CME
CONTINUING MEDICAL EDUCATION

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

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. Gilbert Manso, MD, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. John Cannell, MD, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 2 hours.

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

Reprint requests: InnoVision Communications, 169 Saxony Rd, Suite 103, Encinitas, CA 92024; phone, (760) 633-3910 or (866) 828-2962; fax, (760) 633-3918; e-mail, alternative.therapies@innerdoorway.com. Or visit our online CME Web site by going to http://www.alternative-therapies.com and selecting the Continuing Education option.

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)

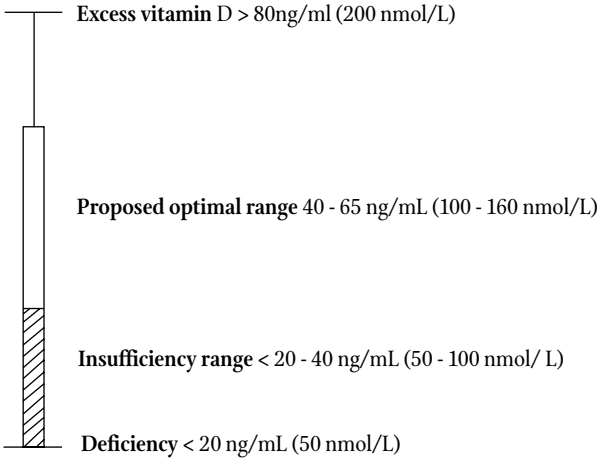
Based on our review of the literature, we propose that the optimal—"sufficient and safe"—range for 25(OH)D correlates with serum levels of 40–65 ng/mL (100–160 nmol/L).[55] This proposed optimal range is compatible with other published recommendations: Zittermann[11] states that serum levels of 40–80 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.



***** Modified from: Vasquez A. *Integrative Orthopedics: Concepts, Algorithms, and Therapeutics.* Houston; Natural Health Consulting Corporation. 2004: 417-419 with permission.

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.

References

1. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999;69(5):842-56.
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(1):204-10.
3. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79(3):362-71.
4. 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(2):288-94.
5. Heaney RP. Long-latency deficiency disease: insights from calcium and vitamin D. *Am J Clin Nutr.* 2003;78(5):912-9.
6. Holick MF. Calcium and Vitamin D. Diagnostics and Therapeutics. *Clin Lab Med*. 2000;20(3):569-90.
7. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone levels predict coronary heart disease: the Tromso Study. *Eur J Cardiovasc Prev Rehabil*. 2004;11(1):69-74.
8. Sato Y, Kaji M, Metoki N, Satoh K, Iwamoto J. Does compensatory hyperparathyroidism predispose to ischemic stroke? *Neurology.* 2003;60(4):626-9.
9. Fujita T. Calcium paradox: consequences of calcium deficiency manifested by a wide variety of diseases. *J Bone Miner Metab.* 2000;18(4):234-6.
10. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab*. 2001;86(2):888-94.
11. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr.* 2003;89(5):552-72.
12. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer.* 2002;94(6):1867-75.
13. Apperly FL. The relation of solar radiation to cancer mortality in North America. *Cancer Res.* 1941;1:191-5.
14. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology* (Berl). 1998;135(4):319-23.
15. Christiansen C, Rodbro P, Sjo O. "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. *Br Med J.* 1974;2(913):258-9.
16. 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(10):4623-32.
17. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM*. 2002;95:787-96.
18. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet.* 2001;358(9292):1500-3.
19. Goldberg P, Fleming MC, Picard EH. Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. *Med Hypotheses.* 1986 Oct;21(2):193-200.
20. Cantorna MT. Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? *Proc Soc Exp Biol Med*. 2000;223(3):230-3
21. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. *Eur J Clin Nutr.* 2004;58(4):563-7.
22. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. *Int J Epidemiol.* 1981;10(4):337-41
23. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol.* 1990;19(3):559-63.
24. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol.* 2003;41:105-12.
25. Gulati S, Bajpai A, Juneja R, Kabra M, Bagga A, Kalra V. Hypocalcemic heart failure masquerading as dilated cardiomyopathy. *Indian J Pediatr.* 2001;68(3):287-90.
26. Brunvand L, Haga P, Tangsrud SE, Haug E. Congestive heart failure caused by vitamin D deficiency? *Acta Paediatr.* 1995;84(1):106-8.
27. Kini SM, Pednekar SJ, Nabar ST, Varthakavi P. A reversible form of cardiomyopathy. *J Postgrad Med.* 2003;49(1):85-7.
28. Olgun H, Ceviz N, Ozkan B. A case of dilated cardiomyopathy due to nutritional vitamin D deficiency rickets. *Turk J Pediatr.* 2003;45(2):152-4.
29. Price DI, Stanford LC Jr, Braden DS, Ebeid MR, Smith JC. Hypocalcemic rickets: an unusual cause of dilated cardiomyopathy. *Pediatr Cardiol.* 2003;24(5):510-2.
30. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension.* 1997;30(2 Pt 1):150-6.
31. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet.* 1998;352(9129):709-10.
32. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab.* 2001;86(4):1633-7.
33. Chiu KC, Chu A, Vay LWG, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr.* 2004; 79:820-5.
34. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract.* 2003;57(4):258-61.
35. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, Rush D, Wilson PW, Jacques P. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med.* 1996;125(5):353-9.
36. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, Nevitt MC. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum.* 1999;42(5):854-60.
37. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J Neuroimmunol.* 2003;134(1-2):128-32.
38. Gloth FM 3rd, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging.* 1999;3(1):5-7
39. Johnson GH, Willis F. Seizures as the presenting feature of rickets in an infant. *Med J Aust.* 2003;178(9):467; discussion 467-8.
40. Ali FE, Al-Bustan MA, Al-Busairi WA, Al-Mulla FA. Loss of seizure control due to anticonvulsant-induced hypocalcemia. *Ann Pharmacother.* 2004;38(6):1002-5
41. Thys-Jacobs S. Vitamin D and calcium in menstrual migraine. *Headache*. 1994 Oct;34(9):544-6.
42. Thys-Jacobs S, Donovan D, Papadopoulos A, Sarrel P, Bilezikian JP. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. *Steroids*. 1999;64(6):430-5.
43. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc.* 2003;78(12):1463-70
44. Masood H, Narang AP, Bhat IA, Shah GN. Persistent limb pain and raised serum alkaline phosphatase the earliest markers of subclinical hypovitaminosis D in Kashmir. *Indian J Physiol Pharmacol.* 1989;33(4):259-61.
45. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine.* 2003;28(2):177-9.
46. Yamashita H, Noguchi S, Takatsu K, Koike E, Murakami T, Watanabe S, Uchino S, Yamashita H, Kawamoto H. High prevalence of vitamin D deficiency in Japanese female patients with Graves' disease. *Endocr J.* 2001;48(1):63-9.
47. Falkenbach A, Tripathi R, Sedlmeyer A, Staudinger M, Herold M. Serum 25-hydroxyvitamin D and parathyroid hormone in patients with ankylosing spondylitis before and after a three-week rehabilitation treatment at high altitude during winter and spring. *Wien Klin Wochenschr.* 2001;113(9):328-32.
48. Huisman AM, White KP, Algra A, Harth M, Vieth R, Jacobs JW, Bijlsma JW, Bell DA. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol.* 2001;28(11):2535-9.
49. Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs--a brief overview. *Mol Cell Biochem.* 2003;253(1-2):247-54.
50. Trouillas P, Honnorat J, Bret P, Jouvet A, Gerard JP. Redifferentiation therapy in brain tumors: long-lasting complete regression of glioblastomas and an anaplastic astrocytoma under long term 1-alpha-hydroxycholecalciferol. *J Neurooncol.* 2001;51(1):57-66
51. Holick MF. Vitamin D deficiency: what a pain it is. *Mayo Clin Proc*. 2003;78(12):1457-9
52. Wright JV. Vitamin D: Its Role in Autoimmune Disease and Hypertension. *Townsend Letter for Doctors and Patients*. 2004; May #250: 75-78.
53. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. *Am J Clin Nutr.* 1997;65(1):67-71.
54. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr*. 1998;67(2):342-8.
55. Vasquez A. *Integrative Orthopedics: Concepts, Algorithms, and Therapeutics.* Houston; Natural Health Consulting Corporation (www.OptimalHealthResearch.com): 2004. Pages 417-419 and website updates.
56. Mercola J. Available at: http://www.mercola.com/forms/vitamind.htm. Accessed July 23, 2004.
57. Mercola J. Test Values and Treatment for Vitamin D Deficiency. Available at: http://www.mercola.com/2002/feb/23/vitamin_d_deficiency.htm. Accessed July 23, 2004.
58. Berkow R, Fletcher AJ. *The Merck Manual of Diagnosis and Therapy.* Fifteenth Edition. Rathway; Merck Sharp and Dohme Research Laboratories. 1987: 928, 974-5.
59. Bucci LR, Pillors M, Medlin R, Henderson R, Stiles JC, Robol HJ, Sparks WS. Enhanced uptake in humans of coenzyme Q10 from an emulsified form. Third International Congress of Biomedical Gerontology; Acapulco, Mexico: June 1989.
60. Bucci LR, Pillors M, Medlin R, Klenda B, Robol H, Stiles JC, Sparks WS. *Enhanced blood levels of coenzyme Q-10 from an emulsified oral form.* In Faruqui SR and Ansari MS (editors). Second Symposium on Nutrition and Chiropractic Proceedings. April 15-16, 1989 in Davenport, Iowa
61. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 2004;79(5):717-26.
62. O'Leary JA, Klainer LM, Neuwirth RS. The management of hypoparathyroidism in pregnancy. *Am J Obstet Gynecol.* 1966;94(8):1103-7.
63. Goodenday LS, Gordon GS. No risk from vitamin D in pregnancy. *Ann Intern Med*. 1971;75(5):807-8.
64 Horrobin DF. Interactions between n-3 and n-6 essential fatty acids (EFAs) in the regulation of cardiovascular disorders and inflammation. *Prostaglandins Leukot Essent Fatty Acids.* 1991;44(2):127-31.
65. Utiger RD. The need for more vitamin D. *N Engl J Med*. 1998;338:828-9
66. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338(12):777-83.
67. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med.* 2004;158(6):531-7.
68. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* 2002;76:187-92.
69. Buffington C, Walker B, Cowan GS Jr, Scruggs D. Vitamin D Deficiency in the Morbidly Obese. *Obes Surg.* 1993;3:421-424.
70. Fraser DR. Vitamin D-deficiency in Asia. *J Steroid Biochem Mol Biol.* 2004;89-90:491-5
71. Kauppinen-Makelin R, Tahtela R, Loyttyniemi E, Karkkainen J, Valimaki MJ. A high prevalence of hypovitaminosis D in Finnish medical in- and outpatients. *J Intern Med*. 2001;249(6):559-63.
72. Ellis A. Inertia on folic acid has caused thousands of unnecessary deaths. *BMJ*. 2003;326(7398):1054.
73. Grant WB. Personal communication by email, "My current estimate is 47,000 premature cancer deaths/year." June 3, 2004.

CME

CONTINUING MEDICAL EDUCATION

CME TEST INSTRUCTIONS

To receive 2.0 hours of CME credit for this article, visit www.cecmeonline.com, log in, purchase the CME course for $10 and take the online test. This test is valid for 1 year from the date of publication. Within 3 to 4 weeks of InnoVision Communications receiving your completed online test, you will receive a CME certificate.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. InnoVision Communications designates these educational activities on an hour-for-hour basis toward category 1 credit of the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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

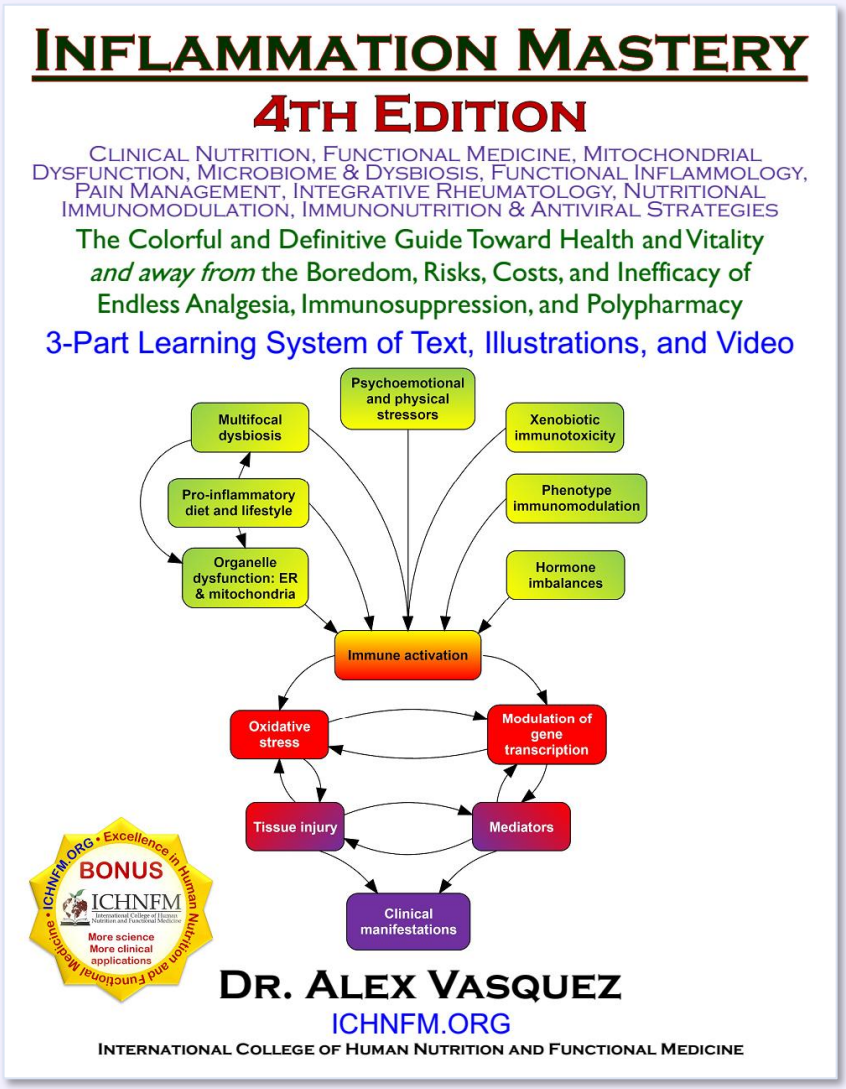
8. Since vitamin D has a wide margin of safety, patients should be administered vitamin D routinely and receive which of the following types of monitoring:
   A. Periodic measurement of serum 1,25-dihydroxyvitamin D (calcitriol) and urinary creatinine
   B. Periodic measurement of serum 25-hydroxyvitamin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

