The ''Vitamin'' D Conundrum:

Why don't the clinical trials agree with the science?

During the Covid epidemic "vitamin" D became front-page news. Because low "vitamin" D levels were associated with poor Covid outcomes most of us now recognize that D is not just a ''bone vitamin" but plays an important role in many parts of our body, especially our immune system. This increased interest in D has also revealed an important mis-match between 80 years of scientific study of ''hormone'' D and D's use in routine medical practice.

Over the last 50 years "vitamin" D deficiency has been shown to be related to numerous chronic illnesses. (1-4) There are thousands of scientific articles documenting that D is a *hormone* playing an important role in almost every organ in the human body. (1-4)

Because of these important scientific findings many prospective treatment trials are being performed. These trials are meant to answer a specific question: *If hormone D deficiency shows up along with diseases that are common in our human population could giving hormone D help prevent or cure these same diseases?* It's an obvious question that should have an obvious answer. Then why have so many of the recent human treatment trials shown negative results?

Poor Design of D Treatment Trials:

Because of the continued, inappropriate use of the word ''vitamin" most of the D treatment trials have been designed as fixed-dose, public-health "vitamin" studies. Because of the way these studies are designed they have consistently reported negative results. Because of these negative trials doctors are currently being advised not to test vitamin D levels or even recommend vitamin D supplementation:

> **Why Is Vitamin D Hype So Impervious to Evidence?**
> https://www.medscape.com/viewarticle/968682
> John M. Mandrola, MD Medscape COMMENTARY February 17, 2022
>
> *The vitamin D story exudes teaching points: it offers a master class in critical appraisal, connecting the concepts of biologic plausibility, flawed surrogate markers, confounded observational studies, and slews of randomized controlled trials (RCTs) showing no benefits on health outcomes. Yet despite the utter lack of benefit seen in trials, the hype continues. And the pandemic has only enhanced this hype as an onslaught of papers have reported the association of low vitamin D levels and COVID-19 disease.*
>
> *My questions are simple: Why doesn't the evidence persuade people? How many nonsignificant trials do we need before researchers stop studying vitamin D, doctors stop (routinely) measuring levels, and patients stop wasting money on the unhelpful supplement? What are the implications for this lack of persuasion?* (5)

D Deficiency is Widespread:

There is no argument that hormone D deficiency is widespread, it's a global phenomenon that has only become worse as most of the world population moved indoors during the Covid epidemic. The advent of air conditioning, sunscreen, computers, and the increasingly extreme declarations that "sun exposure is bad" have produced a profound, global D deficiency. The confusion lies in whether sustaining a ''better'' hormone D level could produce a healthier population.

What Do We Need to Know?

1) What is a ''healthier hormone D level"?

2) If maintained in our population could a "healthier D level" either prevent or treat the myriad of chronic illnesses that have been shown to be related to D deficiency?

3) Why is it so difficult to achieve a consensus of opinion on this particular hormone?

4) Why was D mistakenly called a vitamin and has that mistake prevented us from educating ourselves about how to use this important hormone?

D Deficiency is Rickets:

In the 1800's the childhood disorder, Rickets described a "colicky baby" who wouldn't sleep, wouldn't eat, and couldn't be soothed. Kids with Rickets also had trouble with their teeth; they had lots of early cavities and their teeth came in later than they should. As the disease got worse, they got sick more often, were slower to get well, and eventually had an unwillingness to walk. These are still the symptoms of Rickets but that word is no longer being used to describe the thousands of children who are suffering with these problems. (6)

For two hundred years doctors argued about the cause of Rickets. Some thought that it was caused by a poor diet as it seemed to be more common in poor families living in tenement buildings.

Starting in the early 1900's the X ray machine came along and the doctors discovered that kids with Rickets had distinctive X ray findings showing abnormal bone growth. Bone X ray photos eventually replaced the rest of the clinical symptoms in the medical textbooks and Rickets became labelled a "bone disease" (ignoring all the other well-described symptoms, that are now quite common in pediatric populations). (6)

Despite Medicine's belief that Rickets was a "nutritional disorder" in 1921 Alfred Hess and others demonstrated that babies and toddlers living in New York city tenements could be cured

of Rickets through sun exposure. (7) Thousands of journal articles have followed documenting that D3 is made on the skin from direct exposure to sunlight. (8) If this has been known for over 100 years then why is hormone D still being called a “nutrient” or a “vitamin”?

Why Names Matter:

Humans, who are bald compared to other animals, can absorb the hormone D we make through our skin. But fur-covered animals get D into their body when they lick themselves. So, for most animals D does come through the mouth, but not really by ‘’eating’’. All the animals on our planet; insects, birds, fish, reptiles, and mammals all make D3 (cholecalciferol) from sun exposure.

