KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

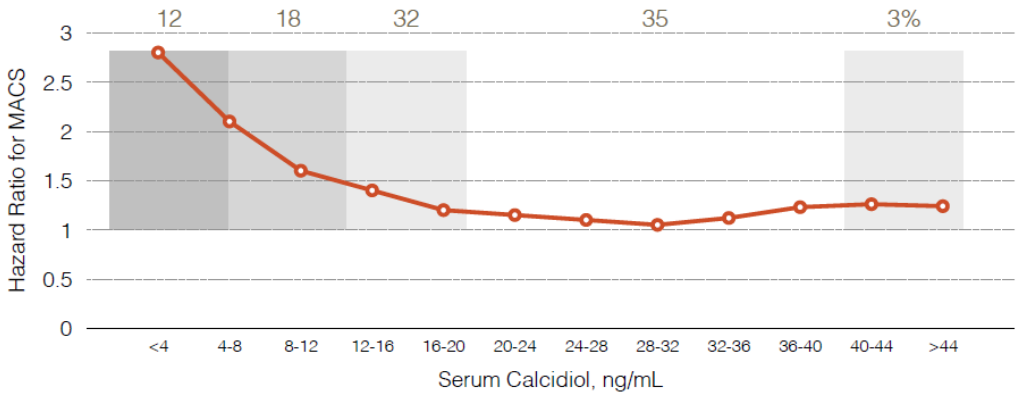
Vitamin D Imbalance - Part One

Hey, everybody. In this presentation, we're going to talk about vitamin D. Like other topics we've covered in blood chemistry elsewhere in the course, this is poorly understood and characterized by conflicting data and misconceptions. It also reflects another theme, which is that there is no one-size-fits-all approach. Most studies only look at averages, only individuals, and what I mean by this will become more clear as we go through the unit.

Vitamin D is critical for health. It promotes calcium absorption in the gut and maintains calcium and phosphate levels in the blood, which in turn enables proper mineralization of bone and protects against osteoporosis, rickets, and fracture. Vitamin D plays a number of other important roles in the body, including regulating cell growth and neuromuscular and immune function.

Using the lower end of the reference range in the U.S. of 30 ng/mL, studies have found that as many as 70 percent of Americans are deficient, and vitamin D deficiency nearly doubled a person's risk of dying, whereas correcting the deficiency with supplements reduced the risk of death by 60 percent. Deficiency of vitamin D has been linked to a wide range of problems, including increased risk of heart attack, increased risk of cancer, higher severity and frequency of asthma symptoms, greater susceptibility to autoimmune diseases such as MS and rheumatoid arthritis, increased risk of type 2 diabetes, and increased risk of death from all causes.

Although many clinicians are now aware of the risk of vitamin D deficiency, fewer are aware of the potential harm of too much vitamin D, and there is research now suggesting that the optimal level of vitamin D might be lower than currently assumed. Vitamin D status is determined by measuring a form called 25(OH)D in the blood. In the U.S., the lab reference range for 25(OH)D is 30 to 74 ng/mL, with some labs. LabCorp goes from 30 to 100 ng/mL, so this, of course, depends on which lab is used. Vitamin D advocacy organizations such as the Vitamin D Council suggest a higher range of 40 to 80 ng/mL, with a target level of 50 ng/mL. However, there is little evidence that raising levels above 50 ng/mL is beneficial, and there is some evidence that that may cause harm. Researchers have linked higher ranges with decreased bone density, heart attack and stroke, kidney stones, and other health problems. Despite the significant impact that vitamin D has on human health, research examining the effects of vitamin D supplementation has yielded inconsistent and sometimes conflicting results. In most studies, taking vitamin D supplements does not decrease the risk of death, cardiovascular disease, or other diseases, though some studies such as the one I mentioned on the last slide have shown some benefit.