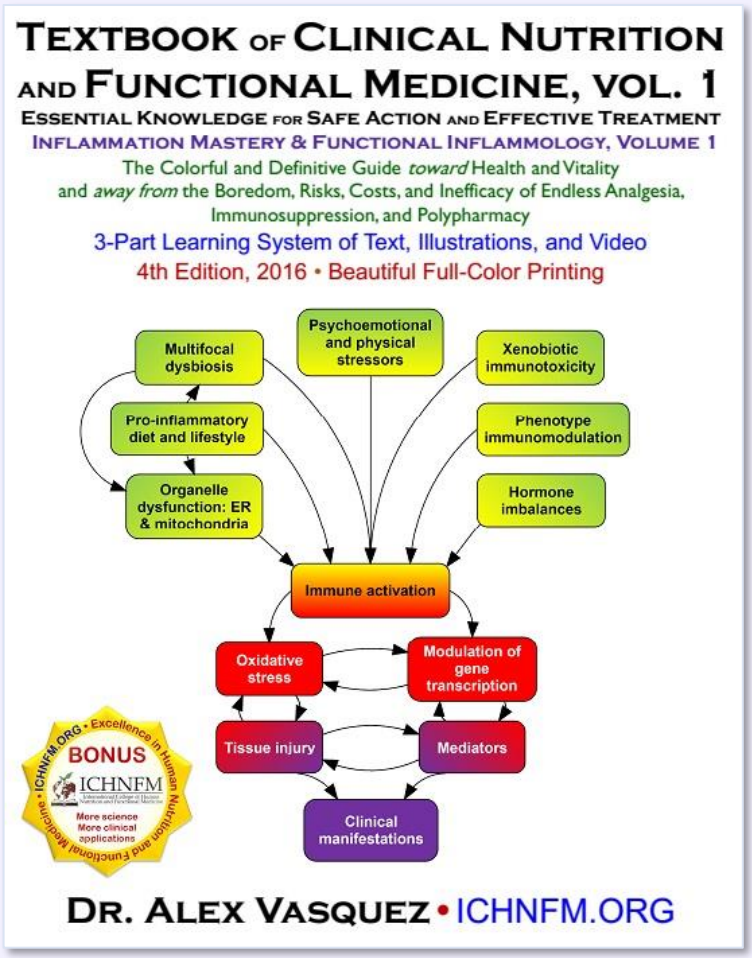
See page 94 for Self-Assessment answers

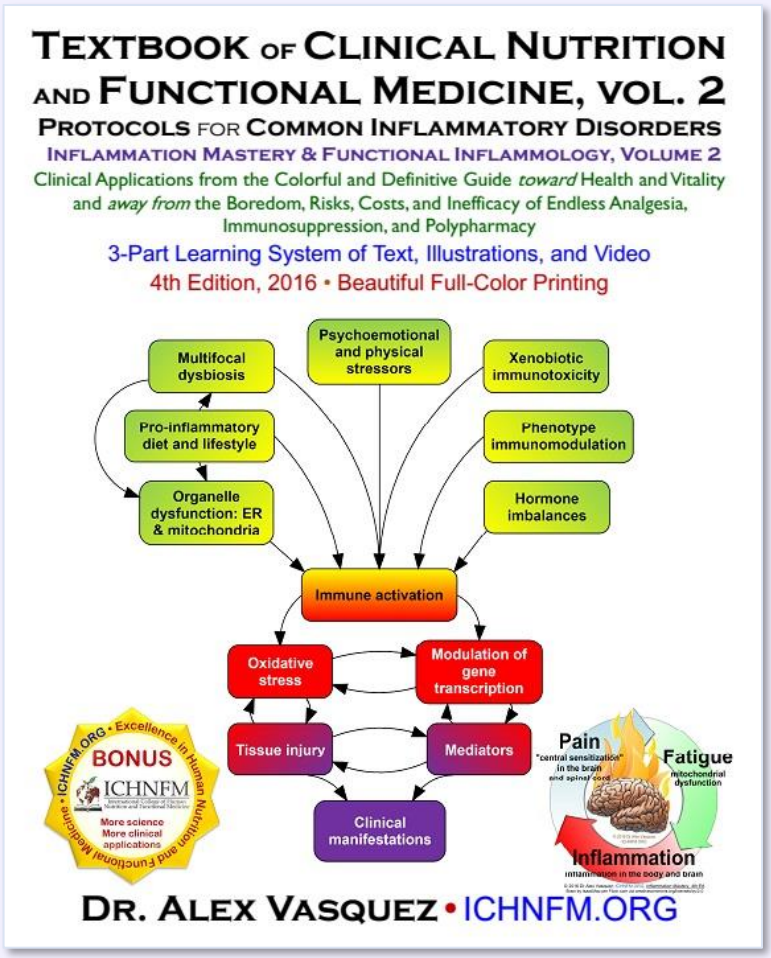
As of 2019 and for the foreseeable future, the most current versions of all major patient management and clinical treatment protocols are published in ***Inflammation Mastery, 4th Edition*** as a single volume of 1,182 pages available in full-color print at discounted pricing directly from ICHNFM from https://www.ichnfm.org/im4, while the digital formats are available via several different platforms, including Amazon's Kindle (free) software, Barnes and Noble's Nook, Apple iBook, etc as hyperlinked below. Per popular request by students who were studying (as a required textbook) only one section at a time, "IM4" was also published in two easier-to-carry separate volumes under the name ***Textbook of Clinical Nutrition and Functional Medicine***, which contain chapters 1-4 (pages 1-712+index) and 5 (713-1154+index), respectively. Video access is included with ***IM4*** and ***TCNFM,1+2***.

Availability in print and digital formats (examples):

- https://www.**ichnfm**.org/im4
- https://www.**amazon**.com/Inflammation-Mastery-4th-Immunosuppression-Polypharmacy-ebook/dp/B01KMZZLAQ
- https://books.**apple**.com/us/author/alex-vasquez/id1139497284
- https://www.**barnesandnoble**.com/w/inflammation-mastery-4th-edition-alex-vasquez/1123259586?ean=9780990620464







bmj.com

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.

Alex Vasquez, *researcher*

Biotics Research Corporation, 6801 Biotics Research Drive, Rosenberg, TX 77471, USA avasquez@bioticsresearch.com

John Cannell, *president*

Vitamin D Council, 9100 San Gregorio Road, Atascadero, CA 93422, USA

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.

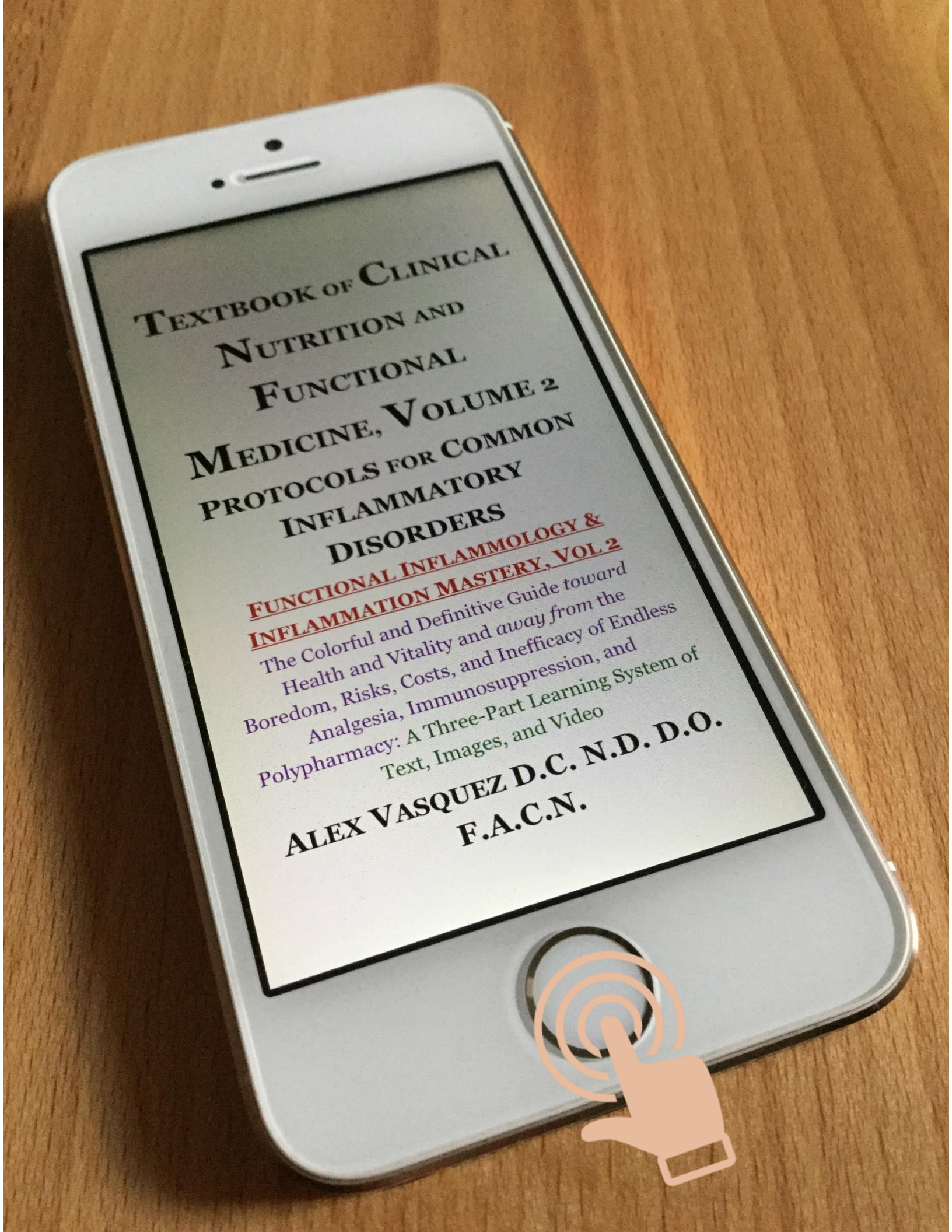
References

1. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ* 2005;330: 1003. (30 April.)[Abstract/Free Full Text]
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.[Abstract/Free Full Text]
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.[Abstract/Free Full Text]
4. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999;69: 842-56.[Abstract/Free Full Text]
5. 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;10: 28-36.[ISI][Medline]

Related Article

Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care
Jill Porthouse, Sarah Cockayne, Christine King, Lucy Saxon, Elizabeth Steele, Terry Aspray, Mike Baverstock, Yvonne Birks, Jo Dumville, Roger Francis, Cynthia Iglesias, Suezann Puffer, Anne Sutcliffe, Ian Watt, and David J Torgerson
BMJ 2005 330: 1003. [Abstract] [Full Text]

BMJ. 2005 Jul 9;331(7508):108-9; author reply 109.
Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy.
Vasquez A, Cannell J.
Comment on: Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. [*BMJ.* 2005] PMID: 16002891 PMCID: PMC558659 DOI:10.1136/bmj.331.7508.108-b


Textbook of Clinical Nutrition and Functional Medicine, Volume 2
Protocols for Common Inflammatory Disorders
Functional Inflammology & Inflammation Mastery, Vol 2
The Colorful and Definitive Guide toward Health and Vitality and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy: A Three-Part Learning System of Text, Images, and Video
Alex Vasquez D.C. N.D. D.O. F.A.C.N.

Comments on:

Articles:
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 - Vol. 365, Number 9471, 07 May 2005, Pages 1621-1628
Summary | Full Text

Add your comments to this article

Viewing 1- of NaN Comments

Comments Page: [1]

Subphysiologic Doses of Vitamin D are Subtherapeutic: Comment on the Study by The Record Trial Group
Alex Vasquez, May 06 2005

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

http://www.ajcn.org/cgi/reprint/69/5/842.pdf 8. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Thomsen J, Charles P, Eriksen EF. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med. 2000;247:260-8 9. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338:777-83 10. Dubbelman R, Jonxis JH, Muskiet FA, Saleh AE. Age-dependent vitamin D status and vertebral condition of white women living in Curacao (The Netherlands Antilles) as compared with their counterparts in The Netherlands. Am J Clin Nutr 1993;58:106-9 11. Kauppinen-Makelin R, Tahtela R, Loyttyniemi E, Karkkainen J, Valimaki MJ. A high prevalence of hypovitaminosis D in Finnish medical in- and outpatients. J Intern Med. 2001;249:559-63 12. 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;10:28-36; quiz 37, 94 13. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. Am J Clin Nutr 1998;67:342-8 14. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. Am J Clin Nutr 1997;65:67-71 15. Harris SS, Dawson-Hughes B, Perrone GA. Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D. J Am Coll Nutr. 1999;18:470-4 16. Barragry JM, France MW, Corless D, Gupta SP, Switala S, Boucher BJ, Cohen RD. Intestinal cholecalciferol absorption in the elderly and in younger adults. Clin Sci Mol Med. 1978;55:213-20 17. Tsai KS, Heath H 3rd, Kumar R, Riggs BL. Impaired vitamin D metabolism with aging in women. Possible role in pathogenesis of senile osteoporosis. J Clin Invest. 1984;73:1668-72 18. Gallagher JC, Riggs BL, Eisman J, Hamstra A, Arnaud SB, DeLuca HF. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: effect of age and dietary calcium. J Clin Invest. 1979;64:729-36 19. Ebeling PR, Sandgren ME, DiMagno EP, Lane AW, DeLuca HF, Riggs BL. Evidence of an age-related decrease in intestinal responsiveness to vitamin D: relationship between serum 1,25-dihydroxyvitamin D3 and intestinal vitamin D receptor concentrations in normal women. J Clin Endocrinol Metab. 1992;75:176-82 20. Gallo-Torres HE. Obligatory role of bile for the intestinal absorption of vitamin E. Lipids. 1970;5:379-84 21. Bucci LR, Pillors M, Medlin R, Henderson R, Stiles JC, Robol HJ, Sparks WS. Enhanced uptake in humans of coenzyme Q10 from an emulsified form. Third International Congress of Biomedical Gerontology; Acapulco, Mexico: June 1989 22. Bucci LR, Pillors M, Medlin R, Klenda B, Robol H, Stiles JC, Sparks WS. Enhanced blood levels of coenzyme Q-10 from an emulsified oral form. In Faruqui SR and Ansari MS (editors). Second Symposium on Nutrition and Chiropractic Proceedings. April 15-16, 1989 in Davenport, Iowa 23. Stepan JJ, Burckhardt P, Hana V. The effects of three-month intravenous ibandronate on bone mineral density and bone remodeling in Klinefelter's syndrome: the influence of vitamin D deficiency and hormonal status. Bone 2003;33:589-596 24. Vasquez A. Health care for our bones: a practical nutritional approach to preventing osteoporosis. [letter] J Manipulative Physiol Ther. 2005;28:213

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

References: None

Back to Top

Viewing 1- of NaN Comments

Comments Page: [1]

Additional articles and book excerpts have been amended to the previous publication in order to provide context and orientation to the author's main works.

