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Calcium and vitamin D in preventing fractures

Data are not sufficient to show inefficacy

EDITOR—The study by Porthouse et al had two major design flaws.[1] Firstly, the dose of vitamin D (800 IU per day) is subphysiological and therefore subtherapeutic. Secondly, their use of "self report" as a measure of compliance is unreliable.

The dose of vitamin D at 800 IU daily was not determined scientifically but determined arbitrarily before sufficient scientific methodology was available.[2-4] Heaney et al determined the physiological requirement of vitamin D by showing that healthy men use 4000 IU cholecalciferol daily,[2] an amount that is safely attainable with supplementation[3] and often exceeded with exposure of the total body to equatorial sun.[4]

We provided six guidelines for interventional studies with vitamin D.[5] Dosages of vitamin D must reflect physiological requirements and natural endogenous production and should therefore be in the range of 3000-10 000 IU daily. Vitamin D supplementation must be continued for at least five to nine months. The form of vitamin D should be D_3 rather than D_2. Supplements should be assayed for potency. Effectiveness of supplementation must include measurement of serum 25-hydroxyvitamin D. Serum 25(OH)D concentrations must enter the optimal range, which is 40-65 ng/ml (100-160 nmol/l).

Since the study by Porthouse et al met only the second and third of these six criteria, their data cannot be viewed as reliable for documenting the inefficacy of vitamin D supplementation.

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Competing interests: AV is a researcher at Biotics Research Corporation, a drug manufacturing facility in the United States that has approval from the Food and Drug Administration.

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THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Appreciate and identify the manifold clinical presentations and consequences of vitamin D deficiency
2. Identify patient groups that are predisposed to vitamin D hypersensitivity
3. Know how to implement vitamin D supplementation in proper doses and with appropriate laboratory monitoring

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While we are all familiar with the important role of vitamin D in calcium absorption and bone metabolism, many doctors and patients are not aware of the recent research on vitamin D and the widening range of therapeutic applications available for cholecalciferol, which can be classified as both a vitamin and a pro-hormone. Additionally, we also now realize that the Food and Nutrition Board's previously defined Upper Limit (UL) for safe intake at 2,000 IU/day was set far too low and that the physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.[1,2] With the discovery of vitamin D receptors in tissues other than the gut and bone—especially the brain, breast, prostate, and lymphocytes—and the recent research suggesting that higher vitamin D levels provide protection from diabetes mellitus, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, several autoimmune diseases, and cancers of the breast, prostate, and colon, we can now utilize vitamin D for a wider range of preventive and therapeutic applications to maintain and improve our patients' health.[3] Based on the research reviewed in this article, the current authors believe that assessment of vitamin D status and treatment of vita-

min D deficiency with oral vitamin D supplements should become a routine component of clinical practice and preventive medicine. Vitamin D supplementation with doses of 4,000 IU/day for adults is clinically safe and physiologically reasonable since such doses are consistent with physiologic requirements.[2] Higher doses up to 10,000 IU/day appear safe and produce blood levels of vitamin D that are common in sun-exposed equatorial populations.[1,2] Periodic assessment of serum 25-OH-vitamin D [25(OH)D] and serum calcium will help to ensure that vitamin D levels are sufficient and safe for health maintenance and disease prevention. Clinical research supporting the use of vitamin D in the management of type 2 diabetes, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, multiple sclerosis, polycystic ovary syndrome, musculoskeletal pain, depression, epilepsy, and the prevention of cancer and type 1 diabetes is presented along with our proposals for the interpretation of serum 25(OH)D laboratory values, for the design of future research studies, and for supplementation in infants, children, adults, and during pregnancy and lactation.

BASIC PHYSIOLOGY OF VITAMIN D

Vitamin D is obtained naturally from two sources: sunlight and dietary consumption. Vitamin D3 (cholecalciferol) is the form of vitamin D produced in the skin and consumed in the diet. Vitamin D2 (ergocalciferol), which is produced by irradiating fungi, is much less efficient as a precursor to the biologically active 1,25-dihydroxyvitamin D (calcitriol). Additionally, since ergocalciferol shows altered pharmacokinetics compared with D3 and may become contaminated during its microbial production, it is potentially less effective and more toxic than cholecalciferol.[4] Although ergocalciferol is occasionally used clinically and in research studies, cholecalciferol is the preferred form of supplementation and will be implied in this article when supplementation is discussed.

Vitamin D can be described as having two pathways for metabolism: one being "endocrine" and the other "autocrine" (within the cell) and perhaps "paracrine" (around the cell). This elucidation, recently reviewed by Heany,[5] is vitally important in expanding our previously limited conception of vitamin D from only a "bone nutrient with importance only for the prevention of rickets and osteomalacia" to an extraordinary molecule with far-reaching effects in a variety of cells and tissues. Furthermore, Heany's distinction of "short-latency deficiency diseases" such as rickets from "long-latency deficiency diseases" such as cancer provides a conceptual handle that helps us grasp an understanding of the differences between the acute manifestations of severe nutritional deficiencies and the delayed manifestations of chronic subclinical nutritional deficiencies.[5]

In its endocrine metabolism, vitamin D (cholecalciferol) is formed in the skin following exposure to sunlight and then travels in the blood to the liver where it is converted to 25-hydroxyvitamin D (calcidiol, 25(OH)D) by the enzyme vitamin D-25-hydroxylase. 25(OH)D then circulates to the kidney for its final transformation to 1,25-dihydroxyvitamin D (calcitriol) by 25-hydroxyvitamin D3-1alpha-hydroxylase (1-OHase).[6] Calcitriol is the most biologically active form of vitamin D and increases calcium and phosphorus absorption in the intestine, induces osteoclast maturation for bone remodeling, and promotes calcium deposition in bone and a reduction in parathyroid hormone (PTH). While increased calcium absorption is obviously important for nutritional reasons, suppression of PTH by vitamin D is also clinically important since relatively lower levels of PTH appear to promote and protect health, and higher levels of PTH correlate with increased risk for myocardial infarction, stroke, and hypertension.[7,8] Relatedly, Fujita[9] proposed the "calcium paradox" wherein vitamin D or calcium deficiency leads to elevations of PTH which increases intracellular calcium and may thereby promote a cascade of cellular dysfunction that can contribute to the development of diabetes mellitus, neurologic diseases, malignancy, and degenerative joint disease.

In its autocrine metabolism, circulating 25(OH)D is taken up by a wide variety of cells that contain both 1-OHase as well as nuclear vitamin D receptors (VDR). Therefore, these cells are able to make their own calcitriol rather than necessarily relying upon hematogenous supply. Cells and tissues that are known to contain 1-OHase, and which therefore make their own calcitriol, include the breast, prostate, lung, skin, lymph nodes, colon, pancreas, adrenal medulla, and brain (cerebellum and cerebral cortex).[3,10] Cells and tissues with nuclear, cytosolic, or membrane-bound VDR include islet cells of the pancreas, monocytes, transformed B-cells, activated T-cells, neurons, prostate cells, ovarian cells, pituitary cells, and aortic endothelial cells.[11] Indeed, given the wide range of cells and tissues that metabolize vitamin D in an autocrine manner, we see that there is biological potential for vitamin D to influence function and pathophysiology in a wide range of metabolic processes and disease states.

Since many cells and tissues of the body have the ability to metabolize vitamin D, we should not be surprised that vitamin D plays a role in the function of these cells. Calcitriol is known to modulate transcription of several genes, notably those affecting differentiation and proliferation such as c-myc, c-fos, and c-sis,[6] and this may partially explain the inverse relationship between sun exposure (eg, vitamin D) and cancer mortality.[12,13] Vitamin D appears to modulate neurotransmitter/neurologic function as shown by its antidepressant[14] and anticonvulsant[15] benefits. Vitamin D is obviously immunoregulatory as manifested by its ability to reduce inflammation,[16,17] suppress and/or prevent certain autoimmune diseases,[18-20] reduce the risk for cancer,[12] and possibly reduce the severity and frequency of infectious diseases, such as acute pneumonia in children.[21]

CLINICAL APPLICATIONS AND THERAPEUTIC BENEFITS OF VITAMIN D

Support for a broad range of clinical applications for vitamin D supplementation comes from laboratory experiments, clinical trials, and epidemiologic surveys. Despite the imperfections of current data, we can still see significant benefits from vitamin D supplementation in a variety of human diseases, as briefly reviewed below.

Cardiovascular Disease

Deaths from cardiovascular disease are more common in the winter, more common at higher latitudes and more common at lower altitudes, observations that are consistent with vitamin D insufficiency.[22] The risk of heart attack is twice as high for those with 25(OH)D levels less than 34 ng/ml (85 nmol/L) than for those with vitamin D status above this level.[23] Patients with congestive heart failure were recently found to have markedly lower levels of vitamin D than controls,[24] and vitamin D deficiency as a cause of heart failure has been documented in numerous case reports.[25-29]

Hypertension

It has long been known that blood pressure is higher in the winter than the summer, increases at greater distances from the equator and is affected by skin pigmentation—all observations consistent with a role for vitamin D in regulating blood pressure.[30] When patients with hypertension were treated with ultraviolet light three times a week for six weeks their vitamin D levels increased by 162%, and their blood pressure fell significantly.[31] Even small amounts of oral cholecalciferol (800 IU) for eight weeks lowered both blood pressure and heart rate.[32]

Type 2 Diabetes

Hypovitaminosis D is associated with insulin resistance and beta-cell dysfunction in diabetics and young adults who are apparently healthy. Healthy adults with higher serum 25(OH)D levels had significantly lower 60 min, 90 min and 129 min postprandial glucose levels and significantly better insulin sensitivity than those who were vitamin D deficient.[33] The authors noted that, compared with metformin, which improves insulin sensitivity by 13%, higher vitamin D status correlated with a 60% improvement in insulin sensitivity. In a recent clinical trial using 1,332 IU/day for only 30 days in 10 women with type 2 diabetes, vitamin D supplementation was shown to improve insulin sensitivity by 21%.[34]

Osteoarthritis

Many practitioners know that vitamin D helps prevent and treat osteoporosis, but few know that the progression of osteoarthritis, the most common arthritis, is lessened by adequate blood levels of vitamin D. Framingham data showed osteoarthritis of the knee progressed more rapidly in those with 25(OH)D levels lower than 36 ng/ml (90 nmol/L).[35] Another study found that osteoarthritis of the hip progressed more rapidly in those with 25(OH)D levels lower than 30 ng/ml (75 nmol/L).[36]

Multiple Sclerosis

The autoimmune/inflammatory disease multiple sclerosis (MS) is notably rare in sunny equatorial regions and becomes increasingly prevalent among people who live farther from the equator and/or who lack adequate sun exposure. In a clinical trial with 10 MS patients, Goldberg, Fleming, and Picard[19] prescribed daily supplementation with approximately 1,000 mg calcium, 600 mg magnesium, and 5,000 IU vitamin D (from 20 g cod liver oil) for up to two years and found a reduction in the number of exacerbations and an absence of adverse effects. This is one of very few studies in humans that employed sufficient daily doses of vitamin D (5,000 IU) and had sufficient duration (2 years). More recently, Mahon et al[37] gave 800 mg calcium and 1,000 IU vitamin D per day for six months to 39 patients with MS and noted a modest anti-inflammatory effect.

Prevention of Type 1 Diabetes

Type 1 diabetes is generally caused by autoimmune/inflammatory destruction of the pancreatic beta-cells. Vitamin D supplementation shows significant preventive and ameliorative benefits in animal models of type 1 diabetes. In a study with more than 10,000 participants, Hypponen et al[18] showed that supplementation in infants (less than one year of age) and children with 2,000 IU of vitamin D per day reduced the incidence of type 1 diabetes by approximately 80%. Relatedly, several studies using cod liver oil as a rich source of vitamin D have also documented significant reductions in the incidence of type 1 diabetes.

Depression

Seasonal affective disorder (SAD) is a particular subtype of depression characterized by the onset or exacerbation of melancholia during winter months when bright light, sun exposure, and serum 25(OH)D levels are reduced. Recently, a dose of 100,000 IU of vitamin D was found superior to light therapy in the treatment of SAD after one month.[38] Similarly, in a study involving 44 subjects, supplementation with 400 or 800 IU per day was found to significantly improve mood within five days of supplementation.[14]

Epilepsy

Seizures can be the presenting manifestation of vitamin D deficiency.[39] Hypovitaminosis D decreases the threshold for and increases the incidence of seizures, and several "anticonvulsant" drugs interfere with the formation of calcitriol in the kidney and further reduce calcitriol levels via induction of hepatic clearance. Therefore, antiepileptic drugs may lead to iatrogenic seizures by causing iatrogenic hypovitaminosis D.[40] Conversely, supplementation with 4,000–16,000 IU per day of vitamin D2 was shown to significantly reduce seizure frequency in a placebo controlled pilot study by Christiansen et al.[15]

Migraine Headaches

Calcium clearly plays a role in the maintenance of vascular tone and coagulation, both of which are altered in patients with migraine. Thys-Jacobs[41] reported two cases showing a reduction in frequency, duration, and severity of menstrual migraine attacks following daily supplementation with 1,200 mg of calcium and 1,200–1,600 IU of vitamin D in women with vitamin D deficiency.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a disease seen only in humans and is classically characterized by polycystic ovaries, amenorrhea, hirsuitism, insulin resistance, and obesity. Animal studies have shown that calcium is essential for oocyte activation and maturation. Vitamin D deficiency was highly prevalent among 13 women with PCOS, and supplementation with 1,500 mg of calcium per day and 50,000 IU of vitamin D2 on a weekly basis normalized menstruation and/or fertility in nine of nine women with PCOS-related menstrual irregularities within three months of treatment.[42]

Musculoskeletal Pain

Patients with non-traumatic, persistent musculoskeletal pain show an impressively high prevalence of overt vitamin D deficiency. Plotnikoff and Quigley[43] recently showed that 93% of their 150 patients with persistent, nonspecific musculoskeletal pain were overtly deficient in vitamin D. Masood et al[44] found a high prevalence of vitamin D deficiency in children with limb pain, and vitamin D supplementation ameliorated pain within three months. Al Faraj and Al Mutairi[45] found vitamin D deficiency in 83% of their 299 patients with low-back pain, and supplementation with 5,000–10,000 IU of vitamin D per day lead to pain reduction in nearly 100% of patients after three months.

Critical Illness and Autoimmune/Inflammatory Conditions

Deficiency of vitamin D is common among patients with inflammatory and autoimmune disorders and those with prolonged critical illness. In addition to the previously mentioned epidemic of vitamin D insufficiency in patients with MS, we also see evidence of vitamin D insufficiency in a large percentage of patients with Grave's disease,[46] ankylosing spondylitis,[47] systemic lupus erythematosus,[48] and rheumatoid arthritis.[20] Clinical trials with proper dosing and duration need to be performed in these patient groups. C-reactive protein was reduced by 23% and matrix metalloproteinase-9 was reduced by 68% in healthy adults following bolus injections of vitamin D that resulted in an average dose of 547 IU per day for 2.5 years.[17] A recent trial of vitamin D supplementation in patients with prolonged critical illness showed a significant and dose-dependent "anti-inflammatory effect" evidenced by reductions in IL-6 and CRP.[16] However, the insufficient dose of only 400 IU per day (administered intravenously) for only ten days precluded more meaningful and beneficial results, and we present guidelines for future studies later in this paper.

Cancer Prevention and Treatment

The inverse relationship between sunlight exposure and cancer mortality was documented by Apperly in 1941.[13] Vitamin D has anti-cancer effects mediated by anti-proliferative and proapoptotic mechanisms[3] which are augmented by modulation of nuclear receptor function and enzyme action,[49] and limited research shows that synthetic vitamin D analogs may have a role in the treatment of human cancers.[50] Grant[12] has shown that inadequate exposure to sunlight, and hence hypovitaminosis D, is associated with an increased risk of cancer mortality for several malignancies, namely those of the breast, colon, ovary, prostate, bladder, esophagus, kidney, lung, pancreas, rectum, stomach, uterus, and non-Hodgkin lymphoma. He proposes that adequate exposure to ultraviolet light and/or supplementation with vitamin D could save more than 23,000 American lives per year from a reduction in cancer mortality alone.

The aforementioned clinical trials using vitamin D in a wide range of health conditions have helped to expand our concept of vitamin D and to appreciate its manifold benefits. However, in light of new research showing that the physiologic requirement is 3,000–5,000 IU/day for adults and that serum levels plateau only after 3-4 months of daily supplementation,[2] we must conclude that studies using lower doses and/or shorter durations have underestimated the clinical efficacy of vitamin D. Guidelines for the critique and design of clinical trials are proposed later in this article to aid clinicians and researchers in evaluating and designing clinical studies for the determination of the therapeutic efficacy of vitamin D.