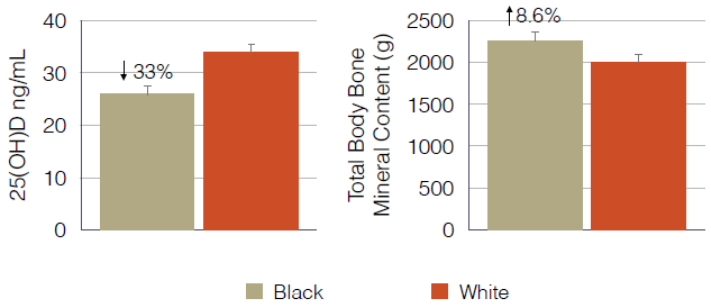


Adjusted hazard ratio for MACS by serum calcidiol. Calcidiol assays were tested in 422,822 subjects (aged>45), while 16,213 had MACS events within 54 months. The population percentage for each range of serum calcidiol is shown at the top of the graph. Only 35% of the subjects lay within the safe range (20-36 ng/mL). At risk are 62% of the subjects who fall below the safe range with hazard ratios of MACS > 1.26 and another 3% who are above the safe range with hazard ratios of 1.13. Error bars represents 95% CIs.

Adapted from: http://www.ncbi.nlm.nih.gov/pubmed/23533239

For example, one study showed that the optimal level of vitamin D is between 20 and 36 ng/mL. Those with levels below 10 were 88 percent more likely to suffer from acute coronary syndrome or early death. Those with levels between 10 and 20 were 25 percent more likely, and those with levels above 36 were 13 percent more likely. Other studies have shown that bone mineral density peaks at 45 ng/mL and then falls again as 25(OH)D levels rise above 45 ng/mL. Still other studies have shown that the risk of kidney stones and cardiovascular disease increases with high 25(OH)D levels above 60 or 70 ng/mL due to elevated serum calcium levels that accompany excess vitamin D. These studies and many other similar studies explain why the Institute of Medicine recommends a much more conservative range of 20 to 50 ng/mL based on an exhaustive review of over 1,000 published studies.

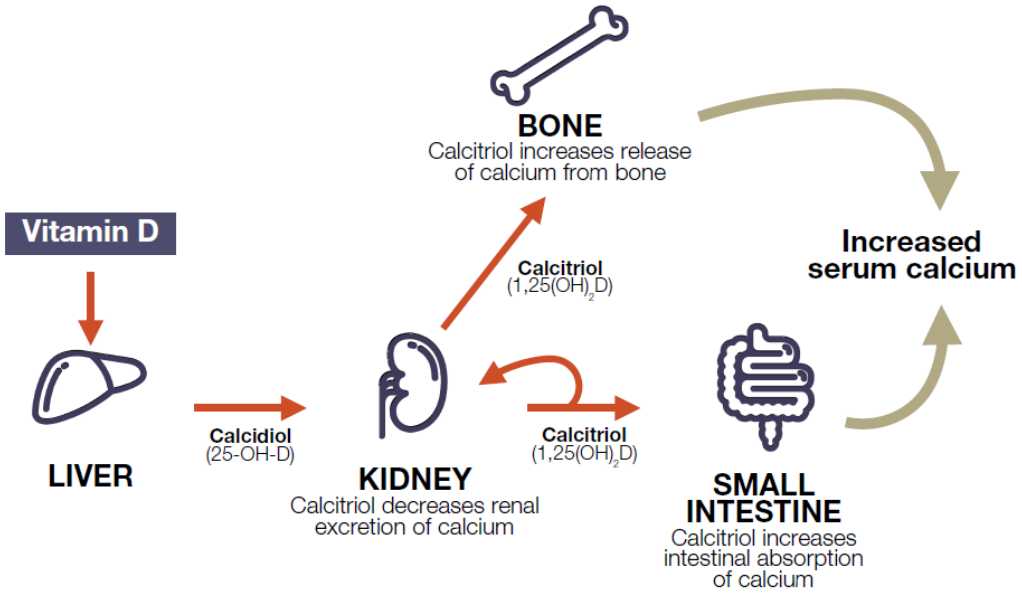
Average 25(OH)D levels and bone mineral content



105 black and white adolescent American girls.
(Similar results have been found in many studies regardless of age.)

