Vitamin 25(OH)D2/3 the basics

Introduction to what's typically tested

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Vitamin D Deficiency-VDD.

It's important to realize a few things about what is considered a deficiency with vitamin D. The mainstream tests target what is referred to and functions as the "storage form", 25 D either as 25(OH)D2 or 25(OH)D3. These two forms can be created from ingesting foods; however dietary sources are a minor contribution when compared to the D3 created from UVB sun exposure. D2 is a plant form that is eaten and then altered by the liver to become 25(OH)D2. D3 is an animal form that is eaten and then altered by the liver to become 25(OH)D3. D3 is also the form that UVB light creates from 7DHC (7-dehydrocholesterol) and additional 25(OH)D3 is created from this source as well. This is where upwards of 90% of humans vitamin D3 originates. (1) Food is a very small contribution as it should be because the body handles oral inputs entirely different, which will be discussed in later posts.

The 25D test is a serum test but "Vitamin D" is a fat soluble molecule, meaning it's stored in fat. A serum 25D test doesn't detect any true storage of 25D, such as what's stored in the liver. The amount of 25D in your serum, using an analogy, is much like the fuel line in your car compared to the fuel tank. The fuel tank in this analogy would be your liver. Think of cod liver oil as a source of fat soluble molecules like Vitamins A and D for context.

The 25D that is in serum is the amount the body created in the liver and was willing to release into serum to begin with. Simply creating through UVB exposure or consuming D2 and D3 doesn't lead directly to this substrate being activated by the liver and being dumped into serum as 25D. The body decides whether it wants to absorb the oral D2 and D3 in the first place. There's no guaranteed "throughput" of D2 and D3 to 25D into serum. Here it's important to note that although we consume (food or supplement) AND make (UVB exposure) D3, this molecule is NOT what gets tested. Testing measures serum levels of the storage form or 25D. This stands to reason because as stated by Heaney et al. 2008 "at typical vitamin D(3) inputs and serum concentrations, there is very little native cholecalciferol [D3] in the body, and 25(OH)D constitutes the bulk of vitamin D reserves." (2) However, when people consume upwards of 2000 IU daily or take large bolus doses (single dose over a short period of time) that is not the case and the amount of D3 in serum is increased and storage occurs. Heaney et al. further stated, "at supraphysiologic inputs, large quantities of vitamin D(3) are stored as the native compound, presumably in body fat, and are slowly released to be converted to 25(OH)D."(2)

There are a few direct sources of 25D, some foods that naturally contain D3 also contain 25D. These include eggs, fish, butter, and honey. However, the 25D is not listed on these foods nutritional labels. Foods that are fortified with vitamin D do not contain 25D. (3, 4)

Storage of Vitamin D

In the context of "storage", serum is considered one location where it resides. Vitamin 25D has a half-life of several weeks and this is the basis for the literature referring to it as "The typical clinical barometer of human vitamin D status". (5) It once WAS an acceptable guide for most healthy people but it's unreliable when there are comorbid conditions present which can alter serum levels. The

reason it's no longer an acceptable guide for healthy individuals is due to the altering (raising) of the serum goal for 25D in 2010. This will be discussed in later posts. "Vitamin D" is a very complex topic and it takes years if not decades to begin to understand its intricacies. In addition to what one may consider storage in serum, the liver is the chief storage organ and considerable amounts accumulate in bone and the kidneys. (6). Recent discoveries by Mason et al. 2019 have added muscle to this list: "there is now evidence that the main circulating metabolite of vitamin D, 25-hydroxyvitamin D, accumulates in skeletal muscle cells, which provide a functional store during the winter months." (7) The 25D molecules that are tested are typically limited to 25(OH)D2 and 25(OH)D3. In my research I have found 13 additional unique forms of 25D:

25(OH)D4	25(OH)D2 sulfate	25(OH)D3 sulfate	25(OH)D4 sulfate
Epi-3-25(OH)D2	Epi-3-25(OH)D3	Epi-3-25(OH)D4	Epi-3-25(OH)D2 Sulfate
Epi-3-25(OH)D3 Sulfate	Epi-3-25(OH)D4 Sulfate	25(OH)D3-Lactone	
25(OH)D3 Glucuronide	25(OH)L3		

This is very important because some analogs of "Vitamin D" are calcium impacting whereas others are not. Additionally, some molecules are more relevant in disease states and others based upon stage of life. For example, forms made in the epimerization pathway are relevant to type 1 diabetes, rheumatoid arthritis, and Alzheimer disease as well as when preterm infants are supplemented. (8,9) In summary, there are two major forms of vitamin 25D tested but testing doesn't reveal actual storage of these molecules nor does it capture the levels of additional unique forms of 25D or the bodies level of the two substrates D2 and D3 from which these molecules are derived. In addition, the "pandemic deficiency" would not exist today if the serum goal for 25D had not been increased in 2010.

The next installment will be an introduction into the overlooked active form of Vitamin D, 1,25(OH)2D2 and 1,25(OH)2D3. These are the "molecules of immune response" whose biological actions result in the creation of Vitamin D Response Elements (VDRE's). These VDRE's I refer to as our "chemical and biological warriors", things like macrophages, T-cells, and anti-microbial peptides. Of crucial interest is the fact that the goal for this analog WAS NOT raised along with the serum 25D goal in 2010 despite its immunologic relevance.

(1) https://www.tandfonline.com/doi/full/10.3109/00365513.2012.681929
(2) https://www.ncbi.nlm.nih.gov/m/pubmed/18541563/
(3) https://pubmed.ncbi.nlm.nih.gov/12743460/
(4) https://www.ncbi.nlm.nih.gov/m/pubmed/24623845/?i=5&from=/12743460/related
(5) https://pubmed.ncbi.nlm.nih.gov/22075270/
(6) Heftmann, E. Steroid Biochemistry. New York, NY: Academic Press; 1970. 34 p.
(7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776467/#!po=0.694444
(8) https://www.ncbi.nlm.nih.gov/m/pubmed/24423328/
(9) https://pubmed.ncbi.nlm.nih.gov/26709675/

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