In the 1940’s the scientists who were convinced that Rickets was related to a poor diet went looking for the missing essential element, the anti-Rickets ‘’vitamin’’ using rat experiments. But rats are slightly different than humans, they come out at night and sleep during the day. Since all animals need D to survive, they could live without sunlight only if they could find an alternate source of D. So, rats evolved a way to use a different D that was, in fact, in their food. It is a much older D, made exclusively by mold (or mushrooms), called D2 (ergocalciferol). So D2 was the first ‘’anti-Rickets factor” to be found and it was actually found in the rats’ moldy food. It was not until 10 years later that D3, what we make on our skin, was discovered on the skin of pigs left in the sun. (9)

Since the 1950’s numerous scientific articles have documented that D2 and D3 are different chemicals and that only some animals can use D2 interchangeably with D3. There are articles that suggest that D2 may block our natural D3 from acting at our vitamin D receptor causing worsening of D deficiency symptoms. In my experience D2 given to people with severe D deficiency frequently makes their symptoms worse. (personal observation)

Predatory animals, like owls who hunt at night, do receive some of their D3 from the raw meat, blood and liver of the animals they devour. But based on the current epidemic of D deficiency in the human population it is obvious that the amount of D3 we consume from raw animal organs is not enough to match our D requirements. Our main source of D always was and still is, the sun. Therefore the term ‘’nutrient“ is obviously not appropriate for D3.

There is an ongoing battle in Medicine between those who believe that, although D2 is not frankly poisonous, (we clearly get some D2 from mushrooms), it should never be given as a pharmaceutical to humans, and those who have not spent the time to learn the difference. D3 is readily available and it should be used instead.

Calling D a ‘’vitamin” Changed How we Learn

In the 1980's Medicine decided that ''if you have a good diet, you don't need vitamins" and medical education about hormone D became less and less. Recently doctors are actually being discouraged from learning about hormone D. In 2021 my courses for clinicians about D and its effects on the microbiome were given full continuing medical education credit by the AAFP. But for the last two years the American Academy of Family Practitioners has specifically excluded from credit any information about hormone D, a de facto suppression of doctors' education about an important hormone of our body.

Understanding D's Role in the Endocrine System:

Hormone D is not, and never has been a ''fat-soluble vitamin". It is a hormone made on our skin in response to sunlight. It controls multiple other hormones at the level of the pituitary. (10) It has forever linked our fertility, metabolism, and sleep to the seasonal availability of food. (11) It is not made in the summer and ''stored'' to use in the winter. It is designed to go up and down producing a ''Winter D State" and a ''Summer D State".

D affects our metabolism through the intestinal microbiome. (11, 12) It is a bacterial growth factor, establishing certain populations of bacteria in the "Summer D State", others in the "Winter D State". (12) The winter weight gain produced by bacterial changes provided an important survival advantage getting us through lean months of winter. But our recent move indoors has produced a continuous "Winter D State" with an accompanying epidemic of obesity. (13)

Correct Hormone D Dosing:

Hormone dosing is always performed to achieve a desired blood level. Experience tells us that if we use hormones as pharmaceuticals our best results are achieved by copying normal physiology as closely as possible. Thus, the term ''bio-identical hormone'' is now in common use. (14) Our experience with thyroid, estrogen, cortisol and testosterone as pharmaceuticals has taught us that unintended, bad outcomes can result from non-physiologic dosing. (15, 16) D is being given in many clinical trials as fixed doses without proper attention to D blood levels. (17)

Fixed Dose Clinical Trials vs. Appropriate Hormone Dosing:

Because of the ''vitamin'' misnomer most prospective human trials of D have been fixed-dose trials, designed as a "public health intervention" such as the VITAL study shown below.

A prospective trial using hormone D correctly to *prevent an undesired outcome* would require:

1) Documenting an "unhealthy, D-deficient blood level" in all participants as they are included in the trial.

2) Achieving an agreed-upon ''healthy D blood level'' in the treatment group and maintaining that "healthy level" (with measured blood levels) for a stated period of time.

3) Comparison of the outcomes of the two groups.

The VITAL Fixed-dose Study:

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease
JoAnn E Manson , Nancy R Cook , I-Min Lee et al. N Engl J Med. 2019 Jan 3;380(1):33-44.
We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (cholecalciferol) at a dose of 2000 IU per day and marine n-3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States.
Results: *A total of 25,871 participants, including 5106 black participants, underwent randomization. Supplementation with vitamin D was not associated with a lower risk of either of the primary end points. During a median follow-up of 5.3 years.* (17)

The VITAL study is an example of the many poorly-designed D trials reported over the last 20 years. It appears to be a well-designed study (prospective, randomized, placebo-controlled) in 25,871 participants, followed for 5.3 years, reporting that 2000 IU's/day of D was ineffective for the prevention of cancer and heart disease. However, careful examination of the results reveals important shortcuts that undermine their claims and reveal a gross misunderstanding of proper hormone study design.