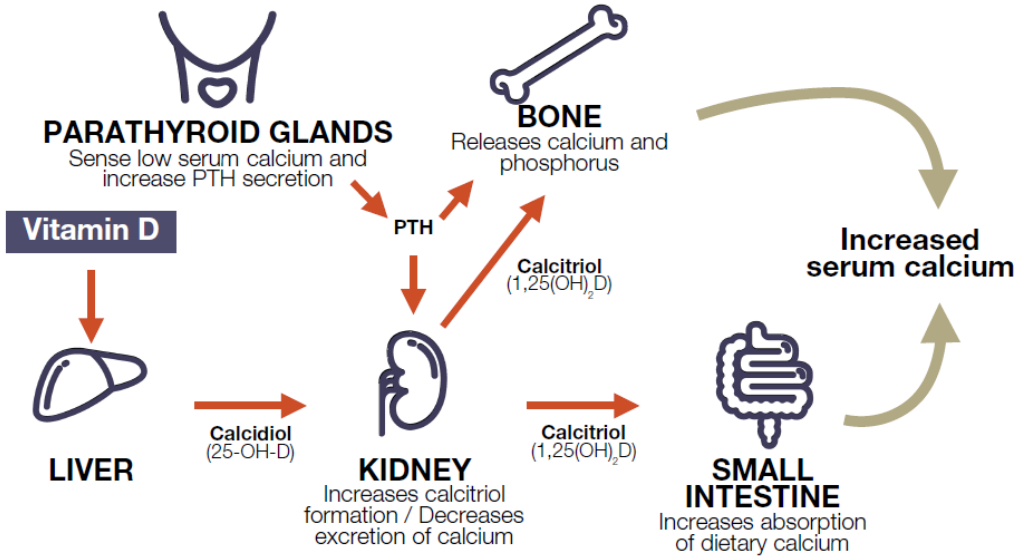
Adapted from: Masterjohn, C. "The Evolution of Diverse Vitamin D Requirements", IHH-UCSF Symposium on the Paleo Approach and Evolutionary Medicine, San Francisco, 2016; Weaver et al. Vitamin D Status and Calcium Metabolism in Adolescent Black and White Girls on a Range of Controlled Calcium Intakes. J Clin Endocrinol Metab. 2008;93:3907-3914

How do we explain this contradictory data? The first important concept to understand, which is not yet widely known, is that the optimal physiologically appropriate 25(OH)D level may vary from population to population based on ethnicity. People with nonwhite ancestry, for example, may be adapted to a lower optimal 25(OH)D than people with white ancestry. Blacks have lower 25(OH)D than whites in the U.S., yet their bone mineral density is typically higher, as the chart on this slide indicates. Other studies have found that non-Caucasians have lower 25(OH)D levels than Caucasians, even at their ancestral latitudes.



Adapted from: Masterjohn, C. "The Evolution of Diverse Vitamin D Requirements", IHH-UCSF Symposium on the Paleo Approach and Evolutionary Medicine, San Francisco, 2016

To understand this, we need to do a short review of vitamin D metabolism. Vitamin D can be obtained from diet, supplements, and endogenous synthesis in response to ultraviolet light exposure. Once vitamin D is in the circulation, it is converted by hepatic hydroxylase into 25(OH)D, and this is what is typically measured on a blood test. As needed, 25(OH)D is converted into 1,25(OH)2D, which is also known as calcitriol. By the way, 25(OH)D is known as calcidiol. This is the biologically active form of vitamin D, calcitriol or 1,25(OH)2D. Calcitriol increases the level of calcium in the blood by increasing the uptake of calcium from the gut, decreasing renal excretion of calcium, and possibly increasing the release of calcium into the blood from the bone, although that is not yet well understood.