BOOK EXCERPTS, CHAPTERS:

- https://www.amazon.com/Dr-Alex-Vasquez/e/B00AT5764Y
- https://www.ichnfm.org/im4
- https://www.ichnfm.org/volume-1-essential-knowledge
- https://www.ichnfm.org/volume-2-inflammatory-disorders

PDF articles: Full-text archives of the author's articles are available per the following:

- **https://ichnfm.academia.edu/AlexVasquez (main archive/repository)**
- https://www.researchgate.net/profile/Alex_Vasquez2 (archive/repository)
- https://www.inflammationmastery.com/reprints (cloud-based PDF folder)
- https://www.ichnfm.org/public

VIDEOS: Access to public videos is available per the following:

- **Main archive: https://vimeo.com/drvasquez**
- See also: https://www.ichnfm.org/public
- And to a lesser extent: https://www.youtube.com/channel/UCPR2pgwFw9L2GUnBgupQ5Aw

WEBSITES:

- **Main: https://www.inflammationmastery.com/**
  - Antiviral: https://www.inflammationmastery.com/antiviral
  - Fibromyalgia: https://www.inflammationmastery.com/fibromyalgia
  - Migraine: https://www.inflammationmastery.com/migraine
  - Complete protocol: https://www.inflammationmastery.com/book-nutrition-functional-medicine
- **Main: https://www.ichnfm.org/ This is actually a very rich website with many blogs and videos**
  - https://www.ichnfm.org/antiviral2019 and the long series starting with https://www.ichnfm.org/antiviral, https://www.ichnfm.org/antiviral2, https://www.ichnfm.org/antiviral3, https://www.ichnfm.org/antiviral4, and continuing…
  - https://www.ichnfm.org/braininflammation

SOCIAL MEDIA UPDATES: Note that updates are made on a regular basis to the following social medial pages, with some overlap but also some topic-specific specialization, which is self-explanatory by the titles of these pages:

- **Dr Alex Vasquez 's Inflammation Mastery https://www.facebook.com/InflammationMastery**
- Migraine Headaches, Hypothyroidism, and Fibromyalgia https://www.facebook.com/MigraineHypothyroidismFibromyalgia
- International Journal of Human Nutrition and Functional Medicine https://www.facebook.com/IJHNFM
- International College of Human Nutrition and Functional Medicine (higher quality and academic news) https://www.facebook.com/IntCollHumNutrFunctMed
- Revista Latinoamericana de Nutrición Humana y Medicina Funcional https://www.facebook.com/RevLatinoNutrHumMedFunc
- Antiviral Nutrition https://www.facebook.com/AntiviralNutrition
- NaturopathicRheumatology https://www.facebook.com/NaturopathicRheumatology

Inflammation Mastery

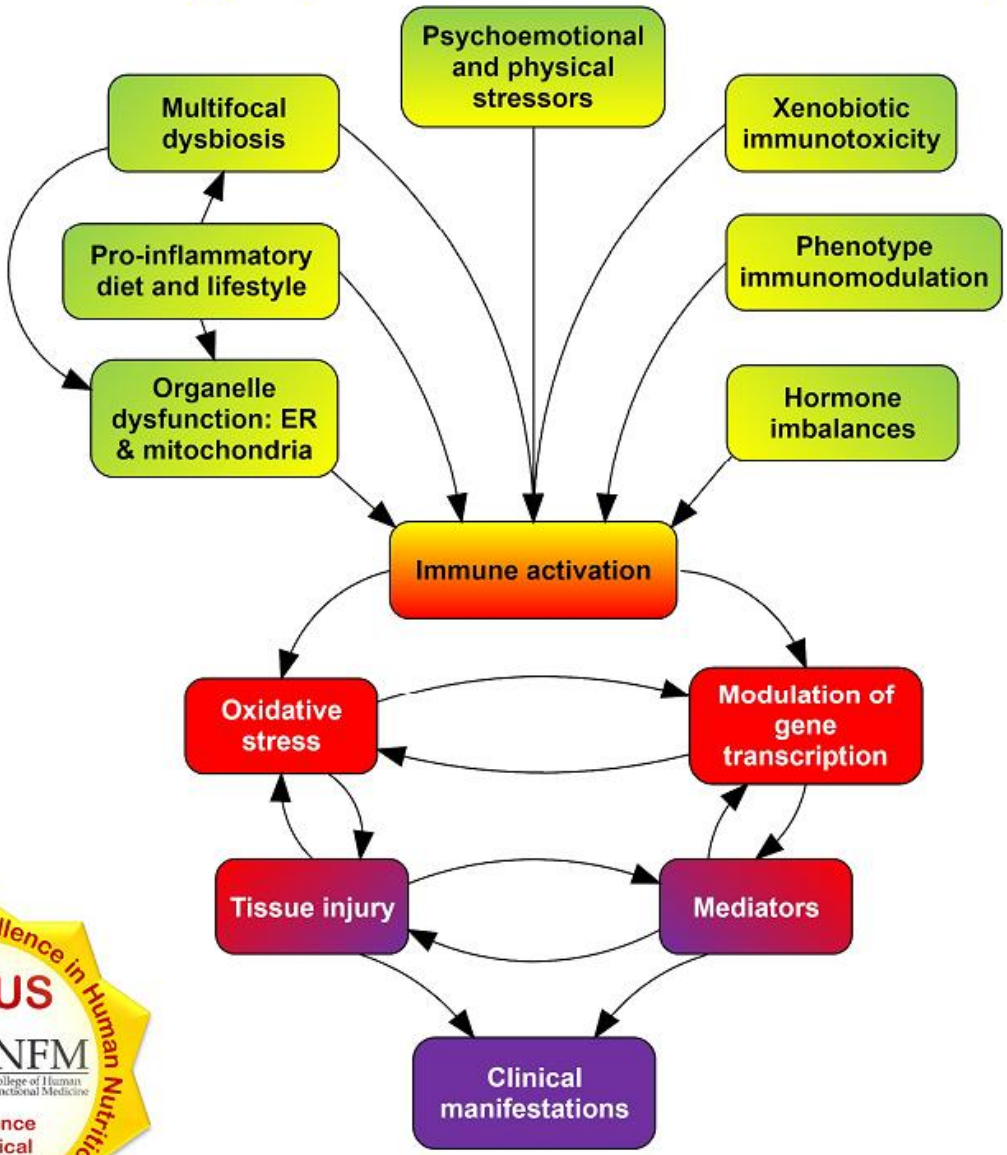
4th Edition

Clinical Nutrition, Functional Medicine, Mitochondrial Dysfunction, Microbiome & Dysbiosis, Functional Inflammology, Pain Management, Integrative Rheumatology, Nutritional Immunomodulation, Immunonutrition & Antiviral Strategies

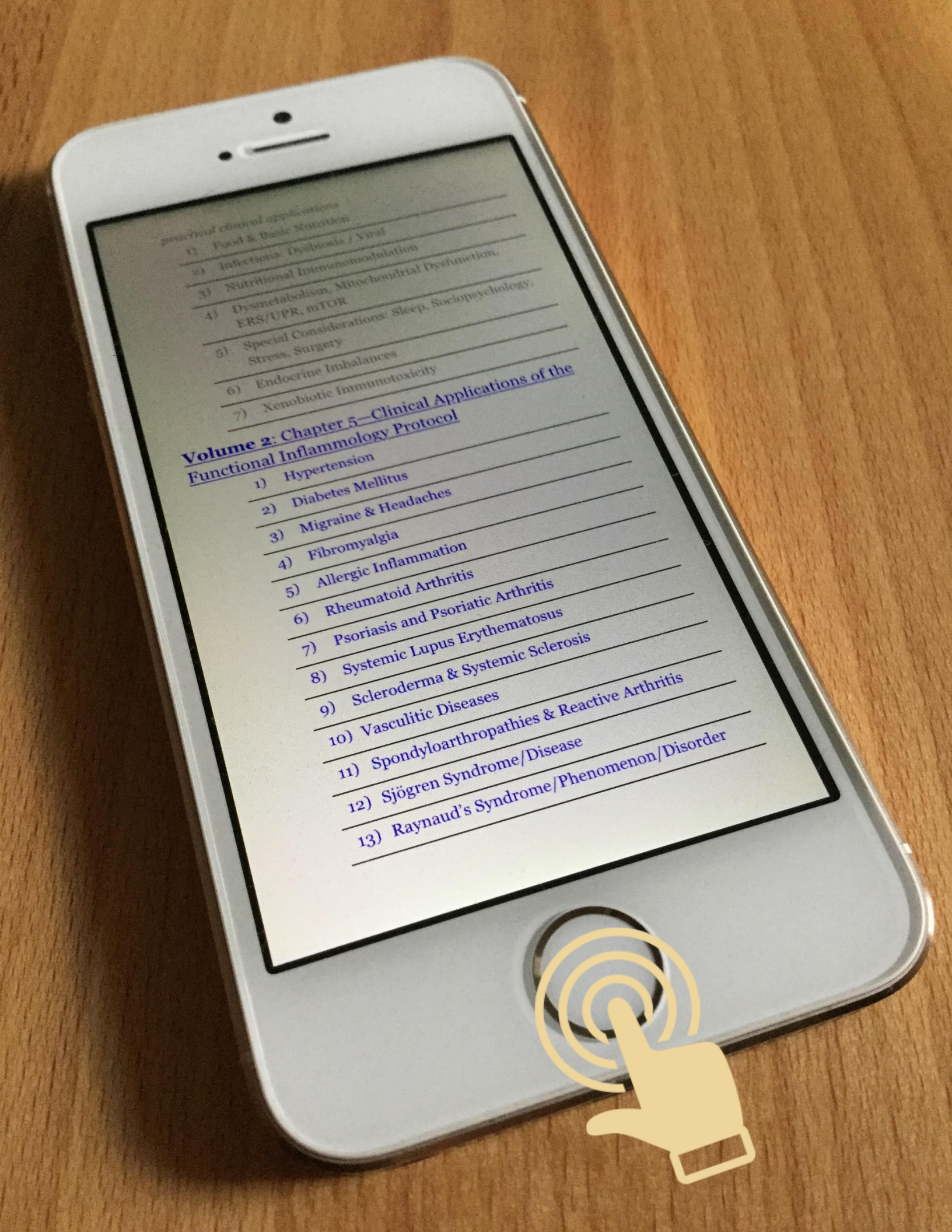
The Colorful and Definitive Guide Toward Health and Vitality

and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy

3-Part Learning System of Text, Illustrations, and Video



Dr. Alex Vasquez
ICHNFM.ORG
International College of Human Nutrition and Functional Medicine


practical clinical applications
1) Food & Basic Nutrition
2) Infections: Dysbiosis / Viral
3) Nutritional Immunomodulation
4) Dysmetabolism, Mitochondrial Dysfunction, ERS/UPR, mTOR
5) Special Considerations: Sleep, Sociopsychology, Stress, Surgery
6) Endocrine Imbalances
7) Xenobiotic Immunotoxicity
Volume 2: Chapter 5—Clinical Applications of the Functional Inflammology Protocol
1) Hypertension
2) Diabetes Mellitus
3) Migraine & Headaches
4) Fibromyalgia
5) Allergic Inflammation
6) Rheumatoid Arthritis
7) Psoriasis and Psoriatic Arthritis
8) Systemic Lupus Erythematosus
9) Scleroderma & Systemic Sclerosis
10) Vasculitic Diseases
11) Spondyloarthropathies & Reactive Arthritis
12) Sjögren Syndrome/Disease
13) Raynaud's Syndrome/Phenomenon/Disorder

Inflammation Mastery

4th Edition: The Colorful and Definitive Guide toward Health and Vitality and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy

A Three-Part Learning System of Text, Images, and Video

Alex Vasquez D.C. N.D. D.O. F.A.C.N.

- Doctor of Osteopathic Medicine, graduate of University of North Texas Health Science Center, Texas College of Osteopathic Medicine (2010)
- Doctor of Naturopathic Medicine, graduate of Bastyr University (1999)
- Doctor of Chiropractic, graduate of University of Western States (1996)
- Fellow of the American College of Nutrition (2013-present)
- Former Overseas Fellow of the Royal Society of Medicine
- Editor, *International Journal of Human Nutrition and Functional Medicine* IntJHumNutrFunctMed.org. Former Editor, *Naturopathy Digest*; Former/Recent Reviewer for *Journal of Naturopathic Medicine*, *Alternative Therapies in Health and Medicine*, *Autoimmune Diseases*, *International Journal of Clinical Medicine*, and *PLOS One*
- Private practice of integrative and functional medicine in Seattle, Washington (2000-2001), Houston, Texas (2001-2006), Portland, Oregon (2011-2013), consulting practice (present)
- Consultant Researcher and Lecturer (2004-present), Biotics Research Corporation
- Teaching and Academics:
    - Director of Programs, International College/Conference on Human Nutrition and Functional Medicine ICHNFM.org
    - Founder and Former Program Director of the world's first accredited university-affiliated graduate-level program in Functional Medicine
    - Adjunct Professor, Integrative and Functional Nutrition in Immune Health, Doctor of Clinical Nutrition program at Maryland University of Integrative Health
    - Former Adjunct Professor (2009-2013) of Laboratory Medicine, Master of Science in Advanced Clinical Practice
    - Former Faculty (2004-2005, 2010-2013) and Forum Consultant (2003-2007), The Institute for Functional Medicine
    - Former Adjunct Professor (2011-2013) of Pharmacology, Evidence-Based Nutrition, Immune and Inflammatory Imbalances, Principles of Functional Medicine, Psychology of Wellness
    - Former Adjunct Professor of Orthopedics (2000), Radiographic Interpretation (2000), and Rheumatology (2001), Naturopathic Medicine Program, Bastyr University
- Author of more than 100 articles and letters published in *JAMA—Journal of the American Medical Association*, *BMJ—British Medical Journal*, *TheLancet.com*, *JAOA—Journal of the American Osteopathic Association*, *Annals of Pharmacotherapy*, *Journal of Clinical Endocrinology and Metabolism*, *Alternative Therapies in Health and Medicine*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics*, *Integrative Medicine*, *Current Allergy and Asthma Reports*, *Nutritional Wellness*, *Evidence-based Complementary and Alternative Medicine*, and *Arthritis & Rheumatism*: Official Journal of the American College of Rheumatology

- 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

[1144] Allen AC et al. A pilot study of the immunological effects of high-dose vitamin D in healthy volunteers. *Mult Scler*. 2012 Dec;18(12):1797-800
[1145] Prietl et al. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D for autoimmune diseases? *Isr Med Assoc J*. 2010;12:136-9
[1146] Smolders J et al. Safety and T cell modulating effects of high dose vitamin D3 supplementation in multiple sclerosis. *PLoS One*. 2010 Dec 13;5(12):e15235
[1147] Hyppönen et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001 Nov 3;358(9292):1500-3
[1148] Terrier B et al. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. *Arthritis Res Ther*. 2012 Oct 17;14(5):R221

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.

CME
CONTINUING MEDICAL EDUCATION

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

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. **Gilbert Manso, MD**, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. **John Cannell, MD**, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 2 hours.