ASSESSMENT OF VITAMIN D STATUS WITH MEASUREMENT OF SERUM 25-OH-VITAMIN D

Current laboratory reference ranges for 25(OH)D were erroneously based on average serum levels for the "apparently healthy" nonrachitic, nonosteomalacic American population, a large proportion of which is vitamin D deficient. Currently, laboratories do not report optimal levels so they will mislead the practitioner unless he or she is aware of current research. For the majority of labs, the bottom of the reference range is set too low due to the previous underappreciation of the clinical benefits of and physiologic requirement for higher vitamin D levels, and the top of the range is too low due to previous misinterpretations of the research resulting in an overestimation of vitamin D toxicity.[1,2,51,52] Therefore, new reference ranges need to be determined based on the current research, and we present our proposals in Figure 1 and in the following outline:

- **Vitamin D Deficiency: less than 20 ng/mL (50 nmol/L).**

Serum 25(OH)D levels below 20 ng/mL (50 nmol/L) are clearly indicative of vitamin D deficiency. However, several authorities note that this level appears to be too low; Heaney[5] and Holick[51] both state that 25(OH)D levels should always be greater than 30 ng/mL (75 nmol/L).

- **Vitamin D Insufficiency: less than 40 ng/mL (100 nmol/L).**

According to Zittermann,[11] hypovitaminosis D, wherein tissue levels are depleted and PTH is slightly elevated, correlates with serum levels of 30–40 ng/mL (75–100 nmol/L). Independently, Dawson-Hughes et al[53] showed that serum levels of PTH begin to elevate when 25(OH)D levels fall below 45 ng/mL (110 nmol/L) in elderly men and women, and these findings were supported by Kinyamu et al[54] who found that optimal PTH status deteriorates when 25(OH)D levels fall below 49

ng/mL (122 nmol/L) in elderly women. Therefore, in order to maintain physiologic suppression of PTH, serum levels of 25(OH)D need to be greater than 40 ng/mL (100 nmol/L).

• Optimal Vitamin D Status: 40–65 ng/mL (100–160 nmol/L)

Based on our review of the literature, we propose that the optimal—"sufficient and safe"—range for 25(OH)D correlates with serum levels of 40–65 ng/mL (100–160 nmol/L).[55] This proposed optimal range is compatible with other published recommendations: Zittermann[11] states that serum levels of 40–80 ng/mL (100–200 nmol/L) are "adequate," and Mahon et al[37] recently advocated an optimal range of 40–100 ng/mL (100–250 nmol/L) for patients with multiple sclerosis. The lower end of our proposed range is consistent with suggestions by Mercola[56,57] who advocates an optimal range of 45–50 ng/mL (115–128 nmol/L) and by Holick[51] who states that levels should be 30–50 ng/mL (75–125 nmol/L). The upper end of our proposed optimal range is modified from the previously mentioned ranges offered by Zittermann[11] (up to 80 ng/mL [200 nmol/L]) and Mahon et al[37] (up to 100 ng/mL [250 nmol/L]). According to the authoritative monograph by Vieth,[1] there is no consistent, credible evidence of vitamin D toxicity associated with levels below 80–88 ng/mL (200 –220 nmol/L). Vieth[1] states, "Although not strictly within the 'normal' range for a clothed, sun-avoiding population, serum 25(OH)D concentrations of 220 nmol/L (88 ng/mL) are consistent with certain environments, are not unusual in the absence of vitamin D supplements, and should be regarded as being within the physiologic range for humans." Similarly, in his very thorough review of the literature, Zittermann[11] concludes that serum 25(OH)D concentrations up to 100 ng/mL (250 nmol/L) are subtoxic. Additional support for the safety of this upper limit comes from documentation that sun exposure alone can raise levels of 25(OH)D to more than 80 ng/mL (200 nmol/L)1 and that oral supplementation with 10,000 IU/day (mimicking endogenous production from sun exposure) in healthy men resulted in serum levels greater than 80 ng/mL (200 nmol/L) with no evidence of toxicity.[2] Until more data becomes available, we have chosen 65 ng/mL (160 nmol/L) rather than 80 ng/mL (200 nmol/L) as the upper end of the optimal range to provide a safety zone between the optimal level and the level which may possibly be associated with toxicity, and to allow for other factors which may promote hypercalcemia, as discussed below. Long-term prospective interventional studies with large groups and clinical trials involving patients with vitamin D-associated illnesses (listed above) will be needed in order to accurately define the optimal range—the serum level of vitamin D that affords protection from illness but which does not cause iatrogenic complications. In reviewing much of the current literature, we found no evidence of adverse effects associated with a 25(OH)D level of 65 ng/mL (160 nmol/L), and we found that this level is considered normal by some medical laboratories[6] and that it can be approximated and safely exceeded with frequent full-body exposure to ultraviolet light[1] or oral administration of physiologic doses of 5,000–10,000 IU cholecalciferol per day for 20 weeks.[2] Prospective studies and interventional clinical trials comparing different serum levels of 25(OH)D with clinical outcomes are necessary to elucidate the exact optimal range in various clinical conditions. While no acute or subacute risks are associated with the 25(OH)D levels suggested here, research shows clear evidence of long-term danger associated with vitamin D levels that are insufficient.

• Vitamin D Excess: Serum Levels Greater than 80 ng/mL (200 nmol/L) with Accompanying Hypercalcemia

Serum levels of 25(OH)D can exceed 80 ng/mL (200 nmol/L) with ultraviolet light exposure in the absence of oral vitamin D supplementation[1,6] and with oral supplementation with 10,000 IU per day as previously mentioned[2]—in neither scenario is toxicity observed. 25(OH)D greater than 80 ng/mL (200 nmol/L) are not indicative of toxicity unless accompanied by clinical manifestations and hypercalcemia. Vieth[1] notes that hypercalcemia due to hypervitaminosis D is always associated with serum 25(OH)D concentrations greater than 88 ng/mL (220 nmol/L), and Holick[6] previously stated, "Vitamin D intoxication does not occur until the circulating levels of 25(OH)D are over 125 ng/mL [312 nmol/L]." Assessment for hypervitaminosis D is performed by measurement of serum 25(OH)D and serum calcium.

MONITORING FOR VITAMIN D TOXICITY WITH 25(OH)D AND SERUM CALCIUM

Hypercalcemia can occur with vitamin D supplementation by either directly causing direct toxicity (rare) or by being associated with a vitamin D hypersensitivity syndrome (more common). If serum calcium becomes abnormally high, then vitamin D supplementation must be discontinued until the cause of the hypercalcemia is identified; however, direct vitamin D toxicity will rarely be the sole cause of the hypercalcemia.

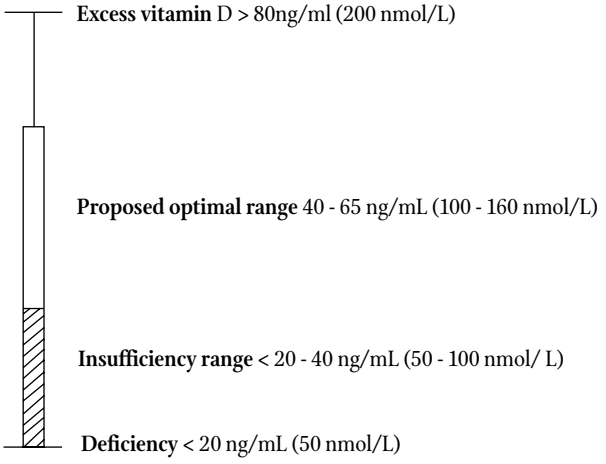

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FIGURE 1. Proposed normal and optimal ranges for serum 25(OH)D levels based on current research*****

The most important indicator of direct vitamin D toxicity is elevated serum calcium associated with a 25(OH)D level greater than 90 ng/ml (225 nmol/L). Elevated 1,25(OH)D levels are commonly—though not always—seen with vitamin D toxicity. Severe vitamin D intoxication is rare and usually seen only with industrial accidents, such as overdosing the fortification of milk, or with long-term administration of more than 40,000 IU of vitamin D per day. Severe hypercalcemia may require urinary acidification and corticosteroids to expedite the reduction in serum calcium.[58]

Induction of vitamin D toxicity generally requires 1–4 months of 40,000 IU per day in infants.[58] In adults, toxicity generally requires several months of supplementation of at least 100,000 IU per day. Hypercalcemia appears to be the mechanism of vitamin D toxicity (rather than a direct toxic effect of the vitamin), and 25-OH-vitamin D levels may be normal in patients who are vitamin D toxic and hypercalcemic, particularly with vitamin D hypersensitivity syndrome. It has therefore been suggested that serum calcium be measured on a weekly and then monthly basis in patients receiving high-dose vitamin D. Manifestations attributable to hypervitaminosis D and hypercalcemia include anorexia, nausea, and vomiting followed by weakness, nervousness, pruritus, polyuria, polydipsia, renal impairment, and soft-tissue calcifications.

As a cause of hypercalcemia, vitamin D hypersensitivity syndromes are more common than vitamin D toxicity, and they generally arise when aberrant tissue uncontrollably produces the most active form of the vitamin—calcitriol. Primary hyperparathyroidism, granulomatous disease (such as sarcoidosis, Crohn's disease, and tuberculosis) and various forms of cancer may cause the syndrome. 25(OH)D levels are normal or even low in vitamin D hypersensitivity while serum calcium and 1,25(OH)D levels are elevated. Additional causes include adrenal insufficiency, hyperthyroidism, hypothyroidism, and adverse drug effects, particularly with thiazide diuretics. Whatever the cause, patients with persistent hypercalcemia should discontinue vitamin D supplementation and receive a thorough diagnostic evaluation to determine the cause of the problem.

Interventional Strategies to Treat Vitamin D Deficiency by Increasing Serum Vitamin D Levels

Human physiology adapted to and was shaped by a natural environment with ample exposure to sunlight.[5, 61] Full-body exposure to ultraviolet light on clear days in equatorial latitudes can easily provide the equivalent of 4,000–20,000 IU of vitamin D.[1,61] Slightly longer durations of full-body sun exposure of approximately 30 minutes (3x the minimal erythemal dose) will produce 50,000 IU of vitamin D in lightly pigmented persons, while 5x longer durations are required for more darkly pigmented people to attain the same vitamin D production.[61] The oral dose of vitamin D required to obtain adequate blood levels depends on latitude, sun exposure, body weight, skin pigmentation, dietary sources, efficiency of absorption, presence of intestinal disease (eg, intestinal resection or malabsorption), and medication use, for example with the vitamin D-depleting actions of common anticonvulsant drugs.[40]

Past and Future Vitamin D Studies: Critique and Design

Nearly all published clinical trials have suffered from flawed design, including inadequate dosing, inadequate duration, wrong type of vitamin D (ie, ergocalciferol, D2), failure to test serum vitamin D levels, and/or failure to ensure that serum vitamin D levels entered into the optimal range. The following guidelines are provided for clinicians and researchers using vitamin D in clinical practice and research to improve the quality of research and patient care.

1. Dosages of vitamin D must reflect physiologic requirements and natural endogenous production and should therefore be in the range of 3,000–10,000 IU per day

The physiologic requirement for vitamin D appears to be 3,000–5,000 IU per day in adult males.[2] Full-body exposure to ultraviolet light (eg, sunshine) can produce the equivalent of 10,000–25,000 IU of vitamin D3 per day.[1] Therefore, intervention trials with supplemental vitamin D should use between 4,000 IU/day, which is presumably sufficient to meet physiologic demands, and 10,000 IU/day, which is the physiologic dose attained naturally via full-body sun exposure. Based on these physiologic criteria, we see that the majority of intervention studies in adults have used inadequate, subphysiologic doses of vitamin D. Therefore, studies that failed to identify therapeutic benefits from vitamin D supplementation were flawed due to insufficient therapeutic intervention—the dose of vitamin D was too low.

2. Vitamin D supplementation must be continued for at least 5-9 months for maximum benefit

Since serum 25(OH)D levels do not plateau until after 3-4 months of supplementation,[2] and we would expect clinical and biochemical changes to become optimally apparent some time after the attainment of peak serum levels, any intervention study of less than 5-9 months is of insufficient duration to determine either maximum benefit or that vitamin D supplementation is ineffective for the condition being investigated. Conversely, since vitamin D supplementation can alter intracellular metabolism within minutes of administration,[11] benefits seen in short-term studies should not be inaccurately attributed to statistical error or placebo effect.

3. Supplementation should be performed with D3 rather than D2

Although cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are both used as sources of vitamin D, D3 is the human nutrient and is much more efficient in raising and sustaining serum 25[OH]D levels. Vitamin D2 is a fungal metabolite and has been associated with adverse effects due to contamination and altered pharmacokinetics.[4] The type of vitamin D must always be clearly stated in published research reports.

4. Supplements should be tested for potency

Some products do not contain their claimed amount. This problem was illustrated in the study by Heaney et al[2] who found that the vitamin D supplement they used in their study, although produced by a well-known company, contained only 83% of its stated value. To ensure accuracy and consistency of clinical trials, actual dosages must be known.

5. Effectiveness of supplementation must include evaluation of serum vitamin D levels

Supplementation does not maximize therapeutic efficacy unless it raises serum 25(OH)D levels into the optimal range. To assess absorption, compliance, and safety, serum 25(OH)D levels must be monitored in clinical trials involving vitamin D supplementation. Assessment of serum levels is important also to determine the relative dose-effectiveness of different preparations of vitamin D, as some evidence suggests that micro-emulsification facilitates absorption of fat-soluble nutrients.[56,59,60] Measurement of 1,25-dihydroxyvitamin (calcitriol) is potentially misleading and is not recommended for the evaluation of vitamin D status.

6. Serum vitamin D levels must enter the optimal range

The majority of clinical intervention studies using vitamin D have failed to use supplementation of sufficient dosage and duration to attain optimal serum levels of vitamin D. Our proposed optimal range for 25(OH)D is 40–65 ng/mL (100–160 nmol/L) and is presented in Figure 1.

The above-mentioned criteria will aid future researchers in designing interventional studies that can accurately evaluate the relationship between vitamin D status and human illness. Clinicians, who are not conducting research but rather are interested in attaining clinical improvement in their patients, should follow these guidelines as well when using vitamin D supplementation in patients, while remembering to monitor for toxicity with the triad of clinical assessments, serum 25(OH)D, and serum calcium. Clinicians and researchers need to remember, however, that optimal clinical effectiveness often depends on synergism of diet, lifestyle, exercise, emotional health, and other factors. Single intervention studies are a reasonable research tool only for evaluating cause-and-effect relationships based on the presumption of a simplistic, linear model that is generally inconsistent with the complexity and multiplicity of synergistic and interconnected factors that determine health and disease. Thus, single intervention studies with vitamin D supplementation will be useful from an intellectual standpoint insofar as they will help us to further define the role of vitamin D in human physiology and pathophysiology. However, optimal clinical results with individual patients are more easily attained with the use of multicomponent treatment plans that address many facets of the patient's health.[55]

Vitamin D Supplementation in Adults

When 28 men and women were administered 4,000 IU per day for up to five months, in the absence of UVB from the sun, serum 25(OH)D levels reached approximately 40 ng/mL (100 nmol/L), and no toxicity was observed.[4] When 67 men were administered 5,000 and 10,000 IU of cholecalciferol per day for twenty weeks, again in the absence of UVB from the sun, serum levels of 25(OH)D increased to approximately 60 ng/mL (150 nmol/L) and 90 ng/mL (225 nmol/L), respectively, and no toxicity was observed.[2] Therefore, given that endogenous vitamin D production following full-body sun exposure at lower latitudes can produce >10,000 IU[1] and that 4,000 IU per day is a safe level of supplementation[4] that meets physiologic needs in adults,[2] we recommend at least 4,000 IU per day for adults, with efficacy and safety ensured by periodic measurement of 25(OH)D and serum calcium.

Vitamin D Supplementation in Pregnant Women

In 1966, two case reports and a brief review of the literature showed no adverse effects of 100,000 IU per day of vitamin D in hypoparathyroid pregnant women.[62] In 1971, a study of 15 hypoparathyroid pregnant women was reported wherein the women received more than 100,000 IU per day of vitamin D with no adverse effects to the mother or child, leading the authors to conclude that there was "no risk from vitamin D in pregnancy."[63] Doses of vitamin D for pregnant women were extensively reviewed by Hollis and Wagner[61] immediately prior to the completion of this article, and the authors concluded that doses of 100,000 IU per day were safe for pregnant women. The authors write, "Thus, there is no evidence in humans that even a 100,000 IU/day dose of vitamin D for extended periods during pregnancy results in any harmful effects." Data from several placebo-controlled clinical trials with pregnant women show that vitamin D supplementation results in superior health status for the mother and infant. The current daily reference intake (DRI) for vitamin D of 200–400 IU per day is therefore "grossly inadequate," and administration of less than 1,000 IU vitamin D per day to pregnant women is scientifically unjustifiable and ethically questionable. Hollis and Wagner[61] conclude that up to 4,000 IU per day is necessary for pregnant women, and this conclusion is consistent with previously cited research on physiologic requirements[2] and endogenous vitamin D production.[1] In order to ensure safety and efficacy in individual patients, we encourage periodic measurement of serum calcium and 25(OH)D levels.

Vitamin D Supplementation in Infants and Children

In Finland from the mid-1950s until 1964, the recommended daily intake of vitamin D for infants was 4,000–5,000 IU, a dose that was proven safe and was associated with significant protection from type 1 diabetes.[61] More recently, in a study involving more than 10,000 infants and children, daily administration of 2,000 IU per day was safe and effective for reducing the incidence of type 1 diabetes by 80%.[18] Thus, for infants and children, doses of 1,000 IU per day are certainly safe, and higher doses should be monitored by serum calcium and 25(OH)D levels.

