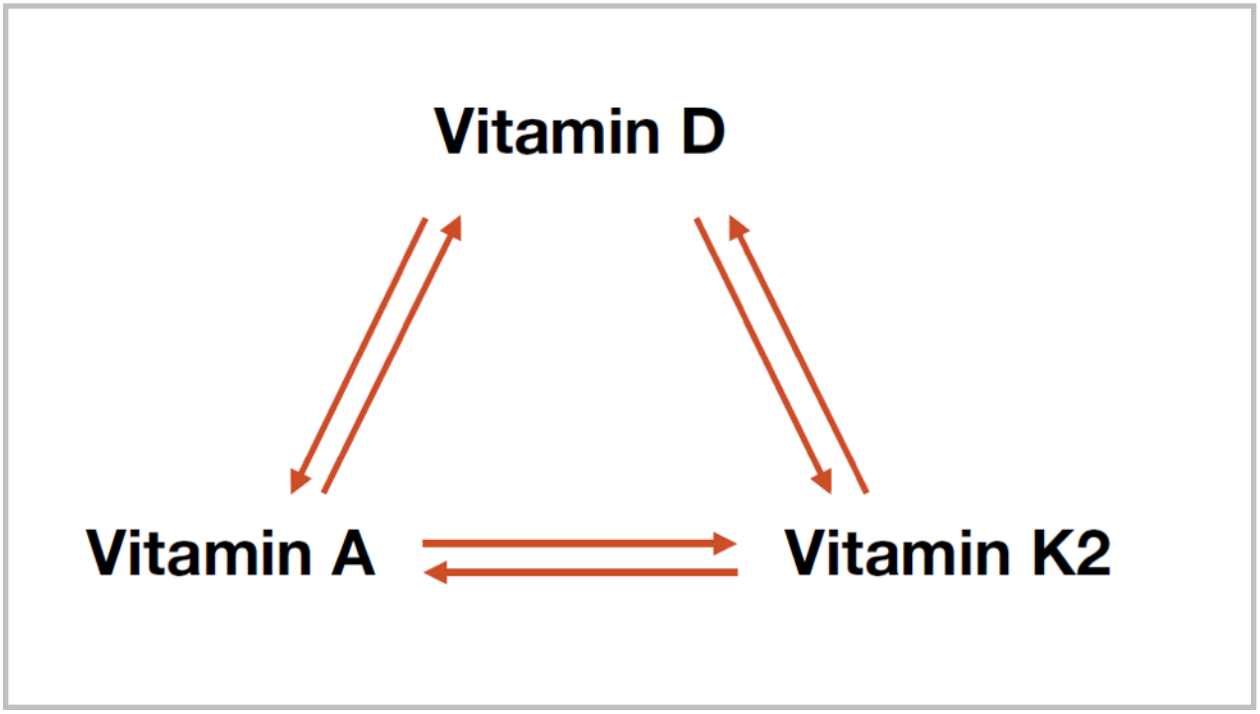
It's important to be aware that in most cases of vitamin D toxicity due to supplements, 1,25(OH)2D is not elevated, and this is because calcitriol is tightly regulated by PTH and FGF23, both of which respond to changes in serum calcium and phosphate. Detoxicity leads to hypercalcemia and hyperphosphatemia and depresses calcitriol. This means that if you see a high calcidiol level, and calcitriol levels are normal, that does not rule out vitamin D toxicity.

Confusing the issue further, when calcidiol or 25(OH)D levels are extremely high, calcitriol levels can fall to undetectable levels, and this happens because PTH and FGF23 suppress the conversion of calcidiol into calcitriol in an attempt to protect against hypercalcemia and hyperphosphatemia. When 25(OH)D is high and 1,25(OH)2D is low, it could actually be vitamin D toxicity, or it could be vitamin D deficiency. This is why it is so important to use other markers such as PTH, serum calcium, and serum phosphorus to clarify the diagnosis.