OBJECTIVES

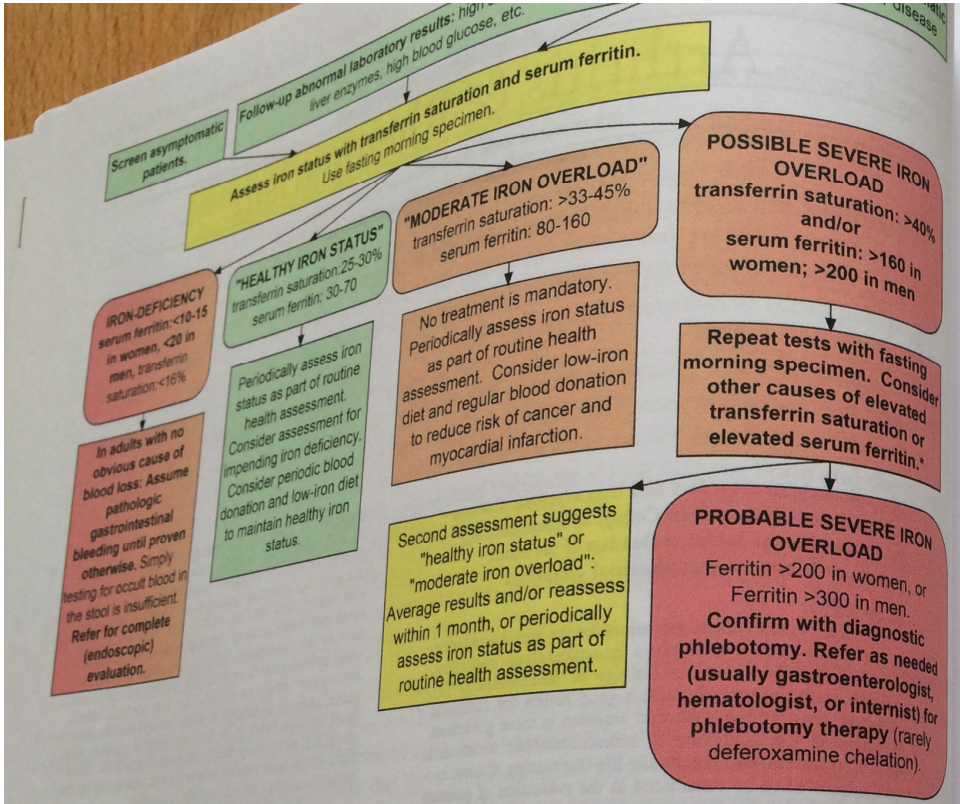
Upon completion of this article, participants should be able to do the following:

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

Reprint requests: InnoVision Communications, 169 Saxony Rd, Suite 103, Encinitas, CA 92024; phone, (760) 633-3910 or (866) 828-2962; fax, (760) 633-3918; e-mail, alternative.therapies@innerdoorway.com. Or visit our online CME Web site by going to http://www.alternative-therapies.com and selecting the Continuing Education option.

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



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.

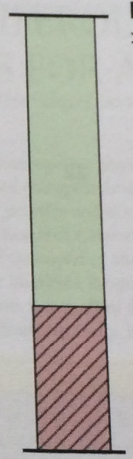
Assess liver status: Liver biopsy or perhaps MRI. Cirrhosis indicates increased risk of hepatocellular carcinoma and reduced life expectancy. Consider liver ultrasound, serum liver enzyme measurement, and serum alpha-fetoprotein o screen for hepatocellular carcinoma every 6 months. Hepatoma surveillance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

International Journal of Human Nutrition and Functional Medicine

International Journal of Human Nutrition and Functional Medicine® www.IntJHumNutrFunctMed.org
(ISSN 2378-4881) is published and © copyrighted by the
International College of Human Nutrition and Functional Medicine® www.ICHNFM.ORG

ICHNFM
International College of Human Nutrition and Functional Medicine

North America • Latinoamerica • Europe

FREE ACCESS

International Journal of Human Nutrition and Functional Medicine (ISSN 2378-4881) www.ICHNFM.org

Photo of town center and Roman aqueduct in Segovia Spain © 2016 by Dr Vasquez

Expert Perspectives • Clinical Nutrition • Research Methodology • Publication Analysis

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

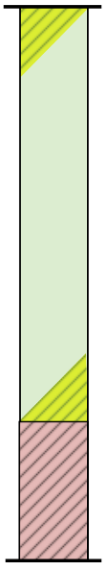
A large percentage of published clinical trials have suffered from flawed design, including inadequate dosing, inadequate duration, wrong type of vitamin D (ie, ergocalciferol, D2), failure to test serum vitamin D levels, and/or failure to ensure that serum vitamin D levels entered into the optimal range. 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.

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.

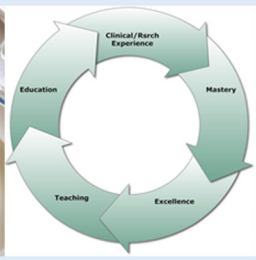
Main citations:

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
2. Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. *BMJ*. 2005 Jul 9;331(7508):108-9
3. 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 Jan;77(1):204-10
4. Gonzalez C. Vitamin D Supplementation: An Update. *U.S. Pharmacist* 2010 Oct uspharmacist.com/article/vitamin-d-supplementation-an-update
5. Vasquez et al. Isoflavones and postmenopausal women. *JAMA*. 2004 Nov 17;292(19):2337
6. Pludowski P, Holick MF, Grant WB, et al. Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol*. 2017 Feb http://dx.doi.org/doi:10.1016/j.jsbmb.2017.01.021
7. Hollis et al. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res*. 2011 Oct;26(10):2341-57
8. Karras et al. Maternal vitamin D levels during pregnancy and neonatal health: evidence to date and clinical implications. *Ther Adv Musculoskelet Dis*. 2016 Aug;8(4):124-35

About the author and presenter: Dr Alex Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic Medicine (Doctor of Osteopathic Medicine, 2010). Dr Vasquez is the author of many textbooks, including Integrative Orthopedics (2004, 2012), Musculoskeletal Pain: Expanded Clinical Strategies (published by the

Institute for Functional Medicine, 2008) now updated and expanded to 1,200 pages as Inflammation Mastery 4th Edition (published as a two-volume set as Textbook of Clinical Nutrition and Functional Medicine), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Brain Inflammation in Migraine and Fibromyalgia (2016), and Mitochondrial Nutrition and Endoplasmic Reticulum Stress in Primary Care (2014). "DrV" has also written more than 100 letters and articles for professional magazines and medical journals such as *Nature Reviews Rheumatology, British Medical Journal* (BMJ), *TheLancet.com*, *Annals of Pharmacotherapy*, *Journal of Clinical Endocrinology and Metabolism*, *Journal of the American Medical Association* (JAMA), *Journal of the American Osteopathic Association* (JAOA), *Alternative Therapies in Health and Medicine*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics* (JMPT), *Current Allergy and Asthma Reports*, *Integrative Medicine*, *Complementary Therapies in Clinical Practice,* and *Arthritis & Rheumatism*—Official Journal of the American College of Rheumatology. Dr Vasquez lectures worldwide to healthcare professionals and provides expert consultations to physicians and patients internationally. As the former Editor of *Naturopathy Digest* and a reviewer for *Journal of Naturopathic Medicine, Alternative Therapies in Health and Medicine*, *PLoS-ONE, Neuropeptides, International Journal of Clinical Medicine, Autoimmune Diseases*, Dr Vasquez is currently the Chief Editor of *International Journal of Human Nutrition and Functional Medicine*.® Additional information with updates and blogs is available at ICHNFM.ORG. All of DrV's books are available at Amazon.com, videos at Vimeo.com/DrVasquez, and selected lecture recordings at iTunes. Dr Vasquez has served as a consultant researcher and lecturer for Biotics Research Corporation in the United States.





International Journal of Human Nutrition and Functional Medicine is a peer-reviewed evidence-based clinically-oriented publication produced quarterly with periodic special releases in print and/or digital formats (per author request/permission and Editor judgment), available as pay-per-issue, free/open access, or as a membership benefit (included or discounted), in English and/or other languages. As the title of the journal indicates, the focus of the journal is human nutrition (i.e., we publish only human-referent information, not animal studies; however, we will publish *translational summaries* of new animal research) and functional medicine, a broad clinical and conceptual discipline that seeks to protect, restore, and optimize human health by appreciating human physiology's systems biology construct and thus the necessity of addressing the totality of factors that influence health and disease outcomes in the *psyche* and *soma* of individual patients as well as the social *corpus* of local and international groups of persons. The journal is dynamic and adaptive; updated information about the journal is available on-line at the website www.IntJHumNutrFunctMed.org. **Statement of Social Responsibility**: Due to the recent mis-use of science and the misuse of prominent positions to mis-direct public opinion away from science and logic, ICHNFM has found necessity in forming a statement of social responsibility. ICHNFM requires—starting in 2015—that educational materials be socially contextualized with a humanistic emphasis; humanism is a philosophical and ethical stance that emphasizes the value and agency of human beings, individually and collectively, and requires critical thinking and evidence (rationalism, empiricism). In direct opposition to any notion that science and intellectual work are and should be separate from the goal of benefiting human life (ie, financial profiteering, or political misuse of science), we affirm that work in the sciences, healthcare, and medicine should hold preeminent the goal of providing benefit to humanity at large and not private or political interests, in particular what we have defined as the goals of healthcare: physical health and psychosocial freedom, both of which are required for the optimization of human potential and human culture. Likewise, faculty members and teaching staff are required to model beneficence, nonmaleficence, ethics, and justice; repeated violations of these ethical considerations will result first in conversation and if not resolved will result in termination of any working relationship because ICHNFM will maintain its ethics and integrity and will not be tainted by affiliation with faculty or presenters who are socially reckless or maleficent, regardless of the scale or medium (ie, including private emails and public/social conversations and comments). ICHNFM will maintain the highest standards of science, clinical applicability, ethics, and social effect/influence/beneficence.

Notable publications in 2014—❶ Lab Fraud in Functional Medicine, ❷ ISIFMC Position on HPS2-THRIVE; ❸ Unified Antiviral Strategy, ❹ Metabolic Correction: www.ichnfm.org/publications/IJHNFM_2014_review.pdf

Journal title, ISSN:	***International Journal of Human Nutrition and Functional Medicine*** **ISSN: 2378-4881**
Abbreviation:	*Int J Hum Nutr Funct Med*
Websites:	**www.IntJHumNutrFunctMed.org and www.ICHNFM.ORG**
Facebook.com	https://www.facebook.com/IJHNFM and https://www.facebook.com/ICHNFM
Editor-in-Chief	**Alex Vasquez DC ND DO FACN**
Review Staff 2014/2015—see website for updated list of reviewers	Sergio Abanades MS MD PhD, Michael Gonzalez MS MHSN DSc PhD FACN, Ryan Bradley ND MPH, Jill Carnahan MD, Deanna Minich PhD FACN, David H Haase MD, Steve Hickey PhD, Jorge R Miranda-Massari DrPh, Tim Jackson DPT CNS, Dorothy D Zeviar EdD LAc MPH CPH, Kenneth Cintron MD, Annette D'Armata NMD, Tariq Shafi MD, Joseph Iaccino DC MS, Nick Karapasas DC, Jerry Bailey DC MS, Ismael Samudio PhD, Pedro Bastos MA MS (PhD candidate at Lund University, Sweden), Maelan Fontes MS (PhD candidate at Lund University, Sweden), Terri Ward CPA, MS, Sayer Ji BA, Julie Jean BS BSN RN, Thomas Easley, Mathieu Bouchard

ICHNFM
International College of Human Nutrition and Functional Medicine

Upcoming CE/CME Events: Delivered to your home or office

What makes this system great:

- Your convenience: Learn at your leisure, at your own pace, in the comfort of your own space. Access the materials anytime, even after completion of the program
- Your preference: Order the monograph in full-color or black-and-white to be delivered to your home or office—see descriptive videos: #1: https://vimeo.com/128642618, #2: https://vimeo.com/129841003
- Discounts: Discount code for printed monograph provided on website
- Applicability: Strong foundation in molecular biology, translated for immediate clinical use
- Discussions, perspectives, experiences: Online forums and live discussions available
- Time-efficiency: Save money, time, energy and *the massive carbon footprint* from the hassle of travel (taxis, airport security and waiting, flying, hotels…) just for a conference; use your travel time for your own *real* vacation—not for work, just to sit in a conference

Important clinical topics:

1. Dysbiosis and the Microbiome
2. Mitochondrial Medicine and Mitochondrial Nutrition in Primary and Specialty Care
3. Nutritional Immunomodulation for the Treatment of Allergy and Autoimmunity
4. Implications of Xenobiotic/POP (Persistent Organic Pollutant) Accumulation in the Pathogenesis of Clinical Disease: Evidence-Based Practical Detoxification Interventions
5. More details posted at http://www.ichnfm.org/course-microbiome-dysbiosis

ICHNFM provides *R.E.A.L.* continuing education

- Rigorous: Experience the difference with *expert-level* CE/CME
- Engaging: Attendees access the material via several different media—text, graphics, audio-video, interactive sessions, and the final exam
- Accountable: Each program requires a "final exam" to demonstrate competency (not simply "attendance") and awards a Certificate of Achievement with the CE/CME hourly credits
- Life-changing: At every step of the way in the preparation of these educational materials, the primary goals are to improve clinician intellectual understanding and clinical skills, ultimately culminating in improved healthcare delivery and clinical practice success

ICHNFM
International College of Human Nutrition and Functional Medicine

"Throughout the centuries there were men who took first steps down new roads armed with nothing but their own vision. .... The great creators—the thinkers, the artists, the scientists, the inventors—stood alone against the men of their time. Every great new thought was opposed. Every great new invention was denounced. ... But the men of unborrowed vision went ahead. They fought, they suffered and they paid. But they won."

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

Intended for healthcare professionals

Research

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study

BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l1161 (Published 03 April 2019)
Cite this as: BMJ 2019;365:l1161

Linked editorial

The remarkable impact of bivalent HPV vaccine in Scotland

Linked opinion

Bivalent HPV vaccine in Scotland is having a considerable and sustained effect

- Article
- Related content
- Article metrics
- Rapid responses
- Response

Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination

(Word count without footnotes and citations: 934)

In April 2019, Palmer et al [1] published a retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland, and the authors attributed a reduction in HPV prevalence among unvaccinated women with “herd protection.” However the authors did not mention Scotland’s population-wide public health campaigns to address endemic

vitamin D deficiency. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. Vitamin D deficiency results in impaired mucosal and immune defenses and correlates in a dose-dependent manner with increased cervicovaginal HPV infection [2]. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century with landmark publications such as Vieth's authoritative documentation of safety in 1999 [3], Zittermann's "Vitamin D in preventive medicine" in British Journal of Nutrition in 2003 [4], and Vasquez's "Clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers" in 2004 [5] followed by an important partial summary of vitamin D usage guidelines in British Medical Journal in 2005 [6]. These and similarly themed articles have contributed to increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections and various types of cancer. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements to combat the high prevalence of vitamin D deficiency in Scotland [11].

Widespread vitamin D deficiency in Scotland was followed by widespread recommendations for vitamin D supplementation starting in 2006 and 2009. In 2006, Burleigh and Potter published in Scottish Medical Journal [12] stating that, "The prevalence of vitamin D deficiency is high in older outpatients in this geographical area." In 2007, Hyppönen and Power [13] showed that among British adults "Prevalence of hypovitaminosis D in the general population was alarmingly high during the winter and spring, which warrants action at a population level rather than at a risk group level." In 2008, Rhein [14] further specified that "Vitamin D deficiency is widespread in Scotland." In 2009, the Scottish Government acknowledged the need to educate its population about the importance of vitamin D3 supplementation [15]. From that time until the present, the Scottish Government, United Kingdom National Health Services, and various advocacy groups and programs (e.g., ScotsNeedVitaminD.com[16], Healthy Start, which provides vitamin D supplements to all children and pregnant women in Scotland [17]) continue assertive public health campaigns recommending vitamin D supplementation and increased vitamin D production via sun exposure via the "Shine on Scotland" program initiated in 2009 [18] for all of its citizens [19-23].