Options for Raising Vitamin D Blood Levels

We have two practical options for increasing vitamin D levels in the body: oral supplementation and/or exposure to ultraviolet radiation. Sunlight is commonly unavailable on rainy or cloudy days, during the winter months, and in particular geographic locations. Topical sunscreens block vitamin D production by 97%-100%. Furthermore, since many people work indoors where sunshine is inaccessible, or they are partially or fully clothed when outside, reliance on sunshine to provide optimal levels of vitamin D is generally destined to provide unsatisfactory and inconsistent biochemical and clinical results. The use of UVB tanning beds can increase vitamin D levels; but this option is more expensive and time-consuming than oral supplementation, and excess ultraviolet radiation exposure expedites skin aging and encourages the development of skin cancer. Given the impracticalities and disadvantages associated with relying on sun exposure to provide optimal levels of vitamin D year-round, for the majority of patients, oral vitamin D supplementation is the better option for ensuring that biochemical needs are consistently met.

Vitamin D is either absent or present in non-therapeutic amounts in dietary sources. One of the only major dietary sources of vitamin D is cod-liver oil, but the amount required to obtain a target dose of 4,000 IU per day would require patients to consume at least three tablespoons of cod-liver oil, or the amount contained in >18 capsules of most commercial preparations.[55] Clearly this would be unpalatable and prohibitively expensive for most patients, and it would result in very low compliance. Additionally, such a high dose of cod-liver oil may produce adverse effects with long-term use, particularly with regard to excess vitamin A, and perhaps an increased tendency for bleeding and reduced biological activity of gamma-linolenic acid due to the high content of eicosapentaenoic acid.[55,64] Oral supplementation with "pure" vitamin D supplements allows the dose to be tailored to the individual needs of the patient.

DISCUSSION AND CONCLUSIONS

Vitamin D is not a drug, nor should it be restricted to prescription availability. Vitamin D is not a new or unproven "treatment." Vitamin D is an endogenous, naturally occurring, photochemically-produced steroidal molecule with essential functions in systemic homeostasis and physiology, including modulation of calcium metabolism, cell proliferation, cardiovascular dynamics, immune/inflammatory balance, neurologic function, and genetic expression. Insufficient endogenous production due to lack of sufficient sun exposure necessitates oral supplementation to meet physiologic needs. Failure to meet physiologic needs creates insufficiency/deficiency and results in subtle yet widespread disturbances in cellular function which appear to promote the manifestation of subacute long-latency deficiency diseases such as osteoporosis, cardiovascular disease, hypertension, cancer, depression, epilepsy, type 1 diabetes, insulin resistance, autoimmune disease, migraine, polycystic ovary syndrome, and musculoskeletal pain. In case reports, clinical trials, animal studies, and/or epidemiologic surveys, the provision of vitamin D via sunlight or supplementation has been shown to safely help prevent or alleviate all of the aforementioned conditions.

Vitamin D deficiency/insufficiency is an epidemic in the developed world that has heretofore received insufficient attention from clinicians despite documentation of its prevalence, consequences, and the imperative for daily supplementation at levels above the current inadequate recommendations of 200–600 IU.[65] For example, at least 57% of 290 medical inpatients in Massachusetts, USA were found to be vitamin D deficient,[66] and overt vitamin D deficiency was recently found in 93% of 150 patients with chronic musculoskeletal pain in Minnesota, USA.[43] Other studies in Americans have shown vitamin D deficiency in 48% of patients with multiple sclerosis,[37] 50% of patients with fibromyalgia and systemic lupus erythematosus,[48] 42% of healthy adolescents[67] and African American women,[68] and at least 62% of the morbidly obese.[69] International studies are consistent with the worldwide prevalence of vitamin D deficiency in various patient groups, showing vitamin D deficiency in 83% of 360 patients with chronic low-back pain in Saudi Arabia,[45] 73% of Austrian patients with ankylosing spondylitis,[47] up to 58% of Japanese women with Grave's disease,[46] more than 40% of Chinese adolescent girls,[70] and 40%-70% of Finnish medical patients.[71] As a medically valid diagnosis (ICD-9 code: 268.9 Unspecified vitamin D deficiency) with a high prevalence and clinically significant morbidity, vitamin D deficiency deserves equal attention and status with other diagnoses encountered in clinical practice. Given the depth and breadth of the peer-reviewed research documenting the frequency and consequences of hypovitaminosis D, failure to diagnose and treat this disorder is ethically questionable (particularly in pregnant women[61]) and is inconsistent with the delivery of quality, science-based healthcare. Failure to act prudently based on the research now available in favor of vitamin D supplementation appears likely to invite repetition analogous to the previous failure to act on the research supporting the use of folic acid to prevent cardiovascular disease and neural tube defects—a blunder that appears to have resulted in hundreds of thousands of unnecessary cardiovascular deaths[72] and which has contributed to incalculable human suffering related to otherwise unnecessary neural tube defects, cervical dysplasia, cancer, osteoporosis, and mental depression. Currently, Grant[12] estimates that at least 23,000 and perhaps as many as 47,000 cancer deaths[73] might be prevented each year in America if we employed simple interventions (ie, sunshine or supplementation) to raise vitamin D levels. Of course, additional lives may be saved and suffering reduced by alleviating the morbidity and mortality associated with hypertension, autoimmune disease, depression, epilepsy, migraine, diabetes, polycystic ovary syndrome, musculoskeletal pain, osteoporosis, and cardiovascular disease. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases. Safety and effectiveness of supplementation are assured by periodic monitoring of serum 25(OH)D and serum calcium.

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CME TEST QUESTIONS*

THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

In the following questions, only one answer is correct.

1. In clinical trials, augmentation of vitamin D levels with ultraviolet light exposure or oral supplementation has been shown to benefit which of the following conditions:
   A. Osteoporosis; Hypertension
   B. Depression; Multiple sclerosis
   C. Back pain; Insulin resistance
   D. All of the above

2. In the absence of vitamin D supplementation, ultraviolet light exposure (ie, sunshine) can produce 25(OH)D levels that exceed current laboratory reference ranges:
   A. True
   B. False

3. Which of the following can cause hypercalcemia?
   A. Sarcoidosis and Crohn's disease
   B. Adrenal insufficiency and hypothyroidism
   C. Coadministration of vitamin D and thiazide diuretics
   D. All of the above

4. According to the current research literature reviewed in this article, which of the following may be considered long-latency deficiency diseases associated with insufficiency of vitamin D?
   A. Metabolic syndrome
   B. Autoimmune disease such as multiple sclerosis and type 1 diabetes
   C. Depression and cancer
   D. All of the above

5. If a patient has hypovitaminosis D and a vitamin D-responsive condition such as depression, hypertension, insulin resistance, or multiple sclerosis, which of the following is appropriate first-line treatment?
   A. Drugs only
   B. Vitamin D only
   C. Correction of the vitamin D deficiency, and co-administration of medications if necessary
   D. Use of synthetic vitamin D analogs

6. Since vitamin D is highly effective for the prevention and alleviation of several health problems, and because it has a wide range of safety, physiologic doses should be regulated as a prescription drug and prohibited from public access:
   A. True
   B. False

7. Given the prevalence and consequences of vitamin D deficiency, failure to test for and treat vitamin D insufficiency is ethical:
   A. True
   B. False

8. Since vitamin D has a wide margin of safety, patients should be administered vitamin D routinely and receive which of the following types of monitoring:
   A. Periodic measurement of serum 1,25-dihydroxyvitamin D (calcitriol) and urinary creatinine
   B. Periodic measurement of serum 25-hydroxyvitamin D (calcidiol) and serum calcium
   C. Clinical assessments only
   D. Liver function tests and electrocardiography

See page 94 for Self-Assessment answers

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Subphysiologic Doses of Vitamin D are Subtherapeutic: Comment on the Study by The Record Trial Group

May 06 2005

Alex Vasquez, *Researcher, Private Practice, and Researcher at Biotics Research Corporation.*

Dear Editor, Based on recently published research, it is clear that the study by The Record Trial Group [1] on vitamin D and calcium in the prevention of fractures suffered from at least four important shortcomings which negatively skewed their results. First, and most important, the dose of vitamin D used in their study (800 IU/d) is subphysiologic and would therefore not be expected to produce a clinically meaningful effect. The physiologic requirement for vitamin D was determined scientifically in a recent study by Heaney and colleagues [2], who showed that healthy men utilize 3,000 to 5,000 IU of cholecalciferol per day, and several recent clinical trials have been published documenting the safety and effectiveness of administering vitamin D in physiologic doses of at least 4,000 IU per day.[3-5] In fact, studies have shown a dose-response relationship with vitamin D supplementation [6], and low doses (e.g., 600 IU) are clearly less effective than higher doses in the physiologic range (e.g., 4,000 IU).[5] It is important to note that the commonly used dose of vitamin D at 800 IU per day was not determined scientifically; rather this amount was determined arbitrarily before sufficient scientific methodology was available.[2,7] Given that the commonly recommended daily intake of

vitamin D in the range of 200-800 IU is not sufficient for maintaining adequate serum levels of vitamin D [8], it is therefore incumbent upon modern researchers and clinicians to use doses of vitamin D that are consistent with the physiologic requirement as established in current research. Second, the authors recognize that patient compliance in their study population was quite poor. This poor compliance obviously contributed to the purported lack of treatment efficacy. Third, and consistent with recent data published elsewhere [8], virtually all of their patients were still vitamin D deficient at the end of one year of treatment, thereby affirming the inadequacy of the treatment dose. Vitamin D deficiency is common in industrialized nations, particularly those of northern latitudes [9-11], including the UK, where this study was performed. By modern criteria for serum vitamin D levels [12], virtually all of the patients in this study were vitamin D deficient at the beginning of the study, and the insufficient treatment dose of 800 IU/d failed to correct this deficiency even after 1 year of treatment. Given that vitamin D levels must be raised to approximately 40 ng/mL (100 nmol/L) in order to maximally reduce parathyroid hormone levels and bone resorption [13,14], supplementation that does not accomplish the goal of raising serum vitamin D levels into the optimal physiologic range cannot be considered adequate therapy.[12] Fourth, and finally, there is reason to question the bioavailability of their vitamin D3 supplement, as the authors note that their dose-response was generally lower than that seen in other studies. Bioavailability is a prerequisite for treatment efficacy, and the elderly have higher likeliness of comorbid conditions that impair digestion and absorption of nutrients. Specifically, it is well documented that vitamin D absorption is decreased in elderly patients compared to younger controls [15,16], and this is complicated by an age-related reduction in renal calcitriol production [17,18] and intestinal vitamin D receptors [19], thereby further impairing vitamin D metabolism and calcium absorption. Since emulsification of fat soluble vitamins is required for their absorption [20], and since pre-emulsification of nutrients has been shown to increase absorption and dose-responsiveness of the fat-soluble nutrient coenzyme Q [21, 22], it seems apparent that attention to the form (not merely the dose) of nutrient supplementation is clinically important, particularly when working with elderly patients. These shortcomings, when combined, could have lead to an additive or synergistic reduction in treatment potency that skewed their results toward a conclusion of inefficacy. In order to produce more meaningful results in clinical trials, our group published guidelines [12] recommending that future studies 1) ensure patient compliance, 2) use physiologic doses of vitamin D (e.g., 4,000 IU per day), and 3) ensure that serum levels are raised to a minimum of 40 ng/mL (100 nmol/L), since levels below this threshold are associated with increased parathyroid hormone levels, increased bone resorption, and recalcitrance to bone-building interventions.[23,24] Alex Vasquez avasquez@bioticsresearch.com Biotics Research Corporation Rosenberg, Texas, USA 77471 References: 1. Record Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. The Lancet (Early Online Publication), 28 April 2005 2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204-10 3. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr. 2001;73:288-94 4. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine. 2003;28:177-9 5. Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J. 2004 Jul 19;3(1):8 http://www.nutritionj.com/content/pdf/1475-2891-3-8.pdf 6. Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab. 2003;88:4623-32 7. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999;69:842-56

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Competing Interests: Dr. Vasquez is a researcher at Biotics Research Corporation, an FDAapproved drug manufacturing facility in the USA.

References: None

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How to Understand, Refute, and Plan Studies Using Vitamin D

Alex Vasquez DO ND DC FACN

Defining the problems

1. The (primary) problem: Most doctors and researchers have zero expert-level training in Nutrition (let alone Clinical Nutrition, Therapeutic/Interventional Nutrition, Functional Nutrition) and therefore the studies they design using vitamin D are methodologically flawed, as described below.
2. The (secondary) problem: Too many studies using vitamin D (cholecalciferol) have used vitamin D in 1) doses that are inadequate, 2) for durations that are inadequate, and thus these studies are therapeutically underpowered, tending to lead to lackluster or negative (inefficacious) results, thereby leading to the false conclusion that vitamin D is ineffective when in fact it either *is* or *might be* effective.
3. The (tertiary) problem: As a result of therapeutically underpowered studies, too many research articles paint a false picture of inefficacy when in fact vitamin D is or may be highly efficacious; as a result, patients are denied a safe and effective therapeutic route that offers low-cost efficacy, high safety, and numerous collateral benefits.
4. The (quaternary) problem: Another major problem is that too many doctors and researchers are unaware of the major paradigm-shifting studies that should have resulted in major acceptance of vitamin D utilization in preventive public health and clinical medicine; as a result of this ignorance, too many research projects are essentially starting from zero or a very shallow foundation rather than progressively building on a foundation of good science and appropriate pattern recognition. Researchers who have not studied the history of nutrition and the decades of literature are essentially ignorant of the history and direction of the field into which they enter; one can be amused by the prospect of a researcher placed in a position of authority to shape and define the direction of a field which he/she has never studied, ie, many researchers quite obviously wear no clothes.

Guidelines for vitamin D clinical trials were broadly published in 2004 and 2005

In 2004 and 2005, I was the principal author on several publications published in peer-reviewed journals, and in each of these I listed criteria for the design and therefore evaluation of studies using vitamin D; I will list these publications here with hyperlinks to their full text and then describe these criteria with any updates.

1. Vasquez, Manso, Cannell. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med* 2004 Sep[1]: PDF, PMID 15478784
2. Vasquez, Cannell. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. *British Medical Journal* 2005 Jul[2]: PDF, PMID 16002891
3. Vasquez. Subphysiologic doses of vitamin D are subtherapeutic: comment on the study by the Record Trial Group. *TheLancet.com* 2005 May PDF

According to the pioneering clinical trial by Heaney et al (*Am J Clin Nutr* 2003 Jan[3]), "Healthy men seem to use 3000–5000 IU cholecalciferol/d"; a daily dose of 3,000–5,000 IU cholecalciferol/d corresponds to a serum 25-OH-vitamin D of 60 ng/ml (150 nmol/L). However, according to this study, serum 25-OH-vitamin D should be equal to or greater than 80 ng/ml (200 nmol/L) in order to alleviate secondary relative hyperparathyroidism; the daily dose of vitamin D3 required to lower/normalize

serum parathyroid hormone (PTH) is 10,000 IU (250 mcg) per day. Therefore, we can roughly conclude that a reasonable daily dose of vitamin D ranges from 4,000–10,000 IU per day, and that the lowest acceptable serum 25-OH-vitamin D levels corresponding with adequate supplementation is 60 ng/ml (150 nmol/L) whereas a level of 80 ng/ml (200 nmol/L) is required to alleviate secondary (relative) hyperparathyroidism. Several of my publications (listed as #4 and #5 below) have also included a description of the minimal values and optimal therapeutic ranges for serum 25-OH-vitamin D; the perhaps obvious importance of these ranges is to define effective treatment (ie, sufficient vitamin D supplementation/nutriture) and to therefore differentiate adequate from inadequate supplementation dosages.

4. Vasquez. Musculoskeletal Pain: Expanded Clinical Strategies, continuing medical education (CME) monograph commissioned and published by the Institute for Functional Medicine 2008 PDF*
5. Vasquez. Revisiting the five-part nutritional wellness protocol: the supplemented Paleo Mediterranean diet. *Nutritional Perspectives* 2011 Jan PDF* This article from 2011 is excerpted from my 2016 textbook *Inflammation Mastery, 4th Edition* to provide necessary updates; this article also describes the clinical use of vitamin D within the context of a foundational clinical nutrition protocol.

"This insight also illuminates a double-standard in research: whereas no legitimate drug study would use a subtherapeutic dose of a pharmaceutical agent and then (falsely) assert inefficacy, poorly designed and therapeutically underpowered (eg, using 10% of the known effective dose) nutrition studies are published and make headlines and shape policy (mostly by maintaining the status quo of nutritional inaction and ignorance) on weekly basis. For example, a study using an antibiotic or antiseizure drug that failed to administer a therapeutic dosage or achieve a therapeutic serum level would never be accepted for publication in a headlining medical journal; yet, underdosed nutrition studies are commonly published in headlining journals and then reported to mainstream media as proof of the inefficacy of nutritional intervention."
Dr Alex Vasquez

Past and Future Vitamin D Studies: Critique and Design

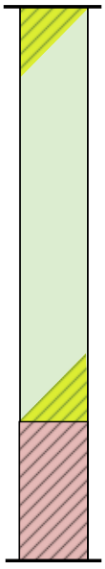
A large percentage of published clinical trials have suffered from flawed design, including inadequate dosing, inadequate duration, wrong type of vitamin D (ie, ergocalciferol, D2), failure to test serum vitamin D levels, and/or failure to ensure that serum vitamin D levels entered into the optimal range. The following guidelines have been provided for clinicians and researchers using vitamin D in clinical practice and research to improve the quality of research and patient care.