First a look at other hypothetical hormone trials designed in the same way as the VITAL study so the problems become obvious. (The hypothetical studies described are both real associations between hormone deficiency and medical problems.)

Hypothetical Prospective Trials of Other Hormones (to make the point).

> ***Hypothetical Thyroid Hormone Trial:*** *Thyroid supplementation for early childhood dental caries and early gum disease.*
>
> *Several studies have reported that childhood hypothyroidism is associated with early childhood dental disease of many types. In order to address this issue and assess the utility of thyroid supplementation for the prevention of early childhood dental caries we performed a double blind, randomized, controlled trial in 2545 children.*

The treated group took 50 mcg of Synthroid daily for three years. The trial had endpoints measured by phone interviews with parents and documented follow-up with participants' dentists.

Is this a good study design?

-Did those in either group (treatment or control) have low thyroid hormone levels at the beginning of the study? What were those levels?
-Were there adjustments made to the doses of the thyroid hormone to keep the thyroid replacement within range during the study?
-Were there blood levels drawn to conclude that the low thyroid hormone level was appropriately treated and the children remained "euthyroid" (normal thyroid level) for the three years?
-Would you let your child receive thyroid hormone for three years without any thyroid hormone levels being drawn and adjusted to keep it in the ''normal, healthy'' range?

Hypothetical Testosterone Trial: *Low testosterone levels have been associated with sleep apnea and other sleep disorders. In order to investigate the role of testosterone supplementation to prevent development of sleep disorders we did a nationwide, randomized, placebo-controlled trial of daily testosterone to prevent sleep disorders of all types.*

24,000 men ages 40-60 were randomized to the treatment or control group. None had documented sleep disorders. 12,000 men were assigned to the treatment group. They received 50 mg of testosterone cream to the skin of the forearm for five years. 1500 of the treatment group had a second testosterone level measured at one year, their testosterone levels had increased by a mean of 100 ng/dl from baseline.

At the end of five years, they were interviewed by questionnaire and their physicians were interviewed by questionnaire regarding any clinical evidence of a sleep disorder developing in the prior years.

Is this a good study design?

-Did the men have low testosterone levels at the beginning of the study? What were those levels?
-Why weren't there testosterone levels done at any time other than one year?
-Would you take testosterone for five years without measuring testosterone levels and adjusting the testosterone to make sure it stayed in the ''normal, healthy'' range?
-Do you think that this study design is a good way to find out whether testosterone supplementation could prevent sleep disorders?

What Did the VITAL Data Really Show?

In the VITAL study the "D deficiency state" was documented in only 2/3rds of the randomized participants. Only 65.5 % (16,956 of 25,871) ever had a D blood level at the start of the study! 65% had a mean D level of 30 ng/ml, but the remaining 35% *were assumed to be low and were followed as though the information were documented even though it wasn't*. It appears that their thinking was: "Everybody's low, why spend the time and money to actually document it?" This is thinking about D deficiency as a "public health issue" not as a hormone that is affecting our bodies in numerous ways.

The study design had no stated, target "healthier blood level", it was just assumed that 2000 IU was a ''good dose". A second D blood level was measured in only 836 treated participants and only once, at one year. Participants were followed for 4 more years but no other D levels were drawn. The outcome was stated to show no effect for the total of 25,871 participants over 5 years but the actual treatment trial was 836 participants (6% of the treatment group) for one year.

This study reports a negative outcome because it is poorly designed. The authors summarized their results in an inaccurate, misleading manner, yet it was accepted and published in the New England Journal of Medicine. The ''vitamin'' word applied to D has given rise to a double standard regarding the rigorousness of the D clinical trials. If this were a new drug study these profound errors of design and reporting would never have been accepted (or overlooked) by the reviewers!

The example above is just one of many fixed-dose D trials with negative outcomes. Poorly designed studies often generate negative outcomes, and studies that support currently held beliefs are always easier to publish. Unfortunately, these poorly run studies confuse our doctors and short-change the rest of us.

Why Aren't Appropriate Trials Being Done?