Vitamin D supplementation has been the subject of many clinical trials documenting anti-

inflammatory, antiviral, and anticancer benefits. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published “Chronical cervical infections and dysplasia (cervical intraepithelial neoplasia [CIN] 1-2): vaginal vitamin D treatment” showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided “very good anti-inflammatory effects” and “good antidysplastic effects” in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they found that vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism and antioxidant status. In 2018, Vahedpoor and colleagues [39] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they observed, “The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively”, thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially invalid and misleading, especially when the authors make no account whatsoever of the national program for vitamin D supplementation which started in the same timeframe. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

[1] Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, Cruickshank M. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019 Apr 3;365:l1161. doi: 10.1136/bmj.l1161
[2] Shim J, Pérez A, Symanski E, Nyitray AG. Association Between Serum 25-Hydroxyvitamin D Level and Human Papillomavirus Cervicovaginal Infection in Women in the United States. J Infect Dis. 2016 Jun 15;213(12):1886-92. doi: 10.1093/infdis/jiw065
[3] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999 May;69(5):842-56
[4] Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003 May;89(5):552-72
[5] 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 https://www.ncbi.nlm.nih.gov/pubmed/15478784
[6] Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. BMJ. 2005 Jul 9;331(7508):108-9 https://doi.org/10.1136/bmj.331.7508.108-b and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC558659/
[7] 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 Jan;77(1):204-10
[8] Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-2014. JAMA. 2017 Jun 20;317(23):2448-2450. doi: 10.1001/jama.2017.4392
[9] "The proportion of adults who report taking dietary supplements (such as vitamins, fish oils, minerals etc) has increased slightly since 1998 (there was no change between 1995 and 1998). In 1998, 15% of men and 16% of women aged 16-64 took some form of dietary supplement, which increased to 20% and 26%, respectively, in 2003." The Scottish Health Survey 2003. Chapter 3 Fruit and Vegetable Consumption and Eating Habits. https://www.webarchive.org.uk/wayback/archive/20180602183443/http://www.... Accessed April 2019
[10] Reddy P, Edwards LR. Magnesium Supplementation in Vitamin D Deficiency. Am J Ther. 2019 Jan/Feb;26(1):e124-e132. doi: 10.1097/MJT.0000000000000538
[11] "Therefore, routine vitamin D supplementation is recommended for all children over 1 year of age and should be continued until 5 years unless the diet is diverse and plentiful." Scottish Government. Nutritional Guidance for Early Years: food choices for children aged 1-5 years in early education and childcare settings. Published: 23 Jan 2006. https://www.gov.scot/publications/nutritional-guidance-early-years-food-... Accessed April 2019
[12] Burleigh E, Potter J. Vitamin D deficiency in outpatients: a Scottish perspective. Scott Med J. 2006 May;51(2):27-31
[13] Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007 Mar;85(3):860-8
[14] Rhein HM. Vitamin D deficiency is widespread in Scotland. BMJ. 2008 Jun 28;336(7659):1451. doi: 10.1136/bmj.39619.479155.3A
[15] Boy wins NHS backing in vitamin D campaign. The Scotsman 2009 December https://www.scotsman.com/news/boy-wins-nhs-backing-in-vitamin-d-campaign... Accessed April 2019
[16] “At scotsneedvitamind.com, we believe the people of Scotland would see health improvements by taking a regular Vitamin D supplement. We think there is enough evidence currently available to make all of us take action, from health care professionals to parents and teachers.” https://scotsneedvitamind.com/about-us/ Accessed April 2019
[17] "The United Kingdom National Health Services created a program called Healthy Start, which offers vouchers for free vitamin D supplements to qualifying pregnant women, women with a baby under one year old and children under the age of five years located in Scotland, Northern Ireland, England and Wales. In April of 2017, the Scottish government partnered with the Healthy Start

program to offer free vitamin D supplements to all Scottish pregnant women, regardless of whether they qualify for vouchers. This joint effort was created to decrease the risk of rickets and other health complications caused by vitamin D deficiency. Scotland offers free vitamin D supplements for all pregnant residents. Posted on: November 28, 2017 by Missy Sturges and John Cannell, MD. https://www.vitamindcouncil.org/scotland-offers-free-vitamin-d-supplemen.... See also: National Health Services Scotland. Vitamin D. https://www2.gov.scot/resource/0038/00386784.pdf Accessed April 2019
[18] Scottish warning over vitamin D levels. 19 September 2010 https://www.bbc.com/news/uk-scotland-11355810 Accessed April 2019
[19] "Following recommendations from the Scientific Advisory Committee on Nutrition (SACN), Scottish Government advice on vitamin D for all age groups has been updated as follows: Everyone age 5 years and above should consider taking a daily supplement of 10 micrograms vitamin D, particularly during the winter months (October – March)." Scottish Government. Vitamin D. https://www2.gov.scot/Topics/Health/Healthy-Living/Food-Health/vitaminD Accessed April 2019
[20] Scottish Government. Vitamin D information for health professionals in Scotland. November 2017 https://www.gov.scot/binaries/content/documents/govscot/publications/pub... Accessed April 2019
[21] "Scots should consider taking vitamin D supplements all-year round, but particularly in autumn and winter, according to new health advice." All Scots advised to take vitamin D says new health guidance. 21 July 2016. https://www.bbc.com/news/uk-scotland-36856176 Accessed April 2019
[22] "International experts are calling for food in Scotland to be fortified with vitamin D, in an attempt to cut the large numbers of people who develop multiple sclerosis at sunshine-deprived northern latitudes." Add vitamin D to Scotland's food – experts: Dosing whole population would help cut levels of multiple sclerosis, say scientists. 23 Dec 2011 https://www.theguardian.com/uk/2011/dec/23/vitamin-d-scotland-food-multi... Accessed April 2019
[23] All Scottish babies should have vitamin D supplement, CMO says. The Pharmaceutical Journal 2017 Nov 30. https://www.pharmaceutical-journal.com/news-and-analysis/news/all-scotti... Accessed April 2019
[24] Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM. 2002 Dec;95(12):787-96
[25] Sánchez-Armendáriz K, García-Gil A, Romero CA, Contreras-Ruiz J, Karam-Orante M, Balcazar-Antonio D, Domínguez-Cherit J. Oral vitamin D3 5000 IU/day as an adjuvant in the treatment of atopic dermatitis: a randomized control trial. Int J Dermatol. 2018 Dec;57(12):1516-1520. doi: 10.1111/ijd.14220
[26] Stallings VA, Schall JI, Hediger ML, Zemel BS, Tuluc F, Dougherty KA, Samuel JL, Rutstein RM. High-dose vitamin D3 supplementation in children and young adults with HIV: a randomized, placebo-controlled trial. Pediatr Infect Dis J. 2015 Feb;34(2):e32-40. doi: 10.1097/INF.0000000000000483
[27] Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. World J Gastroenterol. 2011 Dec 21;17(47):5184-90. doi: 10.3748/wjg.v17.i47.5184
[28] Nimer A, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. World J Gastroenterol. 2012 Feb 28;18(8):800-5. doi: 10.3748/wjg.v18.i8.800

[29] Komolmit P, Kimtrakool S, Suksawatamnuay S, Thanapirom K, Chattrasophon K, Thaimai P, Chirathaworn C, Poovorawan Y. Vitamin D supplementation improves serum markers associated with hepatic fibrogenesis in chronic hepatitis C patients: A randomized, double-blind, placebo-controlled study. Sci Rep. 2017 Aug 21;7(1):8905. doi: 10.1038/s41598-017-09512-7
[30] Jung HC, Seo MW, Lee S, Kim SW, Song JK.Vitamin D3 Supplementation Reduces the Symptoms of Upper Respiratory Tract Infection during Winter Training in Vitamin D-Insufficient Taekwondo Athletes: A Randomized Controlled Trial. Int J Environ Res Public Health. 2018 Sep 14;15(9). pii: E2003. doi: 10.3390/ijerph15092003
[31] Lee MT, Kattan M, Fennoy I, Arpadi SM, Miller RL, Cremers S, McMahon DJ, Nieves JW, Brittenham GM. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. Blood Adv. 2018 May 8;2(9):969-978. doi: 10.1182/bloodadvances.2017013979
[32] Moscarelli L, Annunziata F, Mjeshtri A, Paudice N, Tsalouchos A, Zanazzi M, Bertoni E. Successful treatment of refractory wart with a topical activated vitamin d in a renal transplant recipient. Case Rep Transplant. 2011;2011:368623. doi: 10.1155/2011/368623. Epub 2012 Jan 3.
[33] Aktaş H, Ergin C, Demir B, Ekiz Ö. Intralesional Vitamin D Injection May Be an Effective Treatment Option for Warts. J Cutan Med Surg. 2016 Mar-Apr;20(2):118-22. doi: 10.1177/1203475415602841. Epub 2015 Aug 20
[34] Raghukumar S, Ravikumar BC, Vinay KN, Suresh MR, Aggarwal A, Yashovardhana DP. Intralesional Vitamin D3 Injection in the Treatment of Recalcitrant Warts: A Novel Proposition. J Cutan Med Surg. 2017 Jul/Aug;21(4):320-324. doi: 10.1177/1203475417704180. Epub 2017 Apr 6.
[35] Naresh M. A Study of Effectiveness of Intralesional Vitamin D3 in Treatment of Multiple Cutaneous Warts. IOSR Journal of Dental and Medical Sciences (IOSR -JDMS) 2019:18(3),84-87
[36] Abdel Kareem IM, Ibrahim IM, Fahmy Mohammed SF, Ahmed AA. Effectiveness of intralesional vitamin D3 injection in the treatment of common warts: single-blinded placebo-controlled study. Dermatol Ther. 2019 Mar 28:e12882. doi: 10.1111/dth.12882
[37] Schulte-Uebbing C, Schlett S, Craiut I, Antal L, Olah H. Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment. Dermatoendocrinol 2014 Oct; 6:e27791. doi:10.4161/derm.27791
[38] Vahedpoor Z, Jamilian M, Bahmani F, Aghadavod E, Karamali M, Kashanian M, Asemi Z. Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia: a Randomized, Double-Blind, Placebo-Controlled Trial. Horm Cancer. 2017 Feb;8(1):58-67. doi: 10.1007/s12672-016-0278-x. Epub 2017 Jan 3
[39] Vahedpoor Z, Mahmoodi S, Samimi M, Gilasi HR, Bahmani F, Soltani A, Sharifi Esfahani M, Asemi Z. Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Nutr Metab. 2018;72(2):151-160. doi: 10.1159/000487270. Epub 2018 Feb 21

Competing interests: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, and the human microbiome. Dr Vasquez has served as a consultant to Biotics Research Corporation.

13 April 2019

Alex Vasquez
Physician, author, lecturer, editor
Barcelona, Spain

International Journal of Human Nutrition and Functional Medicine

2015 Spring

1. Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice
2. Interviews with ❶ Drs Lee, ❷ Carnahan, and ❸ Vasquez
3. Review and Open Critique of Shermer's article published in *Scientific American*
4. Vitamin D Iatrogenesis

International Journal of Human Nutrition and Functional Medicine® www.IntJHumNutrFunctMed.org
(ISSN 2378-4881) is published and © copyrighted by the
International College of Human Nutrition and Functional Medicine® www.ICHNFM.ORG

Download PDF
www.ICHNFM.ORG

North America • South America • Europe

FREE ACCESS

International Journal of Human Nutrition and Functional Medicine www.ICHNFM.org

Photos from Spain, France, United States © by Dr Vasquez, 2012-2015

Perspective and Invitation • Evidence-Based Medicine • Nutritional Science • Iatrogenesis

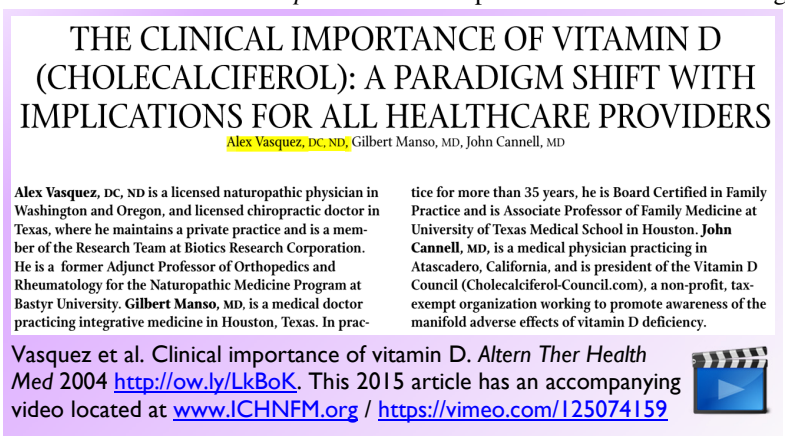
Iatrogenic Induction of Vitamin D Deficiency: The Position Against This Potentially Harmful Practice and Open Invitation for Its Proponents to Articulate Substantiation

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

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. **Gilbert Manso**, MD, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. **John Cannell**, MD, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

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

Citation: Vasquez A. Iatrogenic induction of vitamin D deficiency: The position against this potentially harmful practice and open invitation for its proponents to articulate substantiation. *Int J Hum Nutr Funct Med* 2015;v3(q1):p1

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.