1. Dosages of vitamin D must reflect physiologic requirements and natural endogenous production and should therefore be in the range of 3,000–10,000 IU per day: The physiologic requirement for vitamin D is 3,000–5,000 IU per day in adult males. Full-body exposure to ultraviolet light (eg, sunshine) can produce the equivalent of 10,000–25,000 IU of vitamin D3 per day. Therefore, intervention trials with supplemental vitamin D should use between 4,000 IU/day, which is presumably sufficient to meet physiologic demands, and 10,000 IU/day, which is the physiologic dose attained naturally via full-body sun exposure within a short period of time outdoors. Also, the higher dose of 10,000 IU/day is necessary in some patients who have absorption defects and therefore need a higher oral dose to "force absorption" and/or who are obese and therefore need a higher dose to achieve tissue saturation for a larger body mass. Based on these physiologic criteria, we see that the majority of intervention studies in adults have used inadequate, subphysiologic doses of vitamin D. Therefore, many studies that failed to identify therapeutic benefits from vitamin D supplementation were flawed due to insufficient therapeutic intervention—the dose of vitamin D was too low. This insight also illuminates a double-standard in research: whereas no legitimate drug study would use a subtherapeutic dose of a pharmaceutical agent and then (falsely) assert inefficacy, poorly designed and therapeutically underpowered (eg, using 10% of the known effective dose) nutrition studies are published and make headlines and shape policy (mostly by maintaining the status quo of nutritional inaction and ignorance) on weekly basis. For example, a study using an antibiotic or antiseizure drug that failed to administer a therapeutic dosage or achieve a therapeutic serum level would never be accepted for publication in a headlining medical journal; yet, underdosed nutrition studies are commonly published in headlining journals and then reported to mainstream media as proof of the inefficacy of nutritional intervention.
2. Vitamin D supplementation must be continued for at least 5-9 months for maximum benefit: Since serum 25(OH)D levels do not plateau until after 120 days or 4 months of supplementation, and we would expect clinical and biochemical changes to become optimally apparent some time after the attainment of peak serum levels, any intervention study of less than 6-9 months is of insufficient duration to determine either maximum benefit or inefficacy of vitamin D supplementation. Conversely, since vitamin D supplementation can alter intracellular metabolism within minutes of administration, benefits seen in short-term studies should not be inaccurately

attributed to statistical error or placebo effect. The vitamin D trial does not begin with the initiation of supplementation but rather the study *begins* after the achievement of vitamin D sufficiency (defined below).

3. Supplementation should be performed with D3 rather than D2: Although cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are both used as sources of vitamin D, D3 is the human nutrient and is much more efficient in raising and sustaining serum 25[OH]D levels. Vitamin D2 is a fungal metabolite and has been associated with adverse effects due to contamination and altered pharmacokinetics. The type of vitamin D must always be clearly stated in published research reports.
4. Supplements should be tested for potency: Some products do not contain their claimed amount. This problem was illustrated in the study by Heaney et al[3] who found that the vitamin D supplement they used in their study, although produced by a well-known company, contained only 83% of its stated value. To ensure accuracy and consistency of clinical trials, actual dosages must be known.
5. Effectiveness of supplementation must include evaluation of serum vitamin D levels: Supplementation does not maximize therapeutic efficacy unless it raises serum 25(OH)D levels into the optimal range. To assess absorption, compliance, and safety, serum 25(OH)D levels must be monitored in clinical trials involving vitamin D supplementation. Assessment of serum levels is important also to determine the relative dose-effectiveness of different preparations of vitamin D, as some evidence suggests that emulsification facilitates absorption of fat-soluble nutrients. Measurement of 1,25-dihydroxyvitamin (calcitriol) is potentially misleading and is not recommended for the evaluation of vitamin D status; however, measurement of calcitriol levels is increasingly used clinically to evaluate for the severity or presence of inflammatory and malignant diseases, as discussed in *Inflammation Mastery* (2016).
6. Serum vitamin D levels must enter the optimal range: The majority of clinical intervention studies using vitamin D have failed to use supplementation of sufficient dosage and duration to attain optimal serum levels of vitamin D. Our proposed optimal range for 25(OH)D is 50-100 ng/mL (see updated figure and PDF excerpt).
7. Patients must be taken from a state of absolute or relative deficiency to absolute sufficiency: If patients are deficient at the start and the end of the study, then no adequate treatment has taken place. If patients were not deficient at the start of the study, then little improvement would be expected in moving them from "vitamin D adequate" to "vitamin D supra-adequate" in most cases.

The above-mentioned criteria will aid future researchers in designing interventional studies that can accurately evaluate the relationship between vitamin D status and human illness. Furthermore and by extension, these criteria help us form a checklist with which to evaluate planned and published research.



Excess vitamin D: >100 ng/mL (250 nmol/L)
Higher levels of 25hydroxycholecalciferol are clinically problematic if accompanied by hypercalcemia or urolithogenic hypercalciuria

Optimal-high vitamin D: 90-100 ng/mL (225-250 nmol/L)
These levels can be physiologic, but may be higher than necessary for some patients, excepting severe illness with vitamin D-responsive conditions.

Optimal range: 50-90 ng/mL (125-225 nmol/L)

Sufficiency range: 40-50 ng/mL (100-125 nmol/L)

Insufficiency range: 20-40 ng/mL (50-100 nmol/L)

Deficiency: < 20 ng/mL (50 nmol/L)

Interpretation of serum 25-hydroxy-cholecalciferol levels: Interpretation of any laboratory variable requires clinical contextualization; assessing renal function and measuring 1,25-dihydroxy-cholecalciferol prior to the initiation of vitamin D3 supplementation is reasonable, especially in patients with higher probability of renal insufficiency or granulomatous/malignant/inflammatory disease, respectively.

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Vitamin D-responsive conditions*

- Depression
- Autism
- Seizures/epilepsy
- Musculoskeletal pain, especially low-back pain and "fibromyalgia"
- Opioid dependence for pain
- Hypertension
- Autoimmunity such as systemic lupus erythematosus and multiple sclerosis
- Migraine
- Diabetes and insulin resistance
- Polycystic ovarian syndrome
- Cancer, especially prostate cancer
- Infectious diseases, especially including viral and bacterial infections

*following correction of deficiency

How to Critique Vitamin D Studies—A Checklist

1. Did the study subjects receive at least 4,000-10,000 IU per day? If not, then the study likely used inadequate dosage to produce optimal physiologic effects.
2. Is the duration of the study at least 6-9 months? If not, then body stores of vitamin D were likely not replaced in time for clinical effect to occur. Daily supplementation with vitamin D requires 120 days (4 months) to reach plateau of serum 25-OH-vitamin D levels; therefore, the replenishment or "induction" phase of any clinical trial must have a duration of at least 4 months or—alternatively—use supranormal doses of vitamin D3 in order to more rapidly achieve optimal serum levels and tissue saturation.
3. Did the study use vitamin D3 (cholecalciferol) rather than fungally-derived erogcalciferol? Ergocalciferol is not a human nutrient, and it is more toxic and less effective than is cholecalciferol.
4. Was the product validated for potency? If not, then the intervention may have failed due to an erroneously produced or falsely labeled product.
5. Were serum 25-OH-vitamin D levels measured? If not, the product potency and nutrient absorption were not ensured.
6. Did serum 25-OH-vitamin D levels enter the optimal range at least 2-6 months before the end of the study? If not, then the patients may have been vitamin D deficient for the entire duration of the study.
7. Were the patients deficient at the start of the study and then robustly replaced with vitamin D? If not, then "deficiency→deficiency" is not a competent study design and intervention, nor is "replete→replete." The appropriate intervention is to change deficiency to repletion.
8. Vitamin D supplementation should be stopped for roughly 20-30 days before serum testing because 25-hydroxyvitamin D3 (calcidiol) has a half-life of 15 days.[4] The goal with serum testing of 25-OH-vitamin D levels is to assess tissue saturation, not acute absorption. Testing vitamin D serum levels within a few days of vitamin D supplementation is more likely to reflect absorption and hepatic conversion rather than providing the more important and more accurate assessment of vitamin D tissue stores.

Obviously, clinical trials need to control for factors that increase vitamin D status (eg, sun exposure, fish oil especially cod liver oil) and those which promote vitamin D deficiency, especially antiseizure drugs, cholestyramine. Research and editorial integrity cannot be assumed in mainstream headlining journals.[5]

> "The vitamin D trial does not begin with the initiation of supplementation but rather the study begins after the achievement of minimal vitamin D sufficiency, as documented by a serum 25-OH-vitamin D level of at least 50 ng/ml or 125 nmol/L."
> Dr Alex Vasquez

Clinical take-home

Clinicians, who are not conducting research but rather are interested in attaining clinical improvement in their patients, should follow the above guidelines when using vitamin D supplementation in patients, while remembering to monitor for toxicity with the triad of clinical assessments, serum 25(OH)D, and serum calcium. Clinicians and researchers need to remember, however, that optimal clinical effectiveness often depends on synergism of diet, lifestyle, exercise, emotional health, and other factors. Single intervention studies are a reasonable research tool only for evaluating cause-and-effect relationships based on the presumption of a simplistic, linear model that is generally inconsistent with the complexity and multiplicity of synergistic and interconnected factors that determine health and disease. Thus, single intervention studies with vitamin D supplementation will be useful from an intellectual standpoint insofar as they will help us to further define the role of vitamin D in human physiology and pathophysiology. However, optimal clinical results with individual patients are more easily attained with the use of multicomponent treatment plans that address many facets of the patient's health.

A reasonable goal with vitamin D supplementation is the downward normalization of parathyroid hormone (PTH) levels; relative elevations of PTH (excluding pathologic and primary elevations of PTH) signify compensation for insufficient intake and/or absorption of calcium. According to the clinical trial by Heaney et al[3], the dose required to achieve this is 10,000 IU (250 mcg) per day corresponding to serum 25-OH-vitamin D of 80 ng/ml (200 nmol/L). Therefore, and also given that such levels are physiologically attained with sun exposure, a target of 80 ng/ml (200 nmol/L) is quite reasonable.

2017 vitamin D supplementation guidelines

In early 2017, "vitamin D supplementation guidelines" were published[6] endorsing the following supplementation regimens:

- Neonates (i.e. younger than one month): 1,000 IU/day (25 mcg/day),
- Infants older than 1 month and toddlers: 2000-3000 IU/day (50-75 mcg/day),
- Children and adolescents aged 1 to 18 years: 3000-5000 IU/day (75–125 mcg/day),
- Adults and the elderly: 7000–10,000 IU/day (175–250 mcg/day) or 50,000 IU/week (1250 mcg/week).

The authors also note that obese patients need up to 300% more vitamin D than do persons of normal weight, and that—as noted previously and consistently throughout the literature—"the dose of 10,000 IU/d was also found as the no-observed-adverse-effect level (NOAEL)." Consistent

with the clinical guidelines that I have published since 2008, these 2017 guidelines state "It is generally accepted that a serum 25(OH)D concentration of up to 100 ng/mL (250 nmol/L) is safe for children and adults, with the exception of those who have a hypersensitivity to vitamin D." They further note that "The Endocrine Society guidelines concluded that vitamin D toxicity is not only extremely rare, but 25(OH)D concentration of at least 150 ng/mL (375 nmol/L) is required before there would be evidence of vitamin D toxicity."

Vitamin D's safety and efficacy have already been established, justifying routine use; to continue inertia and inaction is actually dangerous and unethical

We established the safety, efficacy, and clinical imperative of vitamin D supplementation in our landmark review in 2004 by Vasquez, Manso, and Cannell, *Altern Ther Health Med* 2004 Sep[1]:

> "As a medically valid diagnosis (ICD-9 code: 268.9 Unspecified vitamin D deficiency) with a high prevalence and clinically significant morbidity, vitamin D deficiency deserves equal attention and status with other diagnoses encountered in clinical practice. Given the depth and breadth of the peer-reviewed research documenting the frequency and consequences of hypovitaminosis D, failure to diagnose and treat this disorder is ethically questionable (particularly in pregnant women) and is inconsistent with the delivery of quality, science-based healthcare. Failure to act prudently based on the research now available in favor of vitamin D supplementation appears likely to invite repetition analogous to the previous failure to act on the research supporting the use of folic acid to prevent cardiovascular disease and neural tube defects—a blunder that appears to have resulted in hundreds of thousands of unnecessary cardiovascular deaths and which has contributed to incalculable human suffering related to otherwise unnecessary neural tube defects, cervical dysplasia, cancer, osteoporosis, and mental depression. ... Of course, additional lives may be saved and suffering reduced by alleviating the morbidity and mortality associated with hypertension, autoimmune disease, depression, epilepsy, migraine, diabetes, polycystic ovary syndrome, musculoskeletal pain, osteoporosis, and cardiovascular disease."

Given cholecalciferol's low cost, high safety, and numerous direct and collateral benefits, no legitimate reason exists for routinely denying vitamin D3 supplementation to patients; vitamin D supplementation (and/or sun exposure) should be recommended and supported routinely in virtually all patients

> "Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases. Safety and effectiveness of supplementation are assured by periodic monitoring of serum 25(OH)D and serum calcium."[1]

According to the 2011 clinical trial by Hollis et al[7], "Vitamin D supplementation of 4,000 IU/day for pregnant women was safe and most effective in achieving sufficiency in all women and their neonates regardless of race." A 2016 review supported the same dose of 4,000 IU/d for pregnant women.[8]

For active hyperlinks, associated PDF articles and videos, and any updates, please see: http://www.ichnfm.org/d

History of this publication: Posted online 12 Feb 2017, updated 19 Feb, updated 23 Feb to include discussion of the recently released 2017 vitamin D supplementation guidelines.

Main citations:

1. Vasquez A, Manso G, Cannell J. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med*. 2004 Sep-Oct;10(5):28-36
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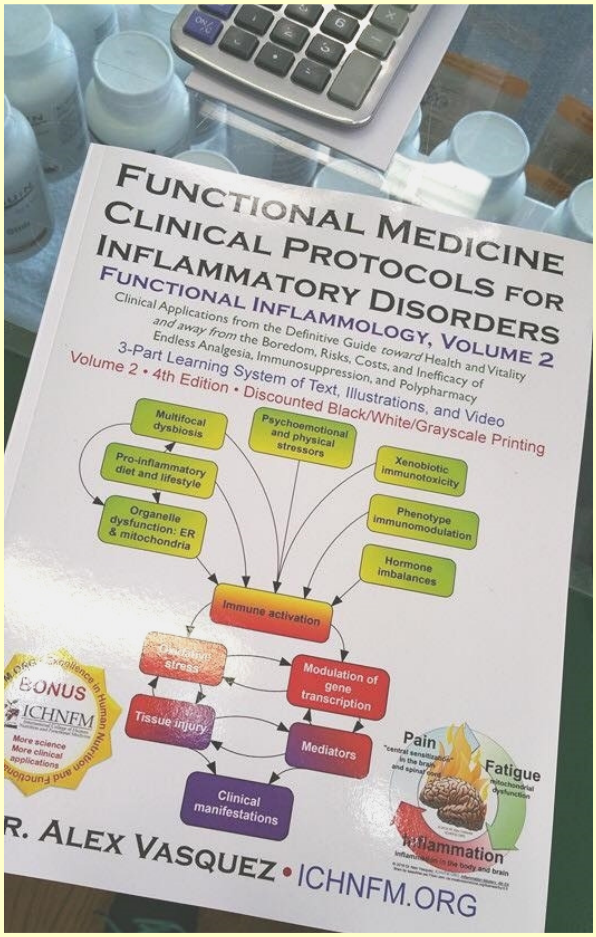

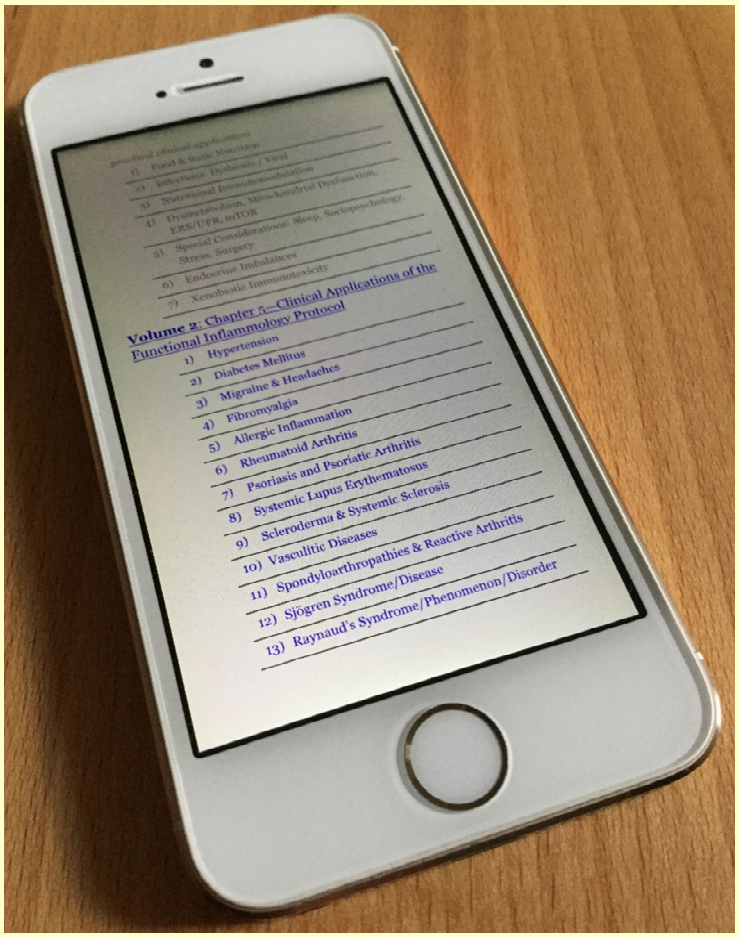

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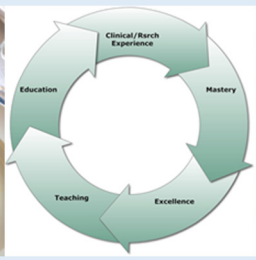