A well-designed study of hormone D to *prevent* the diseases that have been observed in the setting of D deficiency (and produced by D deficiency in animals) would require giving D in a daily, bio-identical manner. Blood levels would have to be maintained in a specific range; 10-20ng/ml, 20-30ng/ml, 30-40ng/ml, 40-50ng/ml, 50-60 ng/ml in both winter and summer adjusting the dose for sun exposure. Then, after many years, each group would be studied to see what had happened to their health. What medical problems had occurred? Did those who maintained a blood level of 10-20 over the 10 years of the study have more medical problems than the group with a blood level of 40-50? In this way a ''healthier D level'' might be

determined. Imagine how expensive it would be to provide staff and follow-up to maintain those blood levels over years. Anyone who has tried to maintain their own D blood level over time knows just how hard it is. Because there is little funding for studies that don't produce a profitable drug, the easier, fixed-dose trials are being performed instead and obviously they don't really answer the questions we have; What is a heathier D level? Would maintaining that level give me better health? Is staying out of the sun really a good thing for me? Am I trading a skin cancer on my ear at age 70 for numerous medical problems over my entire life?

Why Are Doctors Confused by These "vitamin" D Trials?

This one, very flawed, data set generated in the VITAL study described above has been used to publish many, many articles. They all, not surprisingly, show no effect of D on prevention of depression, heart disease, autoimmune disease, macular degeneration, risk of falls and even bone health.

- Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. Manson JE, Cook NR, Lee IM, VITAL Research Group. N Engl J Med. 2019 Jan 3;380(1):33-44.
- Effect of Long-term Vitamin D3 Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores: A Randomized Clinical Trial. (VITAL-DEP (Vitamin D and Omega-3 Trial-Depression Endpoint Prevention) ancillary study to VITAL. Okereke OI, Reynolds CF 3rd, Mischoulon D, et al. JAMA. 2020 Aug 4;324(5):471-480.
- Vitamin D, Marine n-3 Fatty Acids, and Primary Prevention of Cardiovascular Disease Current Evidence. Manson JE, Bassuk SS, Cook NR, et al. VITAL Research Group. Circ Res. 2020 Jan 3;126(1):112-128.
- Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. Hahn J, Cook NR, Alexander EK,et al. BMJ. 2022 Jan 26;376:e066452.
- Supplementation with Vitamin D and Omega-3 Fatty Acids and Incidence of Heart Failure Hospitalization. Djoussé L, Cook NR, Kim E, et al. VITAL Research Group. Circulation. 2020 Mar 3;141(9):784-786.
- Effect of Vitamin D and omega-3 Fatty Acid Supplementation on Risk of Age-Related Macular Degeneration: An Ancillary Study of the VITAL Randomized Clinical Trial. Christen WG, Cook NR, Manson JE, et al. VITAL Research Group. JAMA Ophthalmol. 2020 Dec 1;138(12):1280-1289.
- Vitamin D and OmegA-3 TriaL (VITAL): Effects of Vitamin D Supplements on Risk of Falls in the US Population. Meryl S LeBoff, Elle M Murata, et al. J Clin Endocrinol Metab. 2020 Sep; 105(9): 2929–2938.
- Principal results of the Vitamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. JoAnn E. Manson, Shari S. Bassuk, Julie E. Buring. The Journal of Steroid Biochemistry and Molecular Biology. 2020 vol. 198 pp. 105522
- Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Gencer B, Djousse L, Al-Ramady OT, et al. Circulation. 2021 Dec 21;144(25):1981-1990.
- Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. LeBoff MS, Chou SH, Ratliff KA, et al. N Engl J Med. 2022 Jul 28;387(4):299-309.

Each of these publications appears to be of a separate trial, but they're not. And when someone does a "meta-analysis" which tries to summarize the results of multiple studies they appear as *numerous negative clinical trials*, instead of one highly-flawed data set.

Continuing Dr. John Mandrola's commentary:

The Randomized Controlled Trials Tell a Clear Story
https://www.medscape.com/viewarticle/968682
John M. Mandrola, MD Medscape COMMENTARY February 17, 2022

> *There are hundreds of vitamin D RCTs. The results simplify into one sentence: Vitamin D supplements do not improve health outcomes. Here is a short summary of some recent studies.*
>
> *VITAL, a massive (N > 25,000) RCT with 5 years of follow-up, compared vitamin D supplements to placebo and found no differences in the primary endpoints of cancer or cardiac events. Rates of death from any cause were nearly identical. Crucially, in subgroup analyses, the effects did not vary according to vitamin D levels at baseline.*
>
> *The D-Health investigators randomly assigned more than 21,000 adults to vitamin D or placebo and after 5.7 years of follow-up reported no differences in the primary endpoint of overall mortality. There were also no differences in cardiovascular disease mortality.*

Numerous animal studies and smaller human trials done correctly suggest that hormone D has great potential for reversing and preventing chronic illness. (18,19) Better education of our physicians regarding the proper use of D as a hormone, and appropriately designed, prospective studies are what our patients and our physicians really need.

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