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 ICHNFM.ORG/reprints, direct: http://ow.ly/LkBoK
2. Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. *BMJ*. 2005 Jul 9;331(7508):108-9 http://www.ichnfm.org/reprints/vasquez-2005-cannell-bmj-reprint.pdf
3. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, Cox JE. Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab*. 2008 Jul;93(7):2716-21
4. 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 Jan;77(1):204-10
5. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine*. 2003 Jan 15;28(2):177-9. This study used vitamin D in the form of 25-hydroxy-vitamin D3.
6. 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;3:8
7. Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. *Lupus*. 2015 Apr;24(4-5):483-9
8. Waterhouse et al. Reversing bacteria-induced vitamin D receptor dysfunction is key to autoimmune disease. *Ann N Y Acad Sci.* 2009 Sep;1173:757-65
9. Waterhouse JC. Reversing Bacteria-Induced Vitamin D Receptor Dysfunction to Treat Chronic Disease: Why Vitamin D Supplementation Can Be Immunosuppressive, Potentially Leading to Pathogen Increase. *Townsend Letter for Doctors & Patients* 2009 Jan townsendletter.com/Jan2009/vitaminD0109.htm
10. Mercola J. Clearing Up Confusion on Vitamin D: Why I Don't Recommend the Marshall Protocol. *Mercola.com* 2009 March 14. articles.mercola.com/sites/articles/archive/2009/03/14/clearing-up-confusion-on-vitamin-d--why-i-dont-recommend-the-marshall-protocol.aspx
11. Brady D, et al, "TAP Experts": Vitamin D Testing. TAP Integrative. Feb 18, 2015 www.youtube.com/watch?v=ww_DLRU-27s. Brady D, personal emails in group discussion, July 25-29, 2014.
12. Albert PJ, Proal AD, Marshall TG. Vitamin D: the alternative hypothesis. *Autoimmun Rev*. 2009 Jul;8(8):639-44
13. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999 May;69(5):842-56
14. Sample I. Antibiotics could cure 40% of chronic back pain patients. *The Guardian* 2013 May http://ow.ly/LvBeK
15 "In total, microbiological cultures were positive in 28 (46 %) patients. Anaerobic cultures were positive in 26 (43 %) patients, and of these 4 (7 %) had dual microbial infections, containing both one aerobic and one anaerobic culture." Albert HB, Lambert P, Rollason J, et al. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J*. 2013 Apr;22(4):690-6
16. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes). *Eur Spine J*. 2013 Apr;22(4):697-707
17. Schwalfenberg G. Improvement of chronic back pain or failed back surgery with vitamin D repletion. *J Am Board Fam Med*. 2009 Jan-Feb;22(1):69-74
18. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine* (Phila Pa 1976). 2003 Jan 15;28(2):177-9
19. Terrier B et al. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. *Arthritis Res Ther*. 2012 Oct 17;14(5):R221
20. Eltayeb et al. Vitamin D status and viral response to therapy in hepatitis C infected children. *World J Gastroenterol*. 2015 Jan 28;21(4):1284-91
21. Nimer A, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. *World J Gastroenterol.* 2012 Feb 28;18(8):800-5
22. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007 Sep;167(16):1730-7
23. Hyppönen et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001 Nov 3;358(9292):1500-3
24. Grant WB, Schwalfenberg GK, Genuis SJ, Whiting SJ. An estimate of the economic burden and premature deaths due to vitamin D deficiency in Canada. *Mol Nutr Food Res.* 2010 Aug;54(8):1172-81
25. Mirzaei et al. Gestational vitamin D and the risk of multiple sclerosis in offspring. *Ann Neurol*. 2011 Jul;70(1):30-40
26. Munger et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004 Jan 13;62(1):60-5

Intended for healthcare professionals

Editorials

The remarkable impact of bivalent HPV vaccine in Scotland

BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l1375 (Published 03 April 2019)
Cite this as: BMJ 2019;365:l1375

Linked research

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland

Linked opinion

Bivalent HPV vaccine in Scotland is having a considerable and sustained effect

- Article
- Related content
- Article metrics
- Rapid responses
- Response

Re: Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D

supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century, with key publications starting in 1999 [3-6]. We now have increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements (and sun exposure) to combat the high prevalence of vitamin D deficiency in Scotland [11-23].

Vitamin D supplementation has been the subject of several placebo-controlled trials documenting anti-inflammatory, antiviral, and anticancer effects. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" in which they summarized, "In conclusion, vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism, plasma NO, TAC, GSH and MDA levels." In 2018, Vahedpoor and colleagues [39] published "Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3" in which they noted, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity; use of

nutritional supplements that contain or potentiate vitamin D had started to increase in the population by 2003. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially misleading, especially when these authors make no account whatsoever of the national program for vitamin D supplementation which started in the same time-frame. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

[1] Brotherton JML.The remarkable impact of bivalent HPV vaccine in Scotland. BMJ 2019;365:l1375 https://doi.org/10.1136/bmj.l1375 Published 03 April 2019
[2] Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, Cruickshank M. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019 Apr 3;365:l1161. doi: 10.1136/bmj.l1161
[3] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999 May;69(5):842-56
[4] Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003 May;89(5):552-72
[5] 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 https://www.ncbi.nlm.nih.gov/pubmed/15478784
[6] Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. BMJ. 2005 Jul 9;331(7508):108-9 https://doi.org/10.1136/bmj.331.7508.108-b and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC558659/
[7] 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 Jan;77(1):204-10
[8] Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-2014. JAMA. 2017 Jun 20;317(23):2448-2450. doi: 10.1001/jama.2017.4392
[9] "The proportion of adults who report taking dietary supplements (such as vitamins, fish oils, minerals etc) has increased slightly since 1998 (there was no change between 1995 and 1998). In 1998, 15% of men and 16% of women aged 16-64 took some form of dietary supplement, which increased to 20% and 26%, respectively, in 2003." The Scottish Health Survey 2003. Chapter 3 Fruit and Vegetable Consumption and Eating Habits. https://www.webarchive.org.uk/wayback/archive/20180602183443/http://www.... Accessed April 2019
[10] Reddy P, Edwards LR. Magnesium Supplementation in Vitamin D Deficiency. Am J Ther. 2019 Jan/Feb;26(1):e124-e132. doi: 10.1097/MJT.0000000000000538
[11] "Therefore, routine vitamin D supplementation is recommended for all children over 1 year of age and should be continued until 5 years unless the diet is diverse and plentiful." Scottish Government. Nutritional Guidance for Early Years: food choices for children aged 1-5 years in early education and childcare settings. Published: 23 Jan 2006. https://www.gov.scot/publications/nutritional-guidance-

early-years-food-... Accessed April 2019
[12] Burleigh E, Potter J. Vitamin D deficiency in outpatients: a Scottish perspective. Scott Med J. 2006 May;51(2):27-31
[13] Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007 Mar;85(3):860-8
[14] Rhein HM. Vitamin D deficiency is widespread in Scotland. BMJ. 2008 Jun 28;336(7659):1451. doi: 10.1136/bmj.39619.479155.3A
[15] Boy wins NHS backing in vitamin D campaign. The Scotsman 2009 December https://www.scotsman.com/news/boy-wins-nhs-backing-in-vitamin-d-campaign... Accessed April 2019
[16] “At scotsneedvitamind.com, we believe the people of Scotland would see health improvements by taking a regular Vitamin D supplement. We think there is enough evidence currently available to make all of us take action, from health care professionals to parents and teachers.” https://scotsneedvitamind.com/about-us/ Accessed April 2019
[17] "The United Kingdom National Health Services created a program called Healthy Start, which offers vouchers for free vitamin D supplements to qualifying pregnant women, women with a baby under one year old and children under the age of five years located in Scotland, Northern Ireland, England and Wales. In April of 2017, the Scottish government partnered with the Healthy Start program to offer free vitamin D supplements to all Scottish pregnant women, regardless of whether they qualify for vouchers. This joint effort was created to decrease the risk of rickets and other health complications caused by vitamin D deficiency. Scotland offers free vitamin D supplements for all pregnant residents. Posted on: November 28, 2017 by Missy Sturges and John Cannell, MD. https://www.vitamindcouncil.org/scotland-offers-free-vitamin-d-supplemen.... See also: National Health Services Scotland. Vitamin D. https://www2.gov.scot/resource/0038/00386784.pdf Accessed April 2019
[18] Scottish warning over vitamin D levels. 19 September 2010 https://www.bbc.com/news/uk-scotland-11355810 Accessed April 2019
[19] "Following recommendations from the Scientific Advisory Committee on Nutrition (SACN), Scottish Government advice on vitamin D for all age groups has been updated as follows: Everyone age 5 years and above should consider taking a daily supplement of 10 micrograms vitamin D, particularly during the winter months (October – March)." Scottish Government. Vitamin D. https://www2.gov.scot/Topics/Health/Healthy-Living/Food-Health/vitaminD Accessed April 2019
[20] Scottish Government. Vitamin D information for health professionals in Scotland. November 2017 https://www.gov.scot/binaries/content/documents/govscot/publications/pub... Accessed April 2019
[21] "Scots should consider taking vitamin D supplements all-year round, but particularly in autumn and winter, according to new health advice." All Scots advised to take vitamin D says new health guidance. 21 July 2016. https://www.bbc.com/news/uk-scotland-36856176 Accessed April 2019
[22] "International experts are calling for food in Scotland to be fortified with vitamin D, in an attempt to cut the large numbers of people who develop multiple sclerosis at sunshine-deprived northern latitudes." Add vitamin D to Scotland's food – experts: Dosing whole population would help cut levels of multiple sclerosis, say scientists. 23 Dec 2011 https://www.theguardian.com/uk/2011/dec/23/vitamin-d-scotland-food-multi... Accessed April 2019

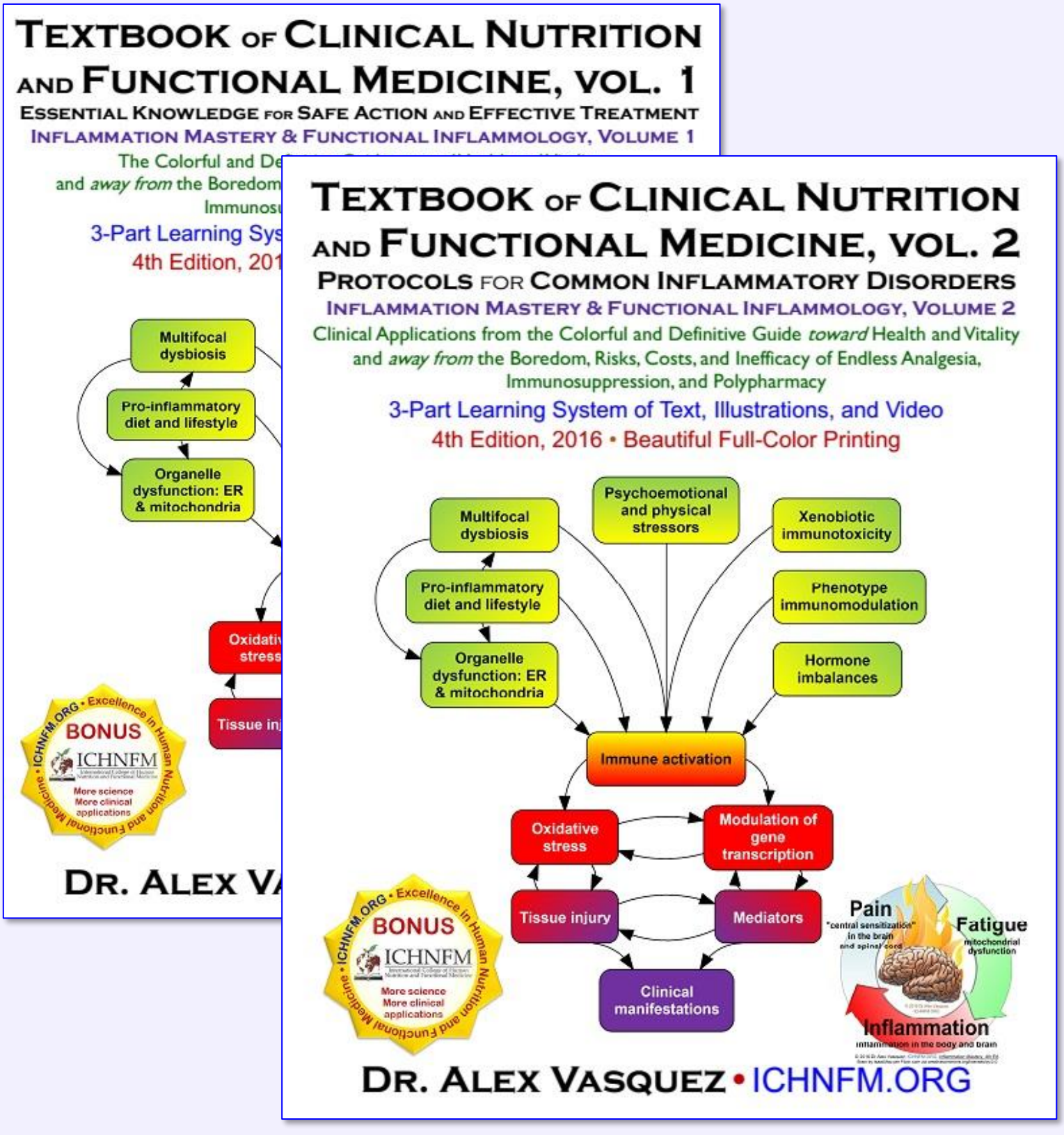
[23] All Scottish babies should have vitamin D supplement, CMO says. The Pharmaceutical Journal 2017 Nov 30. https://www.pharmaceutical-journal.com/news-and-analysis/news/all-scotti... Accessed April 2019
[24] Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM. 2002 Dec;95(12):787-96
[25] Luthold RV, Fernandes GR, Franco-de-Moraes AC, Folchetti LG, Ferreira SR. Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. Metabolism. 2017 Apr;69:76-86. doi: 10.1016/j.metabol.2017.01.007. Epub 2017 Jan 13.
[26] Stallings VA, Schall JI, Hediger ML, Zemel BS, Tuluc F, Dougherty KA, Samuel JL, Rutstein RM. High-dose vitamin D3 supplementation in children and young adults with HIV: a randomized, placebo-controlled trial. Pediatr Infect Dis J. 2015 Feb;34(2):e32-40. doi: 10.1097/INF.0000000000000483
[27] Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. World J Gastroenterol. 2011 Dec 21;17(47):5184-90. doi: 10.3748/wjg.v17.i47.5184
[28] Nimer A, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. World J Gastroenterol. 2012 Feb 28;18(8):800-5. doi: 10.3748/wjg.v18.i8.800
[29] Komolmit P, Kimtrakool S, Suksawatamnuay S, Thanapirom K, Chattrasophon K, Thaimai P, Chirathaworn C, Poovorawan Y. Vitamin D supplementation improves serum markers associated with hepatic fibrogenesis in chronic hepatitis C patients: A randomized, double-blind, placebo-controlled study. Sci Rep. 2017 Aug 21;7(1):8905. doi: 10.1038/s41598-017-09512-7
[30] Jung HC, Seo MW, Lee S, Kim SW, Song JK.Vitamin D3 Supplementation Reduces the Symptoms of Upper Respiratory Tract Infection during Winter Training in Vitamin D-Insufficient Taekwondo Athletes: A Randomized Controlled Trial. Int J Environ Res Public Health. 2018 Sep 14;15(9). pii: E2003. doi: 10.3390/ijerph15092003
[31] Lee MT, Kattan M, Fennoy I, Arpadi SM, Miller RL, Cremers S, McMahon DJ, Nieves JW, Brittenham GM. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. Blood Adv. 2018 May 8;2(9):969-978. doi: 10.1182/bloodadvances.2017013979
[32] Moscarelli L, Annunziata F, Mjeshtri A, Paudice N, Tsalouchos A, Zanazzi M, Bertoni E. Successful treatment of refractory wart with a topical activated vitamin d in a renal transplant recipient. Case Rep Transplant. 2011;2011:368623. doi: 10.1155/2011/368623. Epub 2012 Jan 3.
[33] Aktaş H, Ergin C, Demir B, Ekiz Ö. Intralesional Vitamin D Injection May Be an Effective Treatment Option for Warts. J Cutan Med Surg. 2016 Mar-Apr;20(2):118-22. doi: 10.1177/1203475415602841. Epub 2015 Aug 20
[34] Raghukumar S, Ravikumar BC, Vinay KN, Suresh MR, Aggarwal A, Yashovardhana DP. Intralesional Vitamin D3 Injection in the Treatment of Recalcitrant Warts: A Novel Proposition. J Cutan Med Surg. 2017 Jul/Aug;21(4):320-324. doi: 10.1177/1203475417704180. Epub 2017 Apr 6.
[35] Naresh M. A Study of Effectiveness of Intralesional Vitamin D3 in Treatment of Multiple Cutaneous Warts. IOSR Journal of Dental and Medical Sciences (IOSR -JDMS) 2019:18(3),84-87
[36] Abdel Kareem IM, Ibrahim IM, Fahmy Mohammed SF, Ahmed AA. Effectiveness of intralesional vitamin D3 injection in the treatment of common warts: single-blinded placebo-controlled study.