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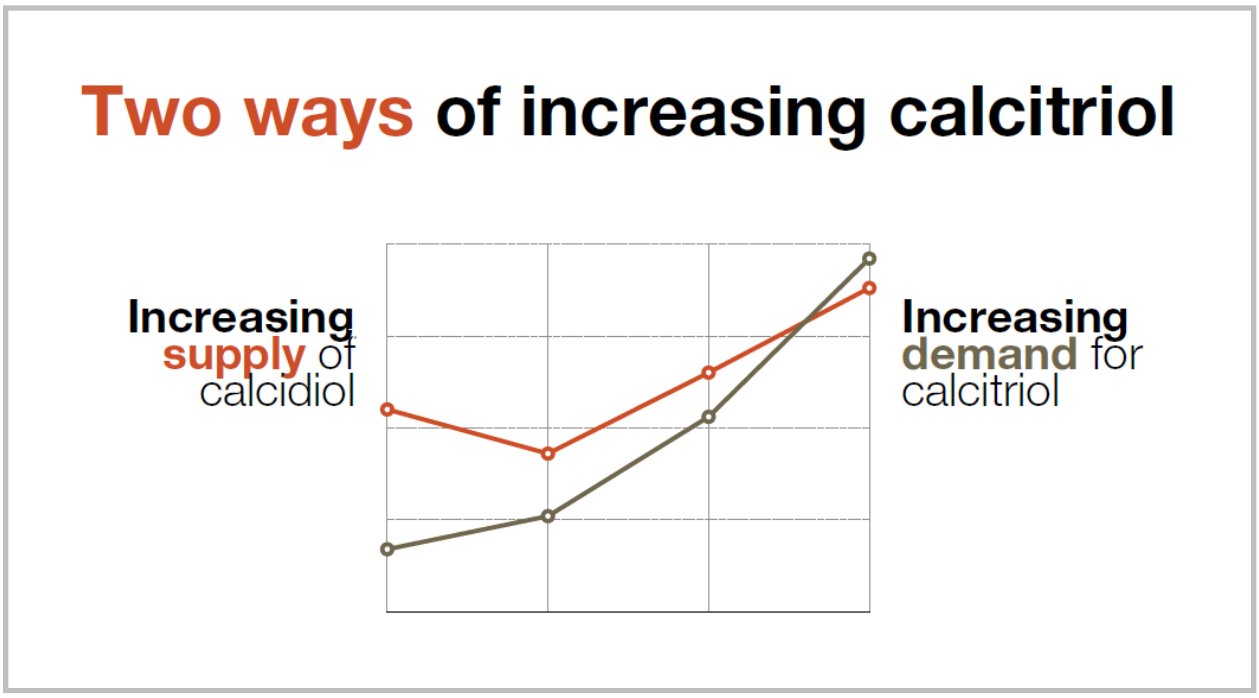
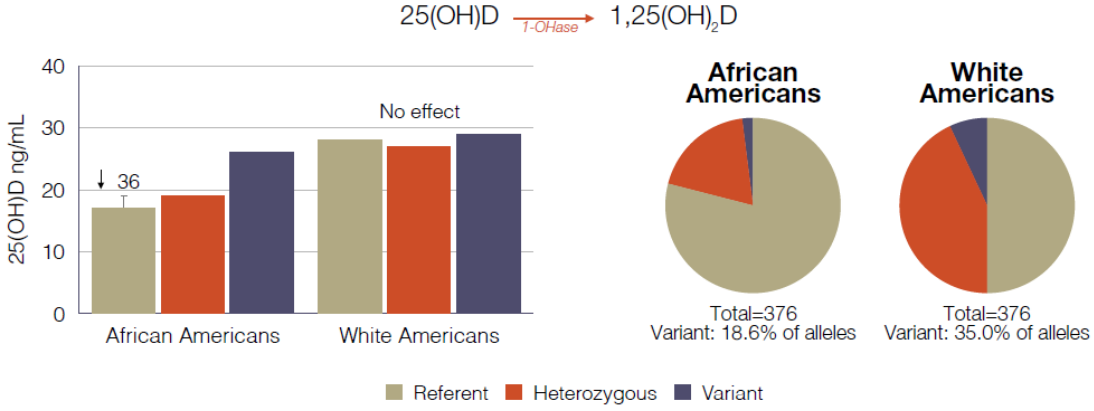
This conversion of 25(OH)D to calcitriol is tightly regulated by parathyroid hormone. Parathyroid hormone, or PTH, increases calcitriol formation, and it helps it increase serum calcium by acting on kidney and bone. On the other hand, 25(OH)D is only loosely regulated. If the calcitriol level and related measures such as PTH and bone health remain normal, even when calcidiol or 25(OH)D levels drop into the deficiency range, does that mean the person is really deficient in vitamin D? Current reference ranges that are globally applied to all without regard to ethnicity would say yes, but this more complete understanding of vitamin D metabolism and research on calcidiol and calcitriol levels, ethnicity, and bone density would say no.