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Chapter XVIII; testimony of Howard Roark in *The Fountainhead* by Ayn Rand

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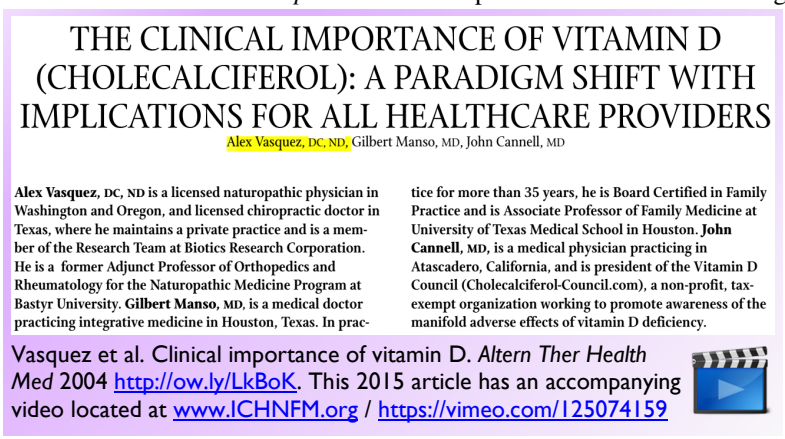
Iatrogenic Induction of Vitamin D Deficiency: The Position Against This Potentially Harmful Practice and Open Invitation for Its Proponents to Articulate Substantiation

Alex Vasquez DC ND DO FACN

Introduction

Vitamin D3 (cholecalciferol) is unique in nutritional science for its impressive safety, low cost, and wide range of clinical applications. The breadth of its clinical applications provides evidence of the importance of this nutrient/hormone in a wide range of physiologic functions, including calcium absorption and bone health, maintenance of gut mucosal integrity, maintenance of muscle strength, anti-inflammatory benefits, modulation of NFkB, antirheumatic and anti-autoimmune benefits, immunosupportive and anti-infection benefits, anti-cancer benefits, cardioprotection, neuroprotection, and ability to prevent deficiency-induced musculoskeletal pain, weakness, and seizures. In 2004, the current author lead the writing of an important review paper for the integrative medicine and functional medicine communities in *Alternative Therapies in Health and Medicine*, and this paper sought to effect a "paradigm shift" in the way vitamin D is perceived by clinicians with the hope that more clinicians would embrace its use for the benefit of their practices and patients.[1] For the eleven years following that publication, the key points of that article and its derivatives—including a letter published in the *British Medical Journal*[2] and a clinical trial published in *Journal of Clinical Endocrinology and Metabolism*[3]— remain strong, and they have been further supported and extended by the accumulation of additional clinical experience and a wide range of scientific investigations, ranging from *in vitro* studies, to animal studies, to clinical trials, to epidemiologic studies and meta-analyses. Humans have an absolute requirement for vitamin D3, with catabolic use of approximately 4,000 IU per day for adults[4], consistent with physiologic production and doses ≥4,000 IU/d used in several successful clinical trials.[5,6,7]

In contrast to this consistent and logical science, the mechanistic understandings and clinical success, a small group of presenters, authors, and clinicians have advocated, not simply against the manifold merits of vitamin D3, but have actually championed the intentional iatrogenic induction of vitamin D deficiency. The purpose of this article is to briefly outline the arguments *for* and *against* and to invite proponents of "medically endorsed nutritional deficiency" to clearly articulate their position, its mechanisms, and to provide a risk/cost-benefit ratio substantiating what is otherwise contrary to the bulk of science and clinical practice on this topic.



THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

Alex Vasquez, DC, ND, Gilbert Manso, MD, John Cannell, MD

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Vasquez et al. Clinical importance of vitamin D. *Altern Ther Health Med* 2004 http://ow.ly/LkBoK. This 2015 article has an accompanying video located at www.ICHNFM.org / https://vimeo.com/125074159

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Background

Vitamin D3 functions via the vitamin D receptor (VDR) to support innate and acquired immune responses via several mechanisms including ❶ regulating inflammation via mechanisms that include modulation of NFkB, ❷ inhibiting viral replication and enhancing anti-viral defenses via elaboration of antimicrobial peptides (AMP), ❸ via the AMP, enhancing innate immunity against cancer, bacteria, fungi and other microbes, ❹ assisting in the maintenance of gastrointestinal integrity, helping prevent intestinal hyperpermeability (per research showing that VDR-knockout animals have "leaky gut" whereas wildtype animals do not), and others. Although not all trials have shown benefit, the vast bulk of clinical research shows improved outcomes in the prevention and treatment of inflammatory and infectious diseases when physiologically appropriate doses of vitamin D3 are used, especially when supplementation guidelines[1,2] are followed.

Controversial position by Waterhouse, Marshall, et al, advocating iatrogenic induction of vitamin D deficiency in the "treatment" of the same infectious and inflammatory conditions that vitamin D has already been shown to prevent or treat

In 2009, Waterhouse et al, relying impressively on several unpublished substantiations and unpublished and non-peer-reviewed conference presentations by Marshall[8], state that in autoimmunity, intracellular bacteria cause vitamin D receptor (VDR) dysfunction within phagocytes leading to a decline in innate immune function that causes susceptibility to additional infections that contribute to inflammatory/autoimmune disease progression. The authors propose treatment aimed at "gradually restoring VDR function with the VDR agonist olmesartan and subinhibitory dosages of certain bacteriostatic antibiotics." They state that with this approach, "Diseases showing favorable responses to treatment so far include systemic lupus erythematosus, rheumatoid arthritis, scleroderma, sarcoidosis, Sjogren's syndrome, autoimmune thyroid disease, psoriasis, ankylosing spondylitis, [reactive arthritis], type I and II diabetes mellitus, and uveitis." The most controversial part of this strategy is the iatrogenic induction of vitamin D deficiency; the authors state, "Disease reversal using this approach requires limitation of vitamin D in order to avoid contributing to dysfunction of nuclear receptors…" In this protocol, patients are advised to strictly avoid all dietary vitamin D and to wear "protective" full-body clothing, hats, sunglasses, and sunscreen to block all possible consumption or production, respectively, of vitamin D3, with the proposed goal being that of specifically inducing profound vitamin D deficiency.

Articles and videos by this same group and advocates of the so-called "Marshall protocol" intermix scientific accuracy (e.g., microbes contribute to inflammatory diseases) with profound inaccuracies (e.g., microbes *cause* overconversion of 25-OH-vitamin D to 1,25-dihydrovitamin D [and perhaps other "immunosuppressive" metabolites], and that administering vitamin D prolongs these diseases); the protocol remains scientifically unsupported, and its availability (on the internet) continues to promote confusion among some doctors and the general public.[9,10,11] I propose here that these positions are easily deflated with minimal effort, and that the arguments espoused lack internal consistency. As an example, when they note that patients benefit from vitamin D supplementation, these proponents countermeasure not with fact but with additional supposition; Albert, Proal, and Marshall[12] state "...symptomatic improvements among those administered vitamin D is the result of 25-D's ability to temper bacterial-induced inflammation by slowing VDR activity. While this results in short-term palliation, persistent pathogens that may influence disease progression, proliferate over the long-term." Thus, when faced with evidence showing that patients have less inflammation and fewer symptoms after receiving vitamin D3, the authors superstitiously attribute this to an analgesic/anti-inflammatory drug-like effect, suppressing symptoms while allowing the disease to fester; their proposal is unsupported by science.

Furthermore, if this proposal were true, then vitamin D ***deficiency*** would *reduce* disease and mortality, and this is contrary to the bulk of the science, which consistently shows improved clinical and population-wide health benefits with enhanced vitamin D nutriture. The landmark 1999 review of "Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety" by Vieth[13] already laid to rest most of the concerns raised by Marshall's group, leaving one to wonder if the latter has read the former; Vieth's article is one of the most powerful ever published in the medical nutrition literature and his clear statements such as "Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations <140 nmol/L, which require a total vitamin D supply of 250 microg (10000 IU)/d to attain" demonstrated clear authority of the literature and paved the way for our 2004 "paradigm shift" paper that followed after (Vasquez et al, *op cit*).

Argument in favor of iatrogenic vitamin D deficiency

Some authors and clinicians state that, in autoimmunity and chronic illnesses, vitamin D is being converted by microbes into metabolites that actually cause immunosuppression by interfering with VDR function, thereby leading to the perpetuation of microbial colonization, which promotes illness. Proponents state that induction of vitamin D deficiency is necessary to deprive microbes of the vitamin D that the microbes will use to create these immunosuppressive VDR antagonists. Microbes and mechanisms are scarcely specified.

*The controversial position by Waterhouse, Marshall, et al, advocates intentional iatrogenic induction of vitamin D **deficiency** in the "treatment" of the same infectious and inflammatory conditions that vitamin D **supplementation** has already been shown to prevent or treat. The authors have not built a sufficient case to overturn one of the safest and most efficacious treatments ever used in the practice of medicine, with numerous clinical and public health benefits, at high safety and low cost.*

Counterarguments against iatrogenic induction of vitamin D deficiency

Counterargument #1—Lack of risk-benefit analysis

Even if the argument were true, the risk-to-benefit ratio would have to be evaluated. Iatrogenic induction of vitamin D deficiency for the supposed purpose of supposedly liberating the VDR from microbial metabolites would have to be justified by

being proven superior to the known and likely effects of vitamin D deficiency, including immunoimpairment, leaky gut, depression, migraine/seizure, pain, increased risk for cancer, autoimmunity, hypertension and cardiovascular disease. Proponents of "iatrogenic hypovitaminosis D as treatment" have failed to substantiate favorable risk:benefit and cost:benefit arguments for their intervention.

Counterargument #2—Lack of consideration for repletion or supranutritional supplementation of vitamin D to overcome VDR impairment

An argument could be made that increasing vitamin D nutriture would help overcome the VDR impairment, even more so considering that serum 25-hydroxyvitamin D, which is directly affected by dietary supplementation, has biological activity, albeit less than that of 1,25-dihydroxyvitamin D. Why not allow vitamin D itself to serve as its own VDR agonist by raising the levels of 25-OH-D and/or 1,25-dihydroxy-D to overcome the supposed microbial monkeywrench?

Counterargument #3—Failure to define microbes, mechanisms

Zero or insufficient mechanistic evidence has been presented.

Counterargument #4—Per the proposed hypothesis, vitamin D supplementation should be harmful and vitamin D deficiency should be beneficial in these prototypic autoimmune diseases when in fact the research shows the opposite to be true

If, as the authors state, microbes are converting vitamin D into an immunosuppressive metabolite, then providing vitamin D supplementation should itself be immunosuppressive; not only has this not been shown, but the opposite has been consistently demonstrated. Providing vitamin D supplementation to autoimmune and chronically ill patients provides benefit. The ultimate proof is shown—as always—in clinical trials, a representative sample of which are provided here:

- Vitamin D supplementation benefits patients with back pain ("despite" the high prevalence of bacterial infection reported in this condition[14,15,16]): ❶ "This article reviews 6 selected cases of improvement/resolution of chronic back pain or failed back surgery after vitamin D repletion... This case series supports information that has recently become apparent in the literature about vitamin D deficiency and its influence on back pain, muscle pain, and failed back surgery. Doses in the range of 4000 to 5000 IU of vitamin D3/day may be needed for an adequate response."[17] ❷ "Findings showed that 83% of the study patients (n = 299) had an abnormally low level of vitamin D before treatment with vitamin D supplements. After treatment, clinical improvement in symptoms was seen in all the groups that had a low level of vitamin D, and in 95% of all the patients (n = 341). CONCLUSIONS: Vitamin D deficiency is a major contributor to chronic low back pain in areas where vitamin D deficiency is endemic. Screening for vitamin D deficiency and treatment with supplements should be mandatory in this setting. Measurement of serum 25-OH cholecalciferol is sensitive and specific for detection of vitamin D deficiency, and hence for presumed osteomalacia in patients with chronic low back pain."[18]
- Vitamin D supplementation benefits patients with lupus/SLE: Cholecalciferol 100,000 IU per week for 4 weeks followed by 100,000 IU of cholecalciferol per month for 6 months in 20 SLE patients with hypovitaminosis D increased serum 25(OH)D levels from 18 ng/mL to 51 ng/mL at 2 months and to 41 ng/mL. "Vitamin D was well tolerated and induced a preferential increase of naïve CD4+ T cells, an increase of regulatory T cells and a decrease of effector Th1 and Th17 cells. Vitamin D also induced a decrease of memory B cells and anti-DNA antibodies."[19] *Comment*: Anti-DNA antibodies are the defining laboratory and pathologic hallmark of SLE; their reduction is worthy of interpretation as a clear indication in reduced disease activity by vitamin D.
- Vitamin D supplementation benefits patients with viral hepatitis: ❶ "Cases treated with vitamin D [vitamin D3 2000 IU/d orally] showed significant higher early (P<0.04) and sustained (P<0.05) virological response. There was a high frequency of vitamin D deficiency among the Egyptian HCV children, with significant decrease in bone density. The vitamin D level should be assessed before the start of antiviral treatment with the correction of any detected deficiency. Adding vitamin D to conventional Peg/RBV therapy significantly improved the virological response and helped to prevent the risk of emerging bone fragility."[20] ❷ "Low vitamin D levels predicts negative treatment outcome, and adding vitamin D [oral vitamin D3 2000 IU/d] to conventional Peg/RBV therapy for patients with HCV genotype 2-3 significantly improves viral response."[21]

Counterargument #5—The Marshall Protocol proponents claim that vitamin D supplementation is harmful despite the fact that essentially all studies have shown clinical benefit and reduced mortality and disease incidence with improved vitamin D nutriture

My conclusion is that iatrogenic vitamin D deficiency is almost certainly harmful and clearly not beneficial, neither in the long-term nor the short-term. Several studies and metaanalyses involving tens of thousands of patients have shown dose-dependent (i.e., causal) benefits of vitamin D supplementation.

- Vitamin D supplementation reduces total mortality (*Arch Intern Med* 2007 Sep[22]): "Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates." *Comment*: Most of the studies reviewed in this meta-analysis used subphysiologic doses of vitamin D; yet they still produced benefit in terms of reduced total mortality, some of which is likely attributable to reductions in the incidence and severity of infections and autoimmunity.
- Vitamin D supplementation in first year of life reduces risk of type 1 diabetes by at least 78%. (*Lancet* 2001 Nov[23]): In this pioneering and prophetic study—amazingly started in 1966 and ended in 1997—the authors assessed the effect of vitamin D supplementation in more than 10,000 infants (n = 10366) to find that "Vitamin D supplementation was associated with a decreased frequency of type 1 diabetes when adjusted for neonatal, anthropometric, and social characteristics (rate ratio [RR] for regular vs no supplementation 0.12, and irregular vs no supplementation 0.16. Children who regularly took the recommended dose of vitamin D (2000 IU daily) had a RR of 0.22 (0.05-0.89) compared with those who regularly received less than the recommended amount. Children suspected of having rickets during the first year of life had a RR of 3.0 compared with those without such a suspicion. Interpretation: Dietary vitamin D supplementation is associated with reduced

risk of type 1 diabetes. Ensuring adequate vitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes." This is a landmark study that should have resulted in routine implementation of vitamin D supplementation in all children because the cost is minimal, the health benefits (including and beyond diabetes) are massive, and the risks are truly almost negligible—in this study of more than 10,000 infants, not a single adverse effect was reported. Note the very clear dose-response relationship and that vitamin D deficiency rickets was associated with a 300% increased risk for diabetes.