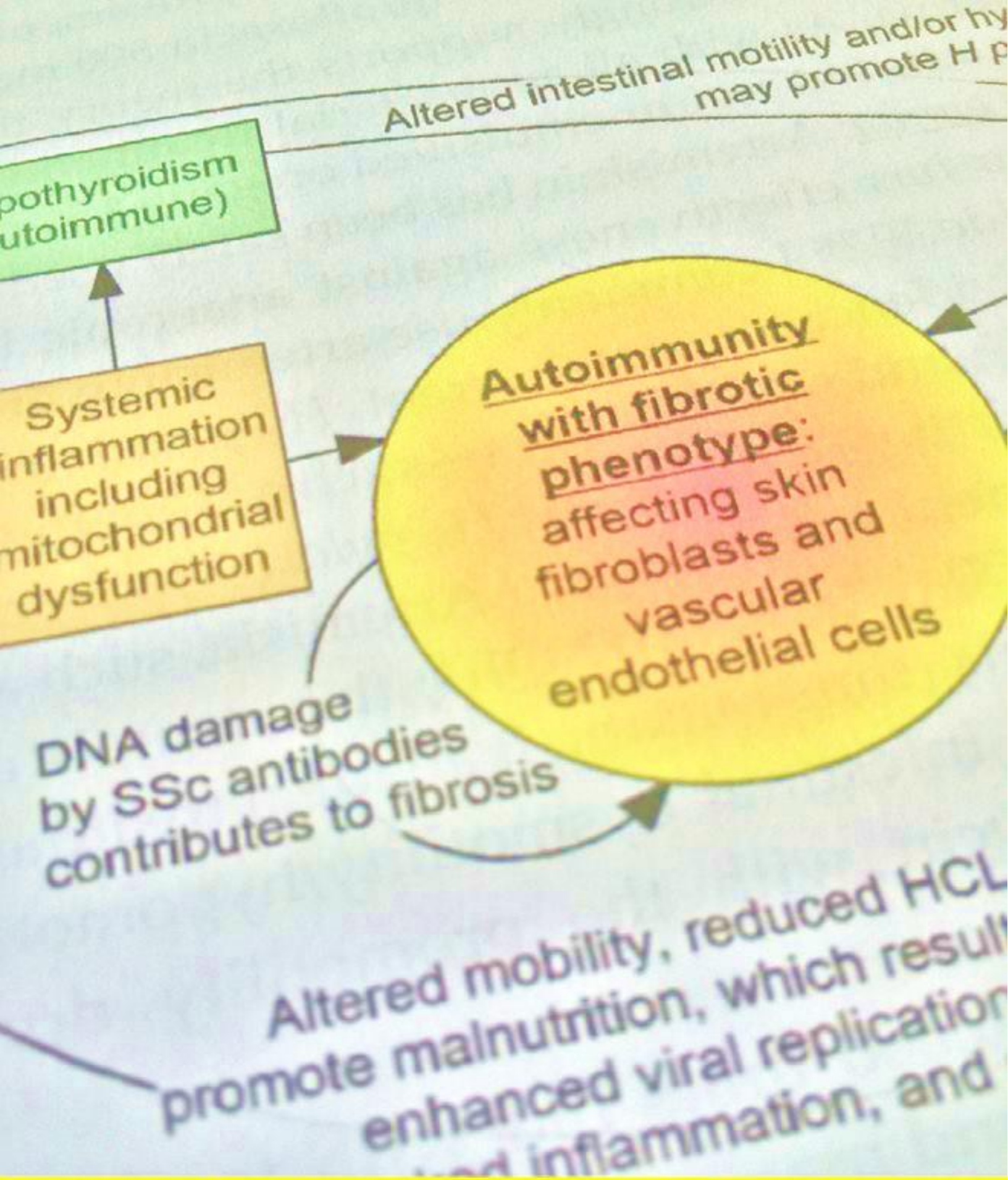
Dermatol Ther. 2019 Mar 28:e12882. doi: 10.1111/dth.12882
[37] Schulte-Uebbing C, Schlett S, Craiut I, Antal L, Olah H. Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment. Dermatoendocrinol 2014 Oct; 6:e27791. doi:10.4161/derm.27791
[38] Vahedpoor Z, Jamilian M, Bahmani F, Aghadavod E, Karamali M, Kashanian M, Asemi Z. Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia: a Randomized, Double-Blind, Placebo-Controlled Trial. Horm Cancer. 2017 Feb;8(1):58-67. doi: 10.1007/s12672-016-0278-x. Epub 2017 Jan 3
[39] Vahedpoor Z, Mahmoodi S, Samimi M, Gilasi HR, Bahmani F, Soltani A, Sharifi Esfahani M, Asemi Z. Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Nutr Metab. 2018;72(2):151-160. doi: 10.1159/000487270. Epub 2018 Feb 21

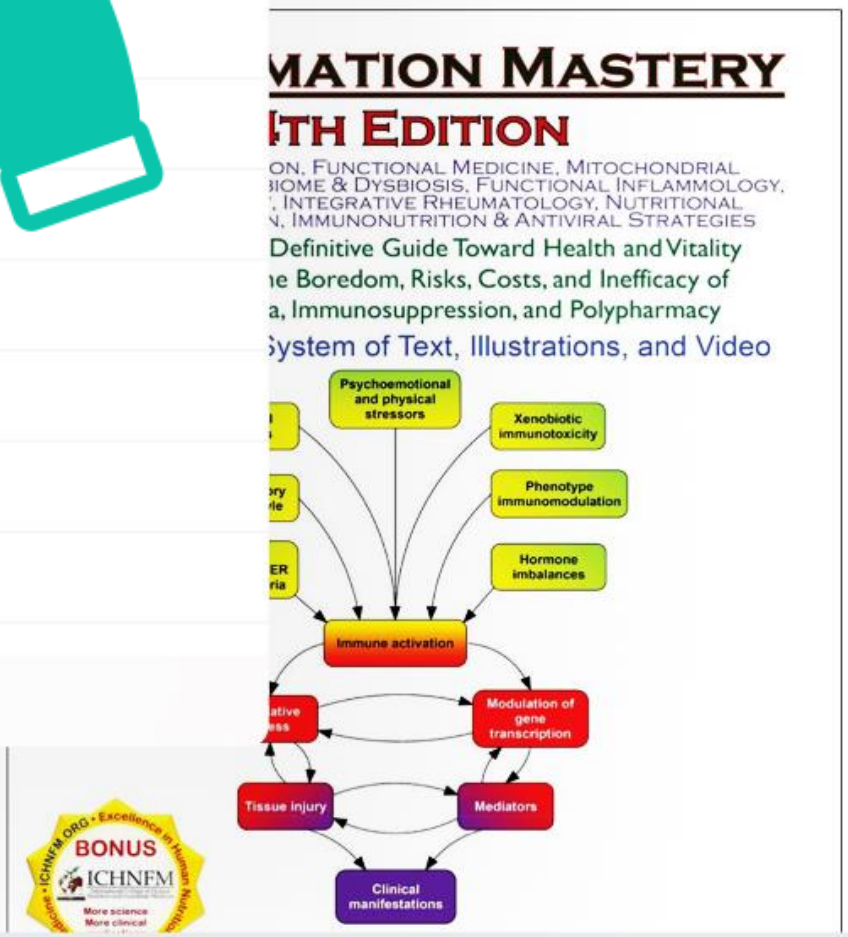
Competing interests: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, and the human microbiome. Dr Vasquez has served as a consultant to Biotics Research Corporation.

11 April 2019
Alex Vasquez
Physician, author, lecturer, editor
Barcelona, Spain

As of 2019 and for the foreseeable future, the most current versions of all major patient management and clinical treatment protocols is published in ***Inflammation Mastery, 4th Edition*** as a single volume of 1,182 pages available in full-color print at discounted pricing directly from ICHNFM from https://www.ichnfm.org/im4, while the digital formats are available via several different platforms, including Amazon's Kindle (free) software, Barnes and Noble's Nook, Apple iBook, etc as hyperlinked below. Per popular request by students who were studying (as a required textbook) only one section at a time, "IM4" was also published in two easier-to-carry separate volumes under the name ***Textbook of Clinical Nutrition and Functional Medicine***, which contain chapters 1-4 (pages 1-712+index) and 5 (713-1154+index), respectively. Video access is included with ***IM4*** and ***TCNFM,1+2***. Availability in print and digital formats (examples): https://www.**ichnfm**.org/im4 , https://books.**apple**.com/us/author/alex-vasquez/id1139497284
https://www.**amazon**.com/Inflammation-Mastery-4th-Immunosuppression-Polypharmacy-ebook/dp/B01KMZZLAQ
https://www.**barnesandnoble**.com/w/inflammation-mastery-4th-edition-alex-vasquez/1123259586?ean=9780990620464







DOWNLOAD FREE SAMPLE: https://www.amazon.com/Dr-Alex-Vasquez/e/B00AT5764Y

The obvious advantages to the digital ebook version are

1) **easy transportation** in your **phone or iPad,**
2) **easy searching** in the **entire book of nearly 1200 pages and 1.5 million words,**
3) **synchronization of notes and highlights across phone, iPad, and your computer**

Chapter and Introduction

Preamble

Volume 1

1. Patient Assessments, Laboratory Interpretation, Clinical Concepts, Patient Management, Practice Management and Risk Reduction: *This chapter introduces/reviews/updates patient assessments, laboratory interpretation, musculoskeletal emergencies, healthcare paradigms; the common and important conditions hemochromatosis and hypothyroidism are also included in this chapter since these need to be considered on a frequent basis in clinical practice*
2. Wellness Promotion & Re-Establishing the Foundation for Health: *Reviewed here are diet, lifestyle, psychosocial health, and—given the pervasiveness of persistent organic pollutants and their increasingly recognized clinical importance—an introduction to environmental medicine*
3. Basic Concepts and Therapeutics in (Nondrug) Musculoskeletal Care and Integrative Pain Management: *Nonpharmacologic management of musculoskeletal problems is preferred over pharmacologic (e.g., NSAID, Coxib, steroid, opioid) management because of the collateral benefits, safety, and cost-effectiveness associated with manual, dietary, botanical, and nutritional treatments. A brief discussion of the current crisis in musculoskeletal medicine is provided for contextualization and emphasis of the importance of expanding clinicians' knowledge of effective nondrug treatments*
4. The Major Modifiable Factors in Sustained Inflammation: *Major components of the "Functional Inflammology Protocol" are reviewed here, from concepts and molecular biology to an emphasis on practical clinical applications*

1) Food & Basic Nutrition

2) Infections: Dysbiosis / Viral

3) Nutritional Immunomodulation

4) Dysmetabolism, Mitochondrial Dysfunction, ERS/UPR, mTOR

5) Special Considerations: Sleep, Sociopsychology, Stress, Surgery

6) Endocrine Imbalances

7) Xenobiotic Immunotoxicity

Volume 2: Chapter 5—Clinical Applications of the Functional Inflammology Protocol

Textbook of Clinical Nutrition and Functional Medicine, Vol. 2

Protocols for Common Inflammatory Disorders

Inflammation Mastery & Functional Inflammology, Volume II

Clinical Applications from the Colorful and Definitive Guide *toward* Health and Vitality and *away from* the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy

3-Part Learning System of Text, Illustrations, and Video

4th Edition, 2016 • Beautiful Full-Color Printing

BONUS

ICHNFM

More science
More clinical
applications

ICHNFM.ORG • Excellence in Human Nutrition and Functional Medicine

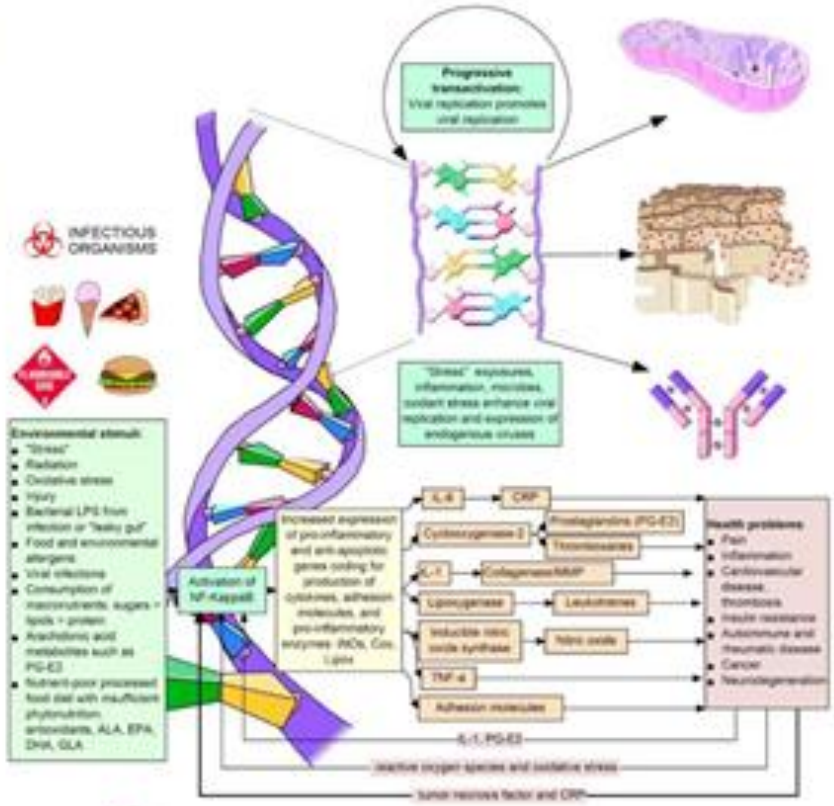
Dr. Alex Vasquez • ICHNFM.ORG

ANTIVIRAL NUTRITION

Against Colds, Flu, Herpes, AIDS, Hepatitis, Ebola, Dengue, and Autoimmunity: A Concept-Based and Evidence-Based Handbook and Research Review for Practical use