The two potential ways of increasing calcitriol are increasing the supply of calcidiol through sun exposure, supplements, or diet or increasing demand for calcitriol via parathyroid hormone. With more substrate from diet, supplements, or sun, more calcidiol is available for the enzymatic conversion to calcitriol. With higher levels of PTH, the kidney produces more of the enzyme that converts calcidiol to calcitriol, so maintaining adequate substrate or supply of calcidiol protects bone health, since it shifts the burden of maintaining serum calcium away from PTH-dependent bone and kidney mechanisms and toward maximizing intestinal absorption of calcium.

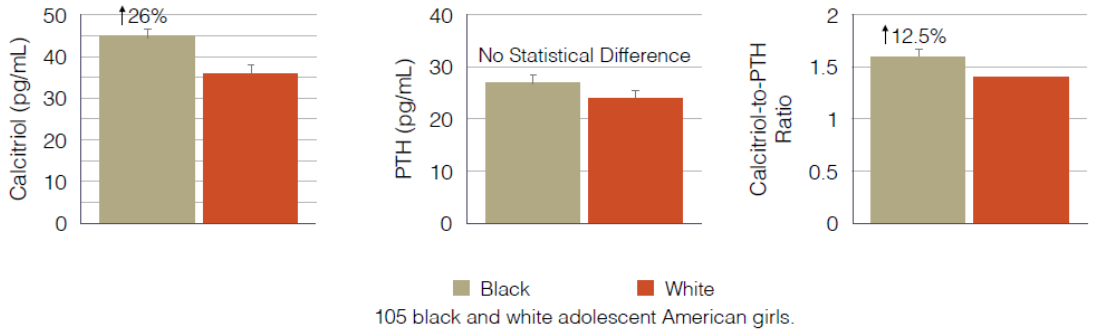
Genetic variation in activation of calcidiol to calcitriol in blacks and whites



Adapted from: Masterjohn, C. "The Evolution of Diverse Vitamin D Requirements", IHH-UCSF Symposium on the Paleo Approach and Evolutionary Medicine, San Francisco, 2016; Signorello, et al. Common Variation in Vitamin D Pathway Genes Predicts Circulating 25-Hydroxyvitamin D Levels among African Americans. PLoS One. 2011;6(12):e28623.

Okay, now let's get back to the question at hand. Recall that blacks have lower calcidiol levels than whites but better bone density. How could this be? One possibility is the genetic variation in the activation of 25(OH)D to calcitriol. In other words, blacks convert calcidiol to calcitriol more effectively, and they require less calcidiol to achieve the necessary amount of calcitriol.