- Estimated health benefits and reduction in economic burden and premature deaths due to vitamin D deficiency in Canada. (*Mol Nutr Food Res* 2010 Aug[24]): "Vitamin D deficiency has been linked to many diseases and conditions in addition to bone diseases, including many types of cancer, several bacterial and viral infections, autoimmune diseases, cardiovascular diseases, and adverse pregnancy outcomes. … It is estimated that the death rate could fall by 37,000 deaths, representing 16.1% of annuals deaths and the economic burden by 6.9% or $14.4 billion ($8.0 billion-$20.1 billion) less the cost of the program."
- Vitamin D reduces risk of multiple sclerosis: ❶ Estimated vitamin D intake and serum 25-hydroxyvitamin D (25[OH]D) during pregnancy were assessed in 35,794 mothers and correlated with offspring incidence of developing MS. "The relative risk of MS was lower among women born to mothers with high milk or vitamin D intake during pregnancy. … The predicted 25[OH]D level in the pregnant mothers was also inversely associated with the risk of MS in their daughters. Comparing extreme quintiles, the adjusted RR was 0.59; (95% CI, 0.37-0.92; p trend = 0.002). *INTERPRETATION*: Higher maternal milk and vitamin D intake during pregnancy may be associated with a lower risk of developing MS in offspring."[25] ❷ " Dietary vitamin D intake was examined directly in relation to risk of MS in two large cohorts of women: the Nurses' Health Study (NHS; 92,253 women followed from 1980 to 2000) and Nurses' Health Study II (NHS II; 95,310 women followed from 1991 to 2001). ... The pooled age-adjusted relative risk (RR) comparing women in the highest quintile of total vitamin D intake at baseline with those in the lowest was 0.67. Intake of vitamin D from supplements was also inversely associated with risk of MS; the RR comparing women with intake of >or=400 IU/day with women with no supplemental vitamin D intake was 0.59. ... CONCLUSION: These results support a protective effect of vitamin D intake on risk of developing MS."[26]

Invitation

Advocates for "intentional induction of vitamin D deficiency as therapy against chronic infections and microbe-induced inflammatory disease" are invited to write a succinct and articulate review detailing the ❶ involved microbes, ❷ mechanisms, ❸ risk:benefit analysis addressing the concerns described previously and in the table below, and ❹ justification of iatrogenic vitamin D deficiency versus nutritional immunoenhancement and targeted antimicrobial therapy.

Proven benefits based on multiple studies of vitamin D3 supplementation include excellent risk:benefit in the prevention and treatment of many conditions*	**Faults needing remediation in favor of "iatrogenic induction of vitamin D deficiency as therapy against infections and infection-induced inflammatory disease" per Marshall, Waterhouse, et al**
1. Alleviation of depression (strong) and improved neurologic function (weak-modest)—antidepressant benefit shown in at least 5 trials; reduced risk for schizophrenia; improved neuromuscular coordination and reduced falls; benefit suggested in neurodegenerative/neuroinflammatory disorders 2. Prevention/alleviation of diabetes types 1 (strong) and 2 (modest)—major reductions in risk; improvements in glycemic control, reduced comorbidities such as depression, hypertension, infection 3. Reduction of cardiovascular risk (modest)—mechanisms include reduction in inflammation and hypertension 4. Prevention/alleviation of nearly all autoimmune diseases (strong)—specifically multiple sclerosis, autoimmune diabetes, and rheumatoid arthritis 5. Reduction musculoskeletal pain (very strong)—back pain, migraine, limb pain, fibromyalgia-like presentations, opioid requirements 6. Normalization of Treg:Th17 ratios; antiinflammatory benefits (strong)—important for changing the immune imbalance that underlies many inflammatory conditions, including metabolic syndrome and autoimmunity 7. Reduced incidence of various cancers, including breast, colon, and prostate (strong)—vitamin D supplementation shown to delay progression of prostate cancer, mechanisms include gene regulation, anti-inflammation, and anti-estrogen 8. Excellent safety, affordability, availability, risk:benefit and cost:effectiveness characteristics: Assess, treat, and monitor. 9. Reduced all-cause mortality (strong)—consistent with above	1. Microbes not identified, model is too nonspecific—molecular mechanisms weakly explained, 2. Lack of peer-reviewed citations in the primary supporting document—many of the citations in *Ann N Y Acad Sci* 2009 Sep are not available for legitimate peer-review and scientific evaluation; having their first 8 citations referenced to their own group and their own impressively-unavailable conference presentations is highly suspect and is actually unprofessional and not in accord with journal publication standards, which require that sources are peer-reviewed and available for evaluation. 3. No risk:benefit analysis provided—benefit not shown to outweigh risks for nontreatment of conditions that respond to vitamin D supplementation; benefit of proposed reduction in VDR-impairing microbial metabolites not shown to outweigh the anticipated increases in depression, diabetes, autoimmunity, migraine, back pain, cancers and all-cause mortality 4. Numerous inconsistencies in their model—for example repeatedly stating that vitamin D is immunosuppressive is erroneous to the point of being illogical given the available data; implying that patients will suffer in the long-term despite proven short-term *and long-term* benefits demonstrated in studies ranging from 3 months to 30 years is inconsistent with current literature at best, illogical fear-mongering at worst *Data strength casually ranked as strong/moderate/weak per literature perusal and prior publications on this topic by author, including *J Clin Endocrinol Metab* 2008 Jul, *BMJ* 2005 Jul, *J Manipulative Physiol Ther* 2005 Mar, *JAMA* 2004 Nov, and especially Vasquez et al. The clinical importance of vitamin D. *Altern Ther Health Med* 2004 Sep; all of these citations freely available FunctionalInflammology.com/reprints

History of this publication: This article was conceived and written by Dr Alex Vasquez; editorial critiques and peer reviews were provided by a quorum of *IJHNFM* reviewers. Publication does not imply endorsement by all members of *IJHNFM* Editorial Review Board. In order to ensure and enhance the openness of the review process, the document was also posted publicly—and specifically to professional forums of licensed healthcare providers—with a request for additional peer-review prior to publication; total number of exposures/invitations is estimated to be 12,000 prior to publication, and the article received more than 400 downloads within the first 24 hours, thereby ensuring that opportunity for peer-review had been achieved. This version is the final version—posted 12 Apr 2015; if any changes, corrections, withdrawals are made or rebuttals/replies posted, these will be made freely available at www.ICHNFM.org and www.IntJHumNutrFunctMed.org.

Disclosures: Dr Vasquez writes and lectures on topics related to nutrition, inflammation, and infectious diseases and has served as a consultant to Biotics Research Corporation, a company that manufactures nutritional supplements in the United States.

Invitation: Authors replying to this invitation need to submit an articulate, well-written reply addressing the conceptual and mechanistic faults outlined in this paper along with risk-benefit and cost-effectiveness assessments, all of which have already been documented in favor of vitamin D3 supplementation.

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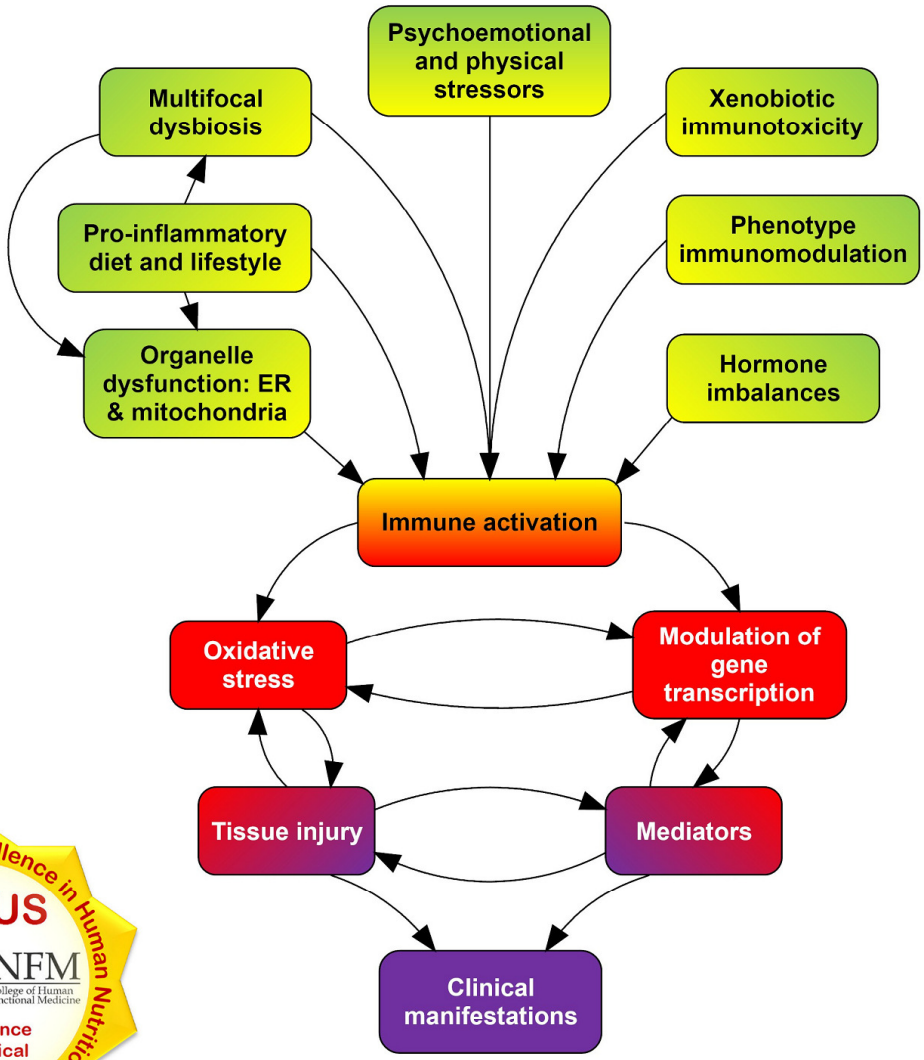

Dr. Alex Vasquez

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- IL-6 reduction: IL-6 can be reduced by multivitamin/mineral supplementation, CoQ10, vitamin D, low-carbohydrate diets, moderate exercise, weight loss, lipoic acid, antidysbiosis/antimicrobial treatments as needed; vitamin A helps maintain iTreg phenotype and activity in an inflammatory milieu,
- IL-17 reduction: IL-17 can be reduced by lipoic acid (per in vitro and ex vivo research),
- IL-21 reduction: Animal studies have shown that vitamin D deficiency increases responsiveness to IL-21 (pro-inflammatory effect), and that vitamin D supplementation reduces responsiveness to IL-21 (anti-inflammatory effect),
- TNF-alpha reduction: TNFa can be reduced by fish oil and biotin (per in vitro and ex vivo research),

- Vitamin D3: Several clinical trials in humans have shown that vitamin D3 supplementation (detailed previously and throughout in this textbook) induces higher number and function of Treg cells within approximately 1 month in adult humans who are "apparently healthy" and those who have autoimmune diseases such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE, lupus).
  - Small study shows that vitamin D increases anti-inflammatory IL-10 and reduces frequency of pro-inflammatory Th-17 cells (*Mult Scler* 2012 Dec[1144]): Four healthy individuals (n=4) took 5000-10,000 IU/day of vitamin D over 15 weeks, after which serum 25(OH) vitamin D levels rose significantly from baseline, with a corresponding increase in IL-10 production by peripheral blood mononuclear cells and a reduced frequency of Th17 cells.
  - Vitamin D supplementation increases regulatory T cells in apparently healthy subjects (*Isr Med Assoc J* 2010 Mar[1145]): In this study, most "healthy" subjects were vitamin D deficient at the start of this study, then received one dose of vitamin D 140,000 IU (nonphysiologic dosing) and were not corrected to optimal vitamin D status. Nonetheless, participants showed an increase in Tregs.
  - T-cell modulating effects of high dose vitamin D3 supplementation in multiple sclerosis (*PLoS One* 2010 Dec[1146]): N=15 RRMS patients were supplemented with 20,000 IU/d vitamin D3 for 12 weeks. "All patients finished the protocol without side-effects, hypercalcemia, or hypercalciuria. The median vitamin D status increased from 50 nmol/L (31-175) at week 0 to 380 nmol/L (151-535) at week 12 (P<0.001). During the study, 1 patient experienced an exacerbation of MS and was censored from the T cell analysis. The proportions of (naïve and memory) CD4+ Tregs remained unaffected. Although Treg suppressive function improved in several subjects, this effect was not significant in the total cohort. An increased proportion of IL-10+ CD4+ T cells was found after supplementation."
  - One of the most important studies ever ignored: Intake of vitamin D and risk of type 1 diabetes *Lancet* 2001 Nov[1147]): This is one of the most important studies ever published in medicine and nutrition, showing that among more than 10,000 infants, vitamin D supplementation 2,000 IU/d for the first year of life showed complete safety and a dose-dependent reduction in autoimmune type-1 diabetes mellitus up to -78% over 30 years of follow-up. If any drug showed this level of safety, affordability, and efficacy, its use would almost certainly be medically and legally mandatory; the continued ignoring of this data by the medical/pediatrician/ObGyn communities is one of many nutritional-medical travesties in medicine and healthcare.

Vitamin D prevention of autoimmune diabetes: lessons learned and ignored

- More than 10,000 human infants were to receive 2,000 IU/d of vitamin D for the first year of life,
- No report of adverse effects.
- Dose-dependent reduction in autoimmune diabetes up to -78% with 30 years of follow-up,
- Published in *The Lancet*
- Virtually completely ignored by the medical and healthcare community

Hyppönen et al. *Lancet*. 2001 Nov

  - Vitamin D restores Treg:Th17 balance in patients with SLE (*Arthritis Res Ther* 2012 Oct[1148]): Cholecalciferol 100,000 IU per week for 4 weeks followed by 100,000 IU of cholecalciferol per

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Vitamin D, 1,25 + 25-Hydroxy					
Test	Low	Normal	High	Reference Range	Units
Calcitriol(1,25 Di-Oh Vit D)			115.8	10.0-75.0	pg/mL
Vitamin D, 25-Hydroxy		53.1		30.0-100.0	ng/mL

Cmp14+Egfr					
Test	Low	Normal	High	Reference Range	Units
Glucose, Serum		90		65-99	mg/dL
Bun		20		6-20	mg/dL
Creatinine, Serum		0.93		0.76-1.27	mg/dL
Egfr If Nonafricn Am		104		>59	mL/min/1.73
Egfr If Africn Am		120		>59	mL/min/1.73
Bun/Creatinine Ratio			22	8-19	1
Sodium, Serum		142		134-144	mmol/L
Potassium, Serum		4.8		3.5-5.2	mmol/L
Chloride, Serum		99		97-108	mmol/L
Carbon Dioxide, Total		26		18-29	mmol/L
Calcium, Serum		9.7		8.7-10.2	mg/dL

Cbc/Diff Ambiguous Default					
Test	Low	Normal	High	Reference Range	Units
Wbc		5.8		3.4-10.8	x10E3/uL
Rbc		5.26		4.14-5.80	x10E6/uL

Ldh					
Test	Low	Normal	High	Reference Range	Units
Ldh		123		121-224	IU/L

Homocyst(E)Ine, Plasma					
Test	Low	Normal	High	Reference Range	Units
Homocyst(E)Ine, Plasma		10.7		0.0-15.0	umol/L

Laboratory results for a 39yoM with psoriasis and psoriatic arthritis: Abnormally increased conversion of 25-OH-cholecalciferol to 1,25-d(OH-cholecalciferol is due expression of 25-hydroxyvitamin D3-1alpha-hydroxylase (1-OHase) in inflammatory tissue/cells. Note that serum calcium is normal, so no immediate threat is present (i.e., hypercalcemia) but of course the clinician has the responsibility to ❶ monitor periodically, ❷ inform the patient of symptoms of hypercalcemia such as headache and abdominal pain, and ❸ search for any predictive risk factors such as renal insufficiency or occult leukemia/lymphoma that could precipitate hypercalcemia. Assessment for hyperparathyroidism (eg, iPTH) is reasonable but not completely necessary; likewise, cancer screening is not absolutely indicated, as it would be in the case of idiopathic hypercalcemia. Also noted is the elevated homocysteine, common in patients with psoriasis; increased cell turnover—dermal hyperproliferation—likely contributes to draining/catabolizing nutrients such as folate. Since this patient's 25-OH-D is plenty sufficient, I had the patient temporarily reduce/discontinue vitamin D supplementation to reduce risk of hypercalcemia given that he is clearly vitamin D sufficient.