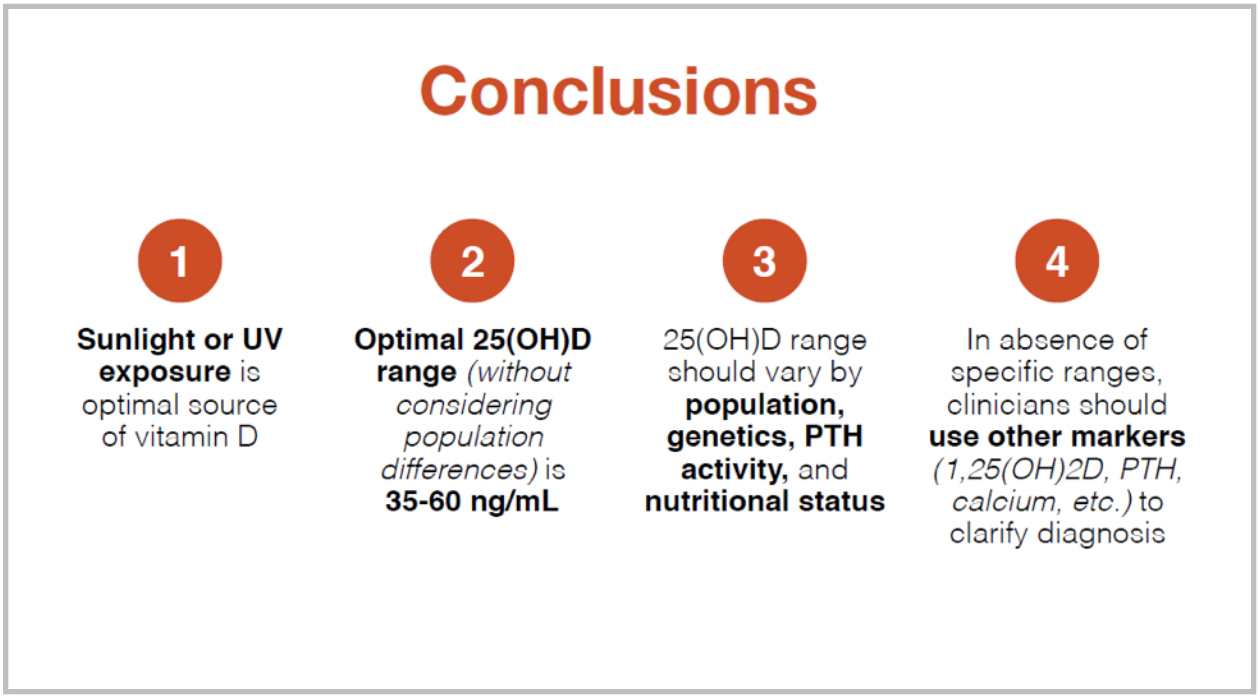
If PTH is high, and calcium and/or phosphorus is low, that would be suggestive of deficiency. If PTH is very low, and serum calcium and/or phosphorus is high, that would be suggestive of toxicity. I put this in a table on this slide, which you can print out to make it easier to reference.

What about toxicity of vitamin D from sun exposure? Again, there is some controversy here. Most studies suggest no reports of vitamin D intoxication from sun exposure alone. The argument is that the daily skin synthesis of 25(OH)D reaches a plateau after 15 percent of the precursor 7-dehydrocholesterol is converted into 25(OH)D, and after that, vitamin D inactive substances such as lumisterol and tachysterol are produced. However, these studies essentially define harm from vitamin D as elevated serum calcium, and it's possible and even probable that elevated vitamin D can cause problems before serum calcium goes out of range. For example, at least two studies have linked kidney stones to latitude, with an increasing incidence of stones at lower latitudes. One study also directly linked kidney stones to sunlight. A Saudi Arabian study found kidney stones were more common in the summer, and 11 of 45 lifeguards in Israel had kidney stones, which is 20 times the rate of the general population. On the other hand, a large study of over 45,000 men 14 years of age or older, for a total of 477,000 person-years of follow-up, found no increased risk of kidney stones with vitamin D intake, but they did not look at sun exposure or 25(OH)D levels.

They also found that are three dietary factors that protect against kidney stones: high levels of potassium, which conferred a 46 percent lower relative risk; high levels of magnesium, which conferred a 29 percent lower relative risk; and then high fluid intake, which conferred a 29 percent lower relative risk.



One final thing: it's crucial to remember that fat-soluble vitamins have a synergistic relationship. I've written elsewhere that vitamin D raises the toxicity threshold of vitamin A significantly, but it is also true that adequate vitamin A and vitamin K2 protect against vitamin D toxicity. Therefore, just as the lower end of the 25(OH)D range should vary based on 1OHase genetics and the amount of PTH required to convert calcidiol to calcitriol, the upper end of the 25(OH)D range should depend on vitamin A and vitamin K2 status. In the developed world, unfortunately, vitamin A and vitamin K2 deficiencies are common, which could be one reason why we see a high risk of morbidity and mortality at 25(OH)D levels that are in the upper end of what is currently considered to be the normal lab range.



All right, are you confused yet? You should be because the research is contradictory and unclear, but this is what I feel we can safely conclude given the research and given an evolutionary perspective: Number one, sunlight or UV exposure is the optimal source of vitamin D and accounts for the majority of 25(OH)D serum levels in the absence of supplementation. Number two, the range of serum 25(OH)D, which the majority of researchers agree, that avoids deficiency or toxicity is between 30 and 60 or 65 ng/mL. That said, the 25(OH)D range should likely vary depending on ethnicity, genetics, PTH activity, and nutritional status, especially vitamins A and K2, potassium, and magnesium, as well as fluid intake. Number four, in the absence of specific ranges, clinicians should use other markers such as PTH, calcitriol, serum calcium, and serum phosphorus to clarify biological vitamin D status.