PTH-mediated conversion of calcidiol to calcitriol in blacks vs. whites



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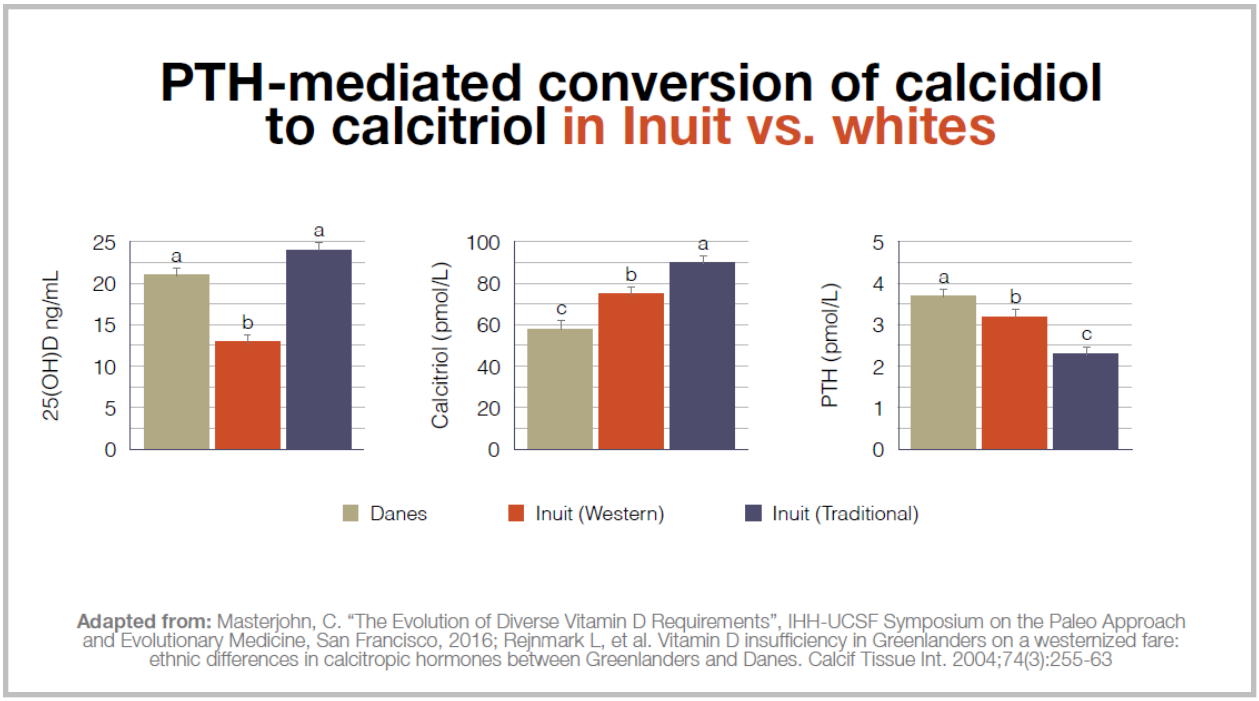
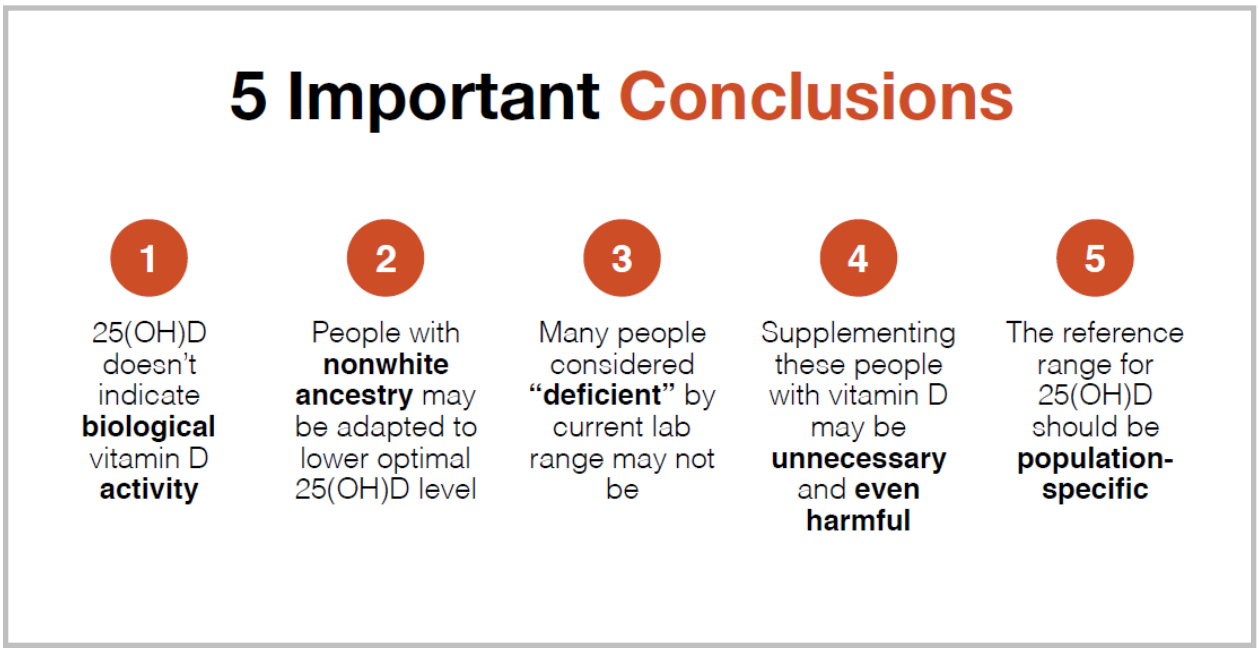
Another possibility is that nonwhites require less PTH to convert calcidiol to calcitriol. American whites consume almost two times as much calcium as blacks. However, blacks may require less PTH to active calcidiol in states of calcium deficiency, again as the charts on this slide suggest.