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THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

Alex Vasquez, DC, ND, Gilbert Manso, MD, John Cannell, MD

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Appreciate and identify the manifold clinical presentations and consequences of vitamin D deficiency
2. Identify patient groups that are predisposed to vitamin D hypersensitivity
3. Know how to implement vitamin D supplementation in proper doses and with appropriate laboratory monitoring

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While we are all familiar with the important role of vitamin D in calcium absorption and bone metabolism, many doctors and patients are not aware of the recent research on vitamin D and the widening range of therapeutic applications available for cholecalciferol, which can be classified as both a vitamin and a pro-hormone. Additionally, we also now realize that the Food and Nutrition Board's previously defined Upper Limit (UL) for safe intake at 2,000 IU/day was set far too low and that the physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.[1,2] With the discovery of vitamin D receptors in tissues other than the gut and bone—especially the brain, breast, prostate, and lymphocytes—and the recent research suggesting that higher vitamin D levels provide protection from diabetes mellitus, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, several autoimmune diseases, and cancers of the breast, prostate, and colon, we can now utilize vitamin D for a wider range of preventive and therapeutic applications to maintain and improve our patients' health.[3] Based on the research reviewed in this article, the current authors believe that assessment of vitamin D status and treatment of vita-

Vasquez A et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med* 2004 Sep-Oct: This article indexed on Medline at ncbi.nlm.nih.gov/pubmed/15478784 and is archived by the author online ICHNFM.ORG/faculty/vasquez/profile.html and https://ichnfm.academia.edu/AlexVasquez

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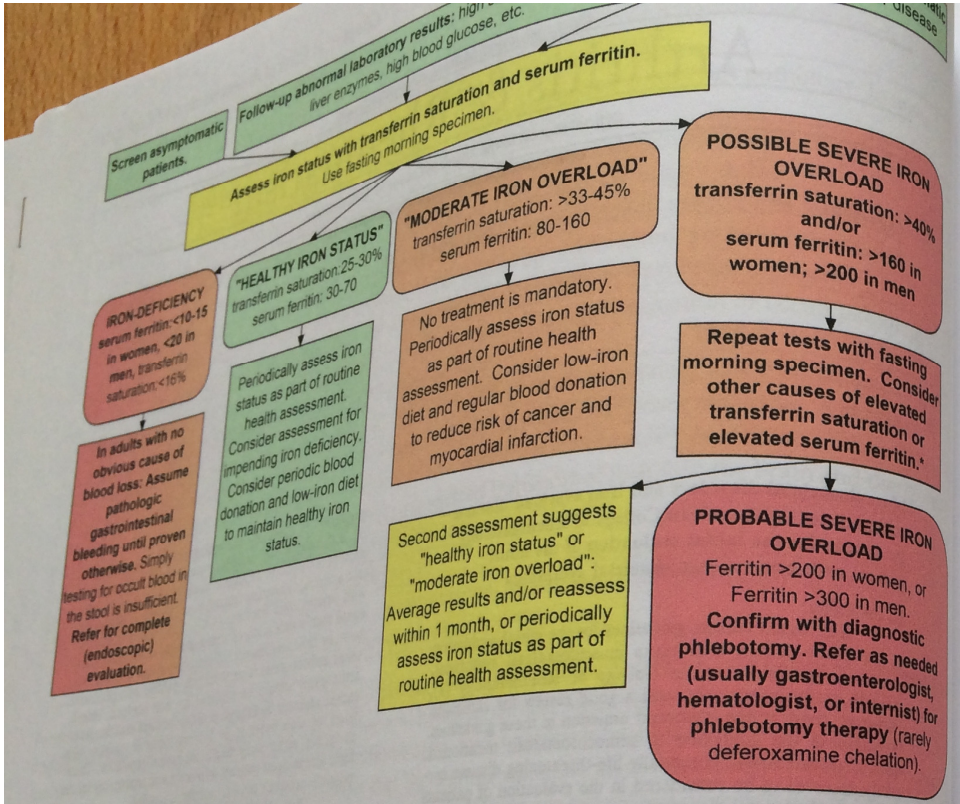


Algorithm for the comprehensive management of iron status: The above flow-chart delineates patien management per iron status.

Basic treatments for severe iron overload:

- **Iron-removal therapy is mandatory:** Phlebotomy therapy is generally performed weekly or twice-weekly deferoxamine chelation is reserved for patients who do not withstand phlebotomy (due to cardiomyopathy, severe anemia, or hypoproteinemia) or may be used concurrently with phlebotomy in some patients. Periodically assess hematologic and iron indexes. Continue with weekly iron removal therapy until patient reaches mild iron-deficiency anemia, then decrease frequency and continue phlebotomy as needed (e.g., 4 times per year).

Laboratory tests and physical examination: Assess general physical condition and hepatic, cardiac, endocrine, and general health status.

Confirm diagnosis: Liver biopsy ("gold standard") or diagnostic phlebotomy; perhaps MRI.

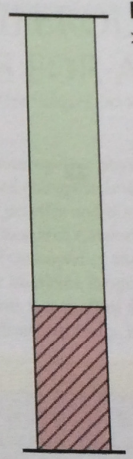
Assess liver status: Liver biopsy or perhaps MRI. Cirrhosis indicates increased risk of hepatocellular carcinoma and reduced life expectancy. Consider liver ultrasound, serum liver enzyme measurement, and serum alpha-fetoprotein o screen for hepatocellular carcinoma every 6 months. Hepatoma surveillance is mandatory in cirrhotic patients.

mplement dietary modifications and nutritional therapies: Avoid iron supplements, multivitamin supplements ith iron, iron-fortified foods, liver, beef, pork, alcohol, and excess vitamin C. Ensure adequate protein intake to place protein lost during phlebotomy. Diet modificatio
ioxidant therapy.

25(OH)D: serum 25(OH) vitamin D

Overview and interpretation:

- **Vitamin D deficiency is a common cause of musculoskeletal pain**[170,1] deficiency is a significant risk factor for cancer, autoimmunity, diabete chronic pain and physical disability.[173,174,175]
- Measurement of serum 25(OH) vitamin D (or empiric treatment with vitamin D3 per day for adults) is indicated in patients with chronic m particularly low-back pain.[176] Optimal vitamin D status correlates wit levels of 50 – 100 ng/mL (125 - 250 nmol/L)—see our review article fo levels greater than 100 ng/mL are unnecessary and increase the risk o



Excess vitamin D
> 100 ng/mL (250 nmol/L) with hyper

Optimal range
50 - 100 ng/mL (125 - 250 nmol/L)

Insufficiency range
< 20- 40 ng/mL (50 - 100 nmol/L)

Deficiency
< 20 ng/mL (50 nmol/L)

Interpretation of serum 25(OH) vitamin D levels. Modified *Alternative Therapies in Health and Medicine* 2004 and Vas *Pain: Expanded Clinical Strategies* 2008.

Advantages:

- Accurate assessment of vitamin D status.

Limitations:

- Patients with certain granulomatous conditions such as sarcoid and patients taking certain drugs such as thiazide diuretics (hy develop hypercalcemia due to "vitamin D hypersensitivity" or patients require frequent monitoring of serum calcium while t supplements.

Comments:

- **Routine measurement and/or empiric treatment with vitami routine component of patient care.**[178]
- Periodic assessment of 25(OH)D and serum calcium are requi and safety of treatment, respectively.
- I'm increasingly convinced of the merit of measuring 1,25-di for the initial assessment of patients with inflammatory/auto

Treatment of Hypovitaminosis D in Infants and Toddlers

Catherine M. Gordon, Avery LeBoff Williams, Henry A. Feldman, Jessica May, Linda Sinclair, Alex Vasquez, and Joanne E. Cox

Division of Adolescent Medicine (C.M.G., A.L.W., J.M., L.S.), Division of Endocrinology (C.M.G., H.A.F.), Clinical Research Program (H.A.F.), and Division of General Pediatrics (J.E.C.), Children's Hospital Boston, Boston, Massachusetts 02115; and Biotics Research Corp. (A.V.), Rosenberg, Texas 77471

Context: Hypovitaminosis D appears to be on the rise in young children, with implications for skeletal and overall health.

Objective: The objective of the study was to compare the safety and efficacy of vitamin D2 daily, vitamin D2 weekly, and vitamin D3 daily, combined with supplemental calcium, in raising serum 25-hydroxyvitamin D [25(OH)D] and lowering PTH concentrations.

Design: This was a 6-wk randomized controlled trial.

Setting: The study was conducted at an urban pediatric clinic in Boston.

Subjects: Forty otherwise healthy infants and toddlers with hypovitaminosis D [25(OH)D $<$ 20 ng/ml] participated in the study.

Interventions: Participants were assigned to one of three regimens: 2,000 IU oral vitamin D2 daily, 50,000 IU vitamin D2 weekly, or 2,000 IU vitamin D3 daily. Each was also prescribed elemental calcium (50 mg/kg·d). Infants received treatment for 6 wk.

Main Outcome Measures: Before and after treatment, serum measurements of 25(OH)D, PTH, calcium, and alkaline phosphatase were taken.

Results: All treatments approximately tripled the 25(OH)D concentration. Preplanned comparisons were nonsignificant: daily vitamin D2 *vs.* weekly vitamin D2 (12% difference in effect, $P = 0.66$) and daily D2 *vs.* daily D3 (7%, $P = 0.82$). The mean serum calcium change was small and similar in the three groups. There was no significant difference in PTH suppression.

Conclusions: Short-term vitamin D2 2,000 IU daily, vitamin D2 50,000 IU weekly, or vitamin D3 2,000 IU daily yield equivalent outcomes in the treatment of hypovitaminosis D among young children. Therefore, pediatric providers can individualize the treatment regimen for a given patient to ensure compliance, given that no difference in efficacy or safety was noted among these three common treatment regimens. **(*J Clin Endocrinol Metab* 93: 2716–2721, 2008)**

Vitamin D deficiency, or hypovitaminosis D, appears to be on the rise in young children, with an increased prevalence noted among African-American breast-fed infants residing in northern latitudes (1). This deficiency has been identified as the leading cause of rickets among infants, as breast milk contains inadequate amounts of vitamin D to support skeletal health in this age group (2, 3). Furthermore, numerous sources of evidence now indicate that vitamin D (cholecalciferol) has several important physiological effects beyond calcium absorption and bone maintenance (4, 5), and early vitamin D

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Abbreviations: ANCOVA, Analysis of covariance; 25(OH)D, 25-hydroxyvitamin D.

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HEALTH CARE FOR OUR BONES: A PRACTICAL NUTRITIONAL APPROACH TO PREVENTING OSTEOPOROSIS

To the Editor:

I appreciate Dr Seaman's recent survey of the literature on osteoporosis.[1] His emphasis on the importance of a "whole-food" approach to nutrition is commendable as is his earlier review of the literature on the proinflammatory nature of the American/Western diet.[2] However, his recent review on osteoporosis lacked any mention of vitamin D, and I am writing to provide supplementary information based on research that our group has recently published elsewhere.[3-5]

Vitamin D deficiency is epidemic in the United States and in other industrialized nations where dietary sources of vitamin D are inadequate and where people spend most of their time indoors and/or otherwise "protected" from ultraviolet radiation by either clothes or sunscreen. Hypovitaminosis D impairs calcium absorption, increases calcium resorption from bone, and contributes significantly to a wide variety of common clinical disorders, including low back pain and generalized musculoskeletal pain.[6]

Not surprisingly, subclinical vitamin D deficiency contributes significantly to the high prevalence of osteoporosis, and when left untreated, vitamin D deficiency impairs responsiveness to bone-building interventions, including bisphosphonate treatment[7] and nutritional-botanical interventions, as we have recently pointed out elsewhere.[5] In our recent review of the literature,[3] we concluded that optimal vitamin D status correlates with serum levels of 25-OH-vitamin D in the range of 40 to 65 ng/mL (100-160 nmol/L). Serum levels of 25-OH-vitamin D must equal or exceed 40 ng/mL (100 nmol/L) to attain effective reduction of serum parathyroid hormone, and our optimal range for vitamin D is consistent with the serum levels seen in populations with adequate sun exposure and is not associated with adverse effects. To attain and maintain optimal vitamin D serum levels in the absence of frequent full-body sun exposure, oral supplementation at levels of 1000 IU/d for infants, 2000 IU/d for children, and 4000 IU/d for adults is required; these dosages are safe and are well supported by peer-reviewed research and clinical trials. Vitamin D toxicity is exceedingly rare at the physiological doses suggested here, provided that the patient does not have hypersensitivity to vitamin D (such as with sarcoidosis) and is not taking medications that promote hypercalcemia (such as thiazide diuretics). Nonetheless, clinicians should periodically monitor serum calcium levels to ensure safety and avoid toxicity.

The addition of vitamin D to the plan suggested by Dr Seaman for the prevention of osteoporosis will certainly improve the efficacy of the nutritional and botanical interventions he reviewed. Vitamin D supplementation, when used at the doses recommended here to attain optimal serum levels and when used along with adjunctive nutritional support, botanical interventions, and a foundational whole-food diet, improves the health of our patients who seek integrative chiropractic care.[8]

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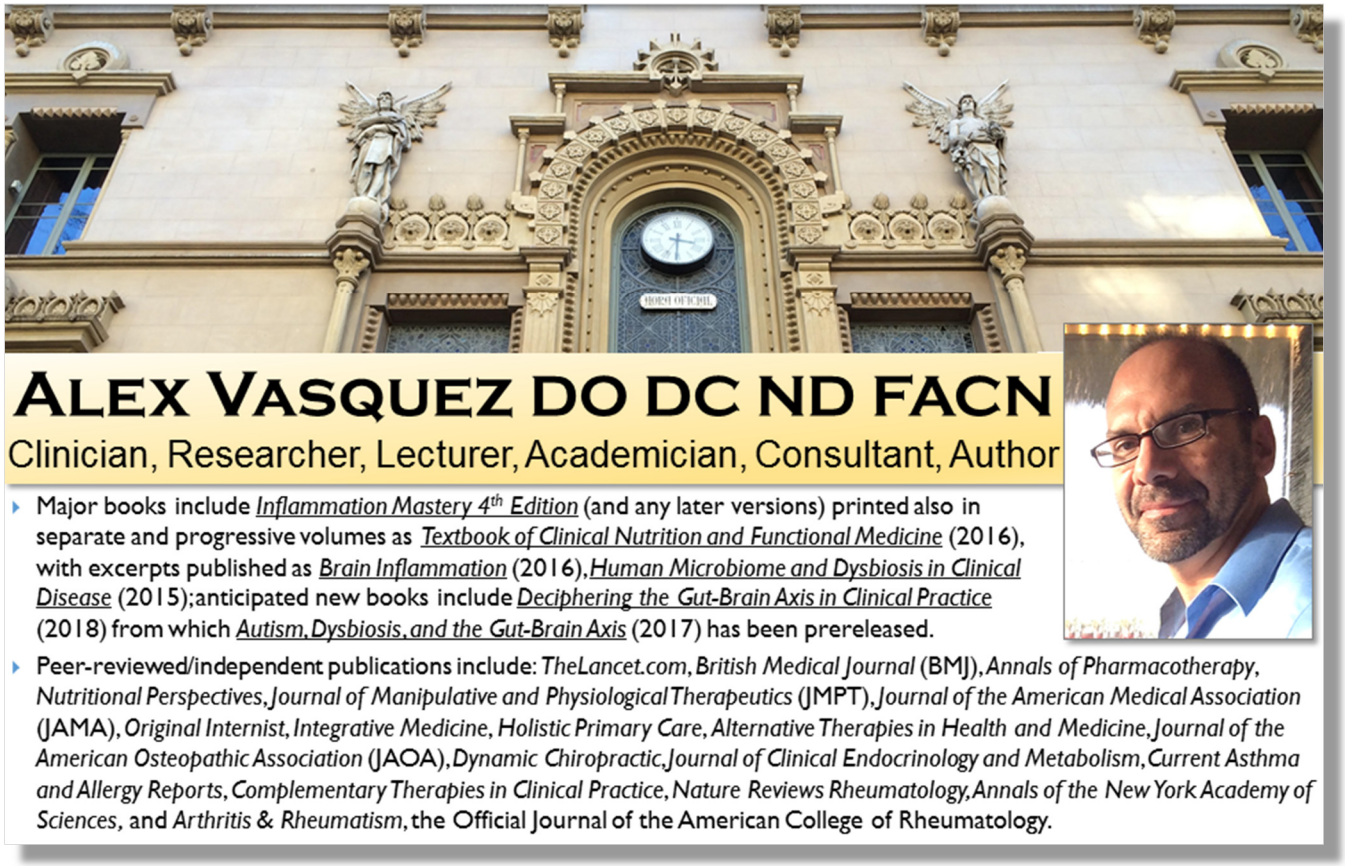
Antiviral Nutrition Update #1 for 2018:
Clinical Trial of Vitamin D3 against HPV/CIN1



The video of this presentation is archived at ichnfm.org/hpv1, and the transcript in PDF format—which is considered the final and citable version—is archived at academia.edu/35808436; any corrections or updates will be made to the PDF file. Observe that this video presentation is truly an *update* subsequent to previous publications and that therefore not all sources are cited; for citations, see the video, and for complete citations regarding the protocol in its entirety, see the book *Antiviral Strategies and Immune Nutrition* or the ebook version titled *Antiviral Nutrition*.

"Hello everyone, Dr Alex Vasquez here with our next video which is going to discuss antiviral nutrition. This will be the first update for 2018.

If I'm providing an update, then obviously that information will be founded upon and predicated upon some previous information. So let's take a look at those sources right now. This series of updates builds upon previously published books, articles, videos and blogs. In 2014, I published a small book called ***Antiviral Strategies and Immune Nutrition***; it's also available as an ebook through the Amazon Kindle platform, that was published under the name of ***Antiviral Nutrition***. I also published kind of an editorial journal article called "Unified Antiviral Strategy" in 2014, you can get that online for free. And I also did a presentation in 2016 at the International Congress on Naturopathic Medicine in Barcelona, you can see that on the internet for free as well and I've provided you the website address. Also in 2014, I published a series of videos which you can find online for free if you're interested in looking at those.

1. **Book**: Antiviral Strategies and Immune Nutrition (2014) https://www.amazon.com/dp/1502894890/
2. **eBook**: Antiviral Nutrition (Kindle ebook, 2014) https://www.amazon.com/dp/B00OPDQG4W
3. **Journal**: Unified Antiviral Strategy published by ICHNFM. *International Journal of Human Nutrition and Functional Medicine* 2014:v2(q4);p1 ichnfm.org/antiviral5

4. **Conference**: Vaccines—The Truth: International Congress on Naturopathic Medicine in Barcelona 2016 ichnfm.org/antiviral4
5. **Tutorials**: AntiViral Strategies and Immune Nutrition: Antiviral Nutrition (video, 2014) https://vimeo.com/109318556

If you want an independent view of some of these topics, the best article that I could recommend for you would be this one from *British Journal of Nutrition* 2007, "Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses." So if you want kind of an independent view of some of the things we're going to talk about today, then you might look at that article, *British Journal of Nutrition*, 2007 October.