Adapted from: Masterjohn, C. "The Evolution of Diverse Vitamin D Requirements", IHH-UCSF Symposium on the Paleo Approach and Evolutionary Medicine, San Francisco, 2016; Rejnmark L, et al. Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes. Calcif Tissue Int. 2004;74(3):255-63

We see a similar phenomenon in Inuit when compared to Danish whites and even a difference between Inuit on a traditional diet and Inuit on a Western diet. As the charts on the slide indicate, the traditional Inuit needs the least PTH to achieve higher calcitriol levels. The Inuit on the Western diet is next, and then the Danes need the most PTH to activate calcidiol into calcitriol.



Now collectively, this suggests five important conclusions. First, although 25(OH)D is the best marker for measuring the available substrate from diet, supplements, and ultraviolet light for conversion to calcitriol, it's not the best marker of biological vitamin D activity. Second, people with nonwhite ancestry may be adapted to a lower optimal 25(OH)D than people with white ancestry. According to the research, we can be most confident that this is true for the traditional Inuit and African Americans and less confident that it is true for Asians. Third, many people who are considered deficient by the current U.S. lab range may not be. Fourth, giving them vitamin D, these people who are borderline deficient, may not only be unnecessary, it may actually be harmful given what some studies show about the U-shaped curve of vitamin D. The fifth conclusion arises naturally from the first four, which is that the reference range for 25(OH)D should probably be different for nonwhites and whites.

25(OH)D + (1000*1,25(OH)2D)

or

25(OH)D + 1,25(OH)2D)

Also, it may be possible to get a better estimate of biological vitamin D activity, which is the most important measurement that we're looking at, by combining calcidiol and calcitriol levels. This can be done by using a formula such as 25(OH)D plus 1,000 x 1,25(OH)2D, where both markers are expressed in the same units, or by simply adding them when 25(OH)D is expressed as ng/mL and when 1,25(OH)2D is expressed as pg/mL. When you use these formulas, black and white girls from the study earlier in the presentation have nearly identical circulating vitamin D activity. Elevations of calcitriol with low 25(OH)D suggest that the low 25(OH)D is due to increased utilization rather than decreased input but do not clarify whether this is from greater demand, such as from elevated PTH, or greater supply, such as from 1OHase genetics. Unfortunately, we don't yet have an established reference range for this biological vitamin D activity measurement that I'm proposing on this slide.