So when we talk about viral infections which is mostly what we're talking about, we're going to talk about viral infections—a particular viral infection called HPV: human papilloma virus—and its relationship to vitamin D status and response to vitamin D supplementation.

So again, kind of laying the foundation and putting all of this in a reasonable context, when we talk about the treatment of viral infections, we have to have a comprehensive way of looking at that, not just talking about virus *here* and virus *there*. As you can imagine, with the book, I've developed not simply an antiviral strategy but also a more cohesive and comprehensive way of looking at viral infections and their clinical complications.

So as I said, in 2014, I'll state it again here, ***if you don't have a structured understanding of a good, comprehensive antiviral strategy, then you really don't have either an understanding or a strategy***. And I can say that, after having gone through three different doctoral programs: we never learned an antiviral strategy, we never learned how to understand viral infections in a comprehensive way that would really leverage the clinical tools that we have for optimal effectiveness. And when you look at my strategy, you get to see some ways that you can intervene and understand how these viral infections progress and how the body responds and that provides you some insight into ways that you could treat these virus-infection-related diseases, whether those are acute infections or persistent infections that go on to have other complications. So at the very least, let's touch upon these major four categories.

1. **Antiviral**: Starting with antiviral interventions, we can target the virus itself.
2. **Antireplication**: We can use antireplication intervention, so that is targeting the machinery of viral replication, we can attack that process as well.
3. **Immunonutrition**: We can use immunomodulation and immunonutrition because obviously, the immune system does usually a very competent job, protecting us from these viral infections. So let's optimize immune function and that usually means nutritional supplementation.
4. **Cell and systemic support**: We can also use cell and systemic support to mitigate some of the consequences of viral infections and of course, I'm talking about inflammation, oxidative stress and of course, mitochondrial dysfunction which accompanies many viral infections.

So when we start to ***deconstruct this phenomenon*** of viral infections and we look at each of these components, we can intervene at each of these levels/layers and provide better treatment, whether we're treating ourselves or whether we're treating our clients. So today, we're going to talk about vitamin D in the treatment of a very common type of viral infection and most of that work is going to put us here in this third category of immunonutrition, but also, you'll see some implications for this antireplication category as well. (See book and video for explanatory diagrams: http://www.ichnfm.org/hpv1)

So let us go ahead and start taking a look at this article that we're going to focus on today which is "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status…" associated with cervical intraepithelial neoplasia. This article comes from *Hormones and Cancer*, February of 2017. You've got the digital object identifier here as well. This is a randomized double-blind placebo-controlled trial with 58 women with cervical intraepithelial neoplasia grade one (CIN1). The intervention was 50,000 international units (IU) of vitamin D3 each two weeks, so that averages out to a bit over 3,500 IU per day for six months. And overall, I consider that intervention to be reasonable; the dose is reasonable but certainly not heroic, nor assertive.[1]

[1] Vasquez A. How to Understand, Refute, and Plan Studies Using Vitamin D. *International Journal of Human Nutrition and Functional Medicine* 2017 http://www.ichnfm.org/d

Vitamin D3 dosed at 4,000 IU per day is considered to be the minimum for replacing vitamin D in patients who are deficient. We might use higher doses closer to 10,000 IU; I think that would have been a bit more robust and not necessarily heroic; six months of duration is certainly the minimum. We wouldn't want to see a study for example for two months or three months or four months but six months is acceptable, and the dose is acceptable. So we can evaluate this study, thinking that this might actually be a reasonable representation of competent clinical practice.

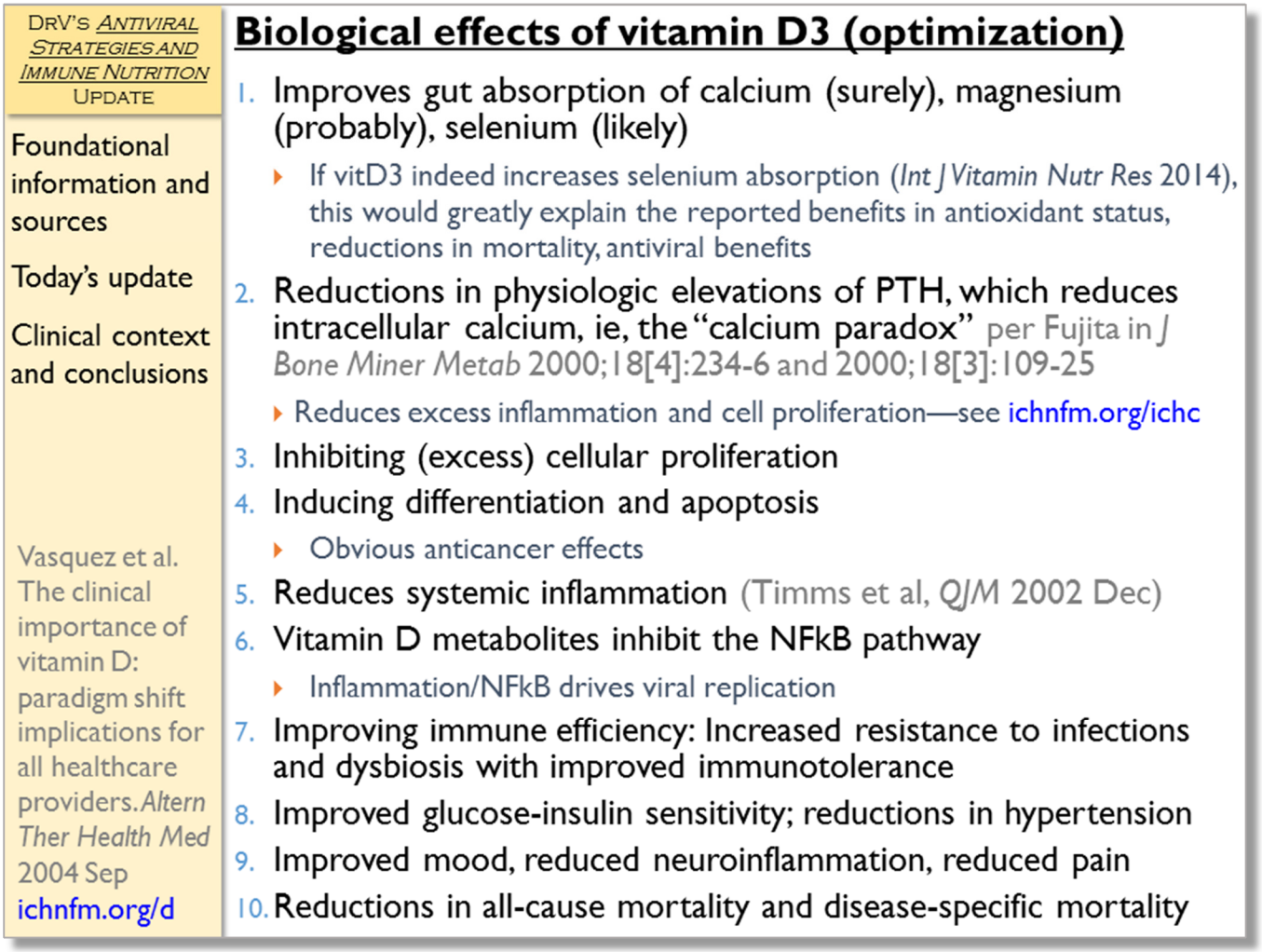
And that's an important place for us to start because a lot of these studies using vitamin D have used **inadequate dosing** and **inadequate duration** and they reached the false conclusion that vitamin D is inefficacious for whatever it is that they're investigating. And really, vitamin D is not at fault. The fault lies with the researchers for poorly designing their studies. I have published guidelines on the use of vitamin D in clinical practice as well as guidelines for designing clinical trials in *Alternative Therapies in Health and Medicine*[2], *British Medical Journal*,[3] and *International Journal of Human Nutrition and Functional Medicine.* You can download those articles from the internet for free at http://www.ichnfm.org/d. Results of the study show the following:

1. After six months of vitamin D administration, a greater percentage of women in the vitamin D group had regressed their cervical intraepithelial neoplasia grade one, 84% success versus 33% in the placebo group.
2. They had improved vitamin D status, that's another thing that we always want to look for in studies; they always need to actually measure vitamin D levels, not simply give people vitamin D and assume it was a properly manufactured supplement with good absorption, et cetera. We actually have to measure vitamin D response by looking at 25 hydroxyvitamin D in the serum.
3. These patients also benefited from showing reduced serum insulin levels and improved insulin sensitivity.
4. They had improved antioxidant defenses, they had elevated glutathione levels, relative to the placebo group and they had reduced oxidative stress as well.
5. Excellent safety.
6. The authors barely mentioned modulation of the vaginal microbiome, and I think that this beneficial microbiome-specific effect is likely of major importance. This is probably where a lot of the power of this intervention is coming from against HPV/CIN1. Not necessarily the systemic administration of vitamin D but the effect that that vitamin D has on systemic inflammation but also immune function and the modification of the vaginal microbiome via improved immune function, via vitamin D supplementation. I think that's probably where the action is here in terms of mechanisms of effect of this intervention.

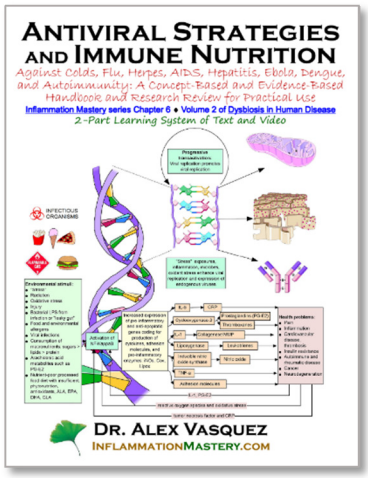
Let's look at some more details and how we might understand this study a bit more; here I will review several of the **Biological effects of vitamin D3**: When we're talking about optimizing serum levels and therefore body reserves. Vitamin D improves gut absorption of **calcium**—we are quite sure about that, **magnesium** probably and also we see some new data showing that vitamin D might also improve **selenium** absorption. If vitamin D3 indeed increases selenium absorption, this would greatly explain the reported benefits in antioxidant status, reductions in mortality and the antiviral benefits that are apparently being reported here. So selenium has antiviral effects, number one, by blocking viral replication and number two, by blocking viral mutagenesis; those are very important when the body is trying to combat these persisting viral infections. Reductions in physiologic elevations of parathyroid hormone which reduces intracellular calcium—this is referred to as the "calcium paradox." I've also published an article detailing "intracellular hypercalcinosis"[4] (reprinted online http://www.ichnfm.org/ichc), and it's also republished in my book *Inflammation Mastery, 4th Edition* as well as in *Textbook of Clinical Nutrition and Functional Medicine, Volume 1*. This reduction of parathyroid hormone reduces intracellular calcium which promotes a reduction in excess inflammation and cell proliferation. Inhibiting excess cellular proliferation is one of the physiologic and clinical benefits of vitamin D. Also, inducing differentiation and apoptosis—obviously effects have anticancer benefits. Vitamin D also reduces systemic inflammation, this has been very well documented. One very nice study back in December of 2002 published in the *Quarterly Journal of Medicine* showed this very conclusively. Vitamin D metabolites inhibit the NFkB pathway. This is very important because **the NFkB pathway drives viral replication. So anything that's going to block that NFkB pathway, whether it's vitamin D, selenium, zinc, et**

[2] Vasquez et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med.* 2004
[3] Vasquez et al. Calcium and vitamin D in preventing fractures: Data are not sufficient to show inefficacy. *BMJ: British Medical Journal* 2005
[4] Vasquez A. Intracellular Hypercalcinosis. *Naturopathy Digest* 2006 September. See reprint online: http://www.ichnfm.org/ichc

cetera, is going to probably provide some antiviral benefit by reducing viral replication. Vitamin D also improves immune efficiency, increased resistance to infections and dysbiosis with improved immunotolerance. People commonly have a simplistic "bipolar" view of the immune system, whether it's "overactive"—resulting in allergies and autoimmunity, or "underactive"—resulting in an increased susceptibility to infections. But what we see with vitamin D is ***actually improved resistance against infections and dysbiosis*** and also ***improved tolerance*** at the same time. The expected result would be a reduction in allergy and autoimmunity; certainly a reduction in autoimmunity has been documented and also some increased resistance to infections. Now in this context, when we're talking about cervical intraepithelial neoplasia (CIN), we have to talk about not simply the HPV virus, the human papillomavirus but also the bacterial microbiome within the vagina which obviously affects the cervix. **So what I suspect is happening in this study is that the administration of vitamin D is improving immune function, modulating the bacterial microbiome within the vagina—obviously that's directly adjacent to the cervix. When the immune system of the vaginal mucosa is improved, that favorably modulates the bacterial microbiome within the vagina to reduce inflammation and the reduced inflammation leads to a reduction in viral mutagenesis and viral replication. I suspect that this is the mechanism of action here.** As I mentioned before, these patients also showed improved glucose insulin sensitivity; that same result has been shown in several other studies, so I think we can believe quite strongly in that. Several studies have shown reductions in elevated blood pressure as well. We consistently see with vitamin D supplementation improved mood, reduced neuroinflammation and reduced pain and—well documented by William Grant's work—reductions in all-cause mortality and disease-specific mortality.

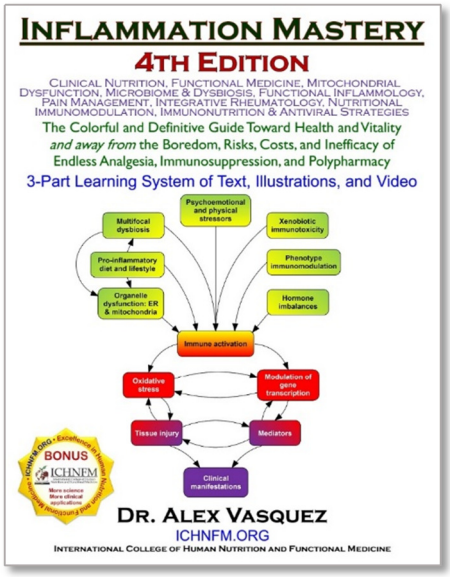


I will conclude with a brief summary and clinical contextualization. This study—"Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" published in February of 2017 in the journal *Hormones and Cancer*—is a small trial but it is placebo-controlled and does provide encouraging data consistent with known benefits of vitamin D supplementation, whether that's provided systemically (for an endocrine effect) or directly vaginally (for endocrine [systemic absorption], and local paracrine and autocrine effects)—specifically the effects that that vitamin D has on the vaginal microbiome via its antiinflammatory and eubiosis-promoting effects.



Enhancement of self-resolution I think is one of the major keys here. Given the well-established fact that most people clear various human papillomavirus infections without consequence, research (such as this) should be emphasizing those natural and endogenous factors that promote viral clearance.

Medical interventions related to HPV disease include PAP smears and these should be continued every one to three years. The controversial anti-HPV vaccination is expensive and has produced many biologically-proven adverse effects, including autoimmunity (e.g., acute disseminated encephalomyelitis[5]), neuroinflammation[6], infertility[7], and death[8]. And of course, that vaccine provides zero collateral benefits.



In contrast, nutritional interventions such as vitamin D and methylfolate or calcium folinate safely provide numerous disease specific and general collateral benefits. What we need in the future are well-performed clinical trials using a complete antiviral nutrition protocol such as the one that I published back in 2014.

So thank you for your attention during this short video. What we're going to talk about in one of the upcoming videos is again, the role of vitamin D in modulating the vaginal microbiome, reducing inflammation and reducing the clinical consequences of various diseases.

Citation: Vasquez A. Antiviral Nutrition Update # 1 for 2018. Video presentation (ichnfm.org/hpv1) and official transcript (academia.edu/35808436) 2018 January

Primary reference—same information in different formats and contexts:

- *Antiviral Strategies and Immune Nutrition* https://www.amazon.com/dp/1502894890/
- also published in digital ebook format as *Antiviral Nutrition* (Kindle ebook) https://www.amazon.com/dp/B00OPDQG4W.
- Also published in *Inflammation Mastery, 4th Edition* https://www.amazon.com/dp/B01KMZZLAQ/ and
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[5] Sekiguchi et al. Two Cases of Acute Disseminated Encephalomyelitis Following Vaccination against Human Papilloma Virus. *Intern Med*. 2016;55(21):3181-3184
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[8] "The adverse reaction reports detail 26 new deaths reported between September 1, 2010 and September 15, 2011 as well as incidents of seizures, paralysis, blindness, pancreatitis, speech problems, short term memory loss and Guillain-Barré Syndrome. The documents come from the FDA's Vaccine Adverse Event Reporting System (VAERS) which is used by the FDA to monitor the safety of vaccines." Lind P. U.S. court pays $6 million to Gardasil victims. *The Washington Times* December 31, 2014 https://www.washingtontimes.com/news/2014/dec/31/us-court-pays-6-million-gardasil-victims/

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