Inflammation Mastery series Chapter 6 • Volume 2 of Dysbiosis in Human Disease

2-Part Learning System of Text and Video



DR. ALEX VASQUEZ

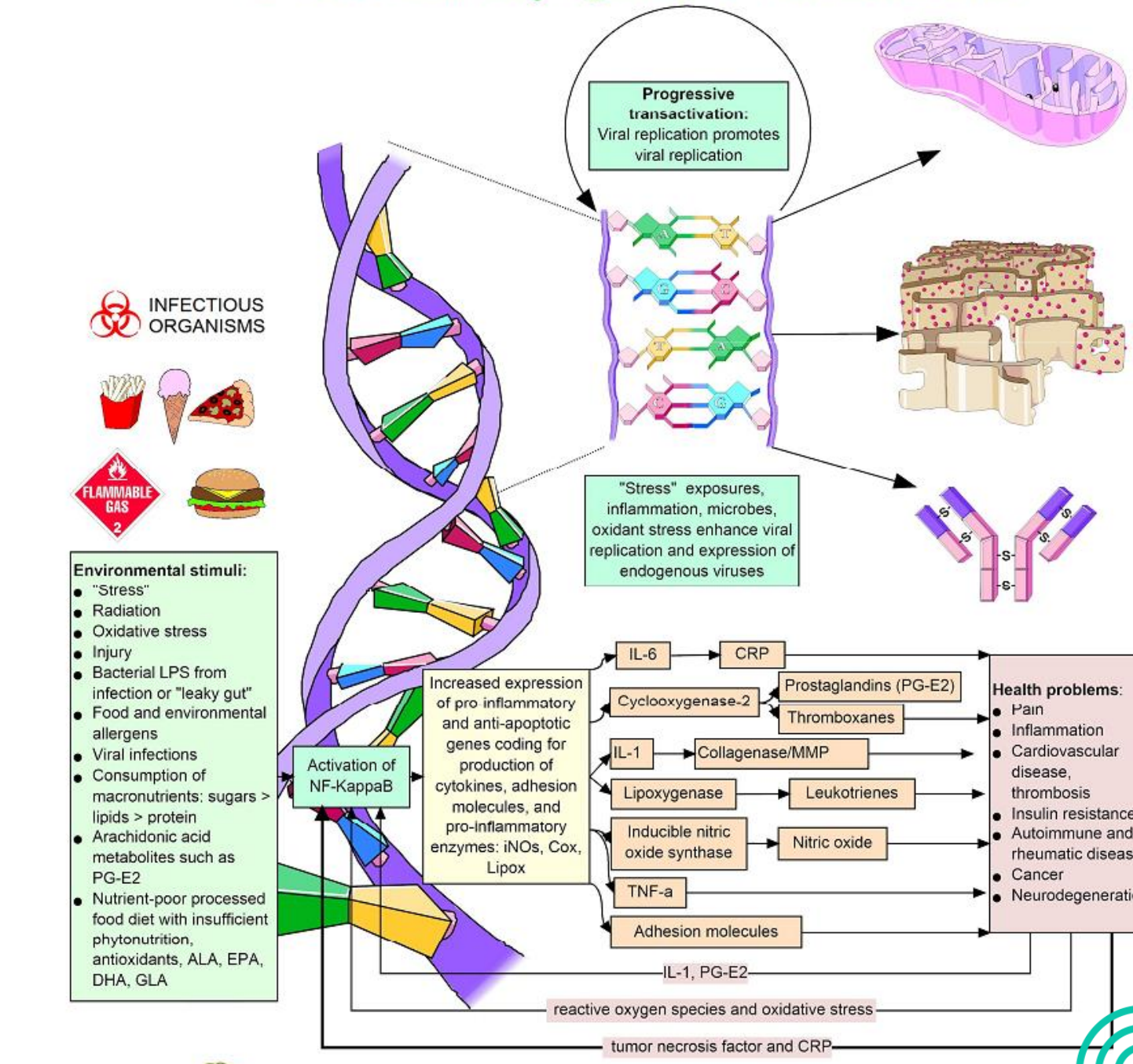
INFLAMMATIONMASTERY.COM

Antiviral Strategies and Immune Nutrition

Against Colds, Flu, Herpes, AIDS, Hepatitis, Ebola, Dengue, and Autoimmunity: A Concept-Based and Evidence-Based Handbook and Research Review for Practical Use

Inflammation Mastery series Chapter 6 ♦ Volume 2 of Dysbiosis in Human Disease

2-Part Learning System of Text and Video



Dr. Alex Vasquez

InflammationMastery.com

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 34, NUMBER 2
PUBLISHED: JUNE 2019

Editorial

Vitamins Against Viruses: Implausible Pro-Vaccine Publications Contrasted Against Ignored Public Health Campaigns and Double-Blind Placebo-Controlled Clinical Trials

Introduction

As an author, presenter, editor, and careful reader of research and public policy, I have been concerned for several years about potentially false attribution of efficacy to vaccines during public health campaigns and major infrastructure investments that concurrently provided access to education, improved sanitation, improved diet (alongside immune-enhancing nutritional supplementation, most commonly with vitamins A and D, zinc, and iron), relocations of millions of people along with changes in their living and working circumstances (which would be expected to change infectious disease patterns, e.g., relocating people away from farms obviously reduces their exposure to *Clostridium tetani* [the anaerobic bacillus of tetanus] which is found primarily in soil contaminated by fecal material from [especially ruminant] animals such as cattle, sheep, and goats). With the April 2019 publication of several very unusual articles stemming from the *British Medical Journal (*BMJ*)*, the time arrived to explore some of these concerns in a structured and public format. A legitimate concern is that science and public opinion are being inappropriately manipulated to favor a pharmaceutical/vaccination paradigm while lower cost, more widely available, safer and more efficacious nutritional interventions are being sidelined or intentionally ignored. In the current instance, overzealous endorsement and praise was given to a pharmaceutical intervention while a nationwide nutritional supplementation program supported by double-blind placebo-controlled trials was completely—and perhaps intentionally and strategically—ignored, then blocked by the journal from further discussion.

Pro-pharma echo chamber resounds: I first became aware of the two new (April 2019) BMJ publications (article by Palmer et al[1] and editorial by Brotherton[2]) via the derived "news" article published on 4 April in *The Guardian* titled "HPV rates tumble after routine vaccination" by Sarah Boseley, the publication's "Health Editor." With review of their website I found that The Guardian has published an impressive number of pro-vaccine articles devoid of critical thought or balanced analysis, including "Cervical cancer could be eliminated in most countries by 2100 – Millions of cases could be prevented with high HPV vaccine and screening coverage" (20 Feb 2019), "Teenage boys to be vaccinated against cancer-causing HPV: Inoculation program will be expanded to cover 12- and 13-year-old boys in England" (24 Jul 2018), "Boys should get HPV jab to protect against cancer, health advisers say: Ministers urged to take swift action to extend immunization under a gender-neutral program" (18 Jul 2018), "Cervical cancer deaths in over-50s predicted to rise sharply in England – Rates of diagnoses and death set to rise in women not vaccinated against HPV, but likely to be almost eradicated in younger women" (19 Dec 2017), and "HPV vaccination should be extended to gay men" (12 Jun 2012). One could hardly envision a more pro-drug publication, regularly producing "news articles" that function as infomercials, glorifying any real or imagined benefits of drugs while making zero or minimal mention of any adverse effects, or refuting adverse effects, but without sufficient substantiation, as in "Cervical cancer vaccination 'most unlikely' to have caused girl's death" (29 Sep 2009). Likewise, the BMJ article was re-reported and exalted throughout print and video media in the United States by outlets such as Fox News' "UK's HPV vaccination program 'dramatically' reduces risk of cervical cancer"[3] and the physician-oriented Medscape.[4] Such articles obviously serve to direct public and political opinion in favor of medicalization to the delight of the pharmaceutical and mainstream medical industries; the combined reach of the original articles and their echo-chamber derivatives is certainly in the tens of millions if not hundreds of millions of people. With regard to the recent article, the imbalanced praise and absence of rational concerns published in favor of the vaccine appeared quite biased; I soon accessed the original research, as discussed below.

BMJ's landmark publications in erroneous conclusions: Anyone who has studied research design is aware of different types of clinical investigations and the limitations inherent in each. The "gold standard" of clinical research has been the randomized double-blind placebo-controlled clinical trial, preferably with a large population-representative cohort, preferably with a cross-over design if practical depending

 ISSN 0317-0209

on the logistics of the intervention. In any placebo-controlled trial, the placebo needs to be an inert substance, not—as is common with pharmaceutical and especially vaccine studies—a mislabeled "placebo" capable of causing harm and therefore reducing and obfuscating the relative risk (RR) compared to the active/test agent. Science is corrupted when unscrupulous researchers use active agents misbranded as "placebos" in order to make a given intervention look comparatively safe and effective (when compared against a harmful placebo, such as the recent studies using high-cost high-dose prescription fish oil against a false placebo of petroleum mineral oil)[5] or comparatively dangerous or ineffective (when compared against a safe and therapeutically active placebo, such as the recent reviews comparing low-dose fish oil against low-dose olive oil, both of which are antiinflammatory and cardioprotective).[6] Thus, the strategic use of inappropriate placebos and/or the intentional ignoring of confounding variables (such as population-wide health campaigns) serves to glorify the preselected pharmaceutical victor while providing the necessary "evidence of effectiveness" and justification for widespread implementation and multimillion $/£/ € purchase. To the extent that such publications obfuscate the data and minimize appreciation of effective nutritional interventions, doctors and patients are inappropriately corralled into drug dependency while nutritional interventions with lower cost, wider availability, greater safety and efficacy—along with the numerous collateral benefits typically seen with nutritional supplementation—are withheld from general consideration. As detailed below, BMJ published a retrospective population-wide study that impossibly ascribed efficacy (by design, such studies cannot determine efficacy) to the HPV vaccine while ignoring the time-synchronized national public health campaign to improve vitamin D nutriture, whereas the latter has numerous lines of evidence supporting its clinically important efficacy against various types of HPV infection.

Dr Vasquez replies with two "rapid responses" posted on BMJ.com: To its credit, BMJ has a "rapid response" system that allows readers to publicly respond to articles and occasionally receive replies from the original authors; from the rapid responses posted, the journal's Editors supposedly choose from among the responses those few deemed worthy of publication in the print and indexed version of the journal, as they did with my 2005 reply to an article that misused vitamin D in a clinical trial and then erroneously reported that vitamin D was inefficacious.[7] For the April 2019 BMJ publications, my first rapid response received no reply; the following two rewritten responses, both of which were posted on BMJ.com in response to the editorial and the original research, are contextualized and provided below. The complete texts of these replies are included here both for the convenience of readers and to also document these posted responses in the event that—as is common these days—the editors delete any legitimate questioning of the high-profit vaccine paradigm. At the time of this writing, my replies are posted online at "Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends" (https://www.bmj.com/content/365/bmj.l1375/rr-4 and externally archived at https://www.academia.edu/39207517) and "Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination" (13 April 2019, https://www.bmj.com/content/365/bmj.l1161/rr-8, externally archived at https://www.academia.edu/39201317).

The editorial posted by the BMJ to accompany and contextualize the original research was unusual in several aspects. First, the editorial is described as "commissioned" which implies that the journal paid the author to write the piece, presumably—as noted by former BMJ Editor Richard Smith[8] –to sell reprints to the pharmaceutical industry and/or governmental and other pro-vaccine groups as "proof" in order to convince people to accept this intervention as valid and thereby promote sales and the resulting profit and political power; as such, their editorial functions as an infomercial and advertisement for vaccine sales. Second, and consistent with the view that the editorial is simply a publicity piece, the journal specifically notes that the editorial was "not peer-reviewed" which is remarkable considering that most people think that all articles in the so-called "top tier" and "big five" medical journals are legitimately processed and refereed prior to publication and indexing in Medline's Pubmed (ncbi.nlm.nih.gov/pubmed/30944088). Third, I noticed that the disclosure as posted "The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: JMLB's employer has received partial, unrestricted support (in the form of equipment) to conduct a randomised trial of primary HPV screening from Roche Molecular Systems" makes zero mention of the author's research supported by Merck, makers of the HPV vaccination being discussed, revealed elsewhere as "JMLB has been an investigator on HPV epidemiology studies that received partial, unrestricted funding from Seqirus/Merck for laboratory components" (Int J Gynecol Obstet 2017; 138 (Suppl. 1): 7–14 DOI: 10.1002/ijgo.12186) and "JMLB has been an investigator in HPV epidemiological studies that have received partial unrestricted grants to support HPV typing components (cervical cancer typing study from Seqirus Australia, recurrent respiratory papillomatosis study from Merck Sharp and Dohme) and is an investigator on the Compass trial, which has received equipment and funding from Roche Molecular Systems and Roche Tissue Diagnostics, but JMLB reports no personal financial benefits" (*The Lancet*, 2019 February thelancet.com/public-health Vol 4;e87). Fourth, Brotherton's editorial is scientifically untenable, giving outlandish praise and stretching the boundaries of biological plausibility in support of the HPV vaccination advocated by the pro-vaccination group for which she works (Victorian Cytology Service [VCS] Foundation);[9]

she states that the results "unequivocally show high vaccine effectiveness" despite the fact that they completely ignored Scotland's concurrent nationwide programs to improve vitamin D status, including giving free vitamin D supplements and advocating sunbathing. Fifth, everyone associated with this publication appears to have ignored the fact that retrospective population-wide studies cannot establish causality as can double-blind placebo-controlled trials but at best can establish temporal relationships, but only if all impactful factors are considered, which was obviously not done with this primary publication nor its glorifying editorial. Sixth, consistent with my model of the pharmaceutical echo chamber and the financial matrimony binding media with drug companies , international newspapers and other media trumpeted to the world the glory of this vaccine, failing to mention any risks, qualifications, other scientific interpretations and therapeutic possibilities. Seventh, the scientifically responsible action that the BMJ could have taken is to issue a public statement clarifying the appropriate interpretation of its published research and reigning in this unscientific hysteria; but the BMJ has failed to do so. The text of my rapid response to the Editorial posted on BMJ.com is as follows:

Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century, with key publications starting in 1999 [3-6]. We now have increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements (and sun exposure) to combat the high prevalence of vitamin D deficiency in Scotland [11-23].

Vitamin D supplementation has been the subject of several placebo-controlled trials documenting anti-inflammatory, antiviral, and anticancer effects. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" in which they summarized, "In conclusion, vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism, plasma NO, TAC, GSH and MDA levels." In 2018, Vahedpoor and colleagues [39] published "Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3" in which they noted, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

 ISSN 0317-0209

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity; use of nutritional supplements that contain or potentiate vitamin D had started to increase in the population by 2003. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially misleading, especially when these authors make no account whatsoever of the national program for vitamin D supplementation which started in the same time-frame. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

Following the posting of my rapid response critiquing the editorial (11 Apr 2019), BMJ posted my resubmitted response rebutting the original research two days later (13 Apr 2019). Some but not all of the problems with the editorial are also noted in and originate from the primary research and therefore my critiques are similar, but not identical, with the second response a bit more refined and also with changes in a few citations. The major errors in the primary article are as follows: First, the study design of "retrospective population study" is incapable of determining causal relationships; at best such a study design can only determine temporal relationships, i.e., two events occurring together within the same time-period or one event following the other. As such, their reporting of any causal relationship is erroneous because this type of study cannot establish causality. Subsequently, the editorial and mass media derivatives are likewise erroneous. Second, attribution of effectiveness to the vaccine while ignoring any and all education surrounding the vaccine conflates inoculation with behavior-modifying education. Telling a young girl in essence that "the vaccination is directed toward a sexually transmitted infection in the form of a virus that could infect her vagina and cervix if she has unprotected sex with a boy" is a behavior-changing conversation likely to reduce sexual intercourse, with boys, especially without barrier protection; this primary study by Palmer and colleagues completely failed to account for any effect of education, instead giving all credit—indeed premature and inappropriate credit—to the vaccine. The age correlation that they reported—less HPV with earlier vaccination—could easily be explained or confounded with earlier education that changes sexual behavior. The authors failed to consider anything other than vaccination, so of course they found a correlation between vaccination and reduced HPV-related disorders. Third, the authors ascribe "herd immunity" to the observation that unvaccinated girls also showed a reduction in HPV-related disorders; but this could have easily and perhaps more convincingly been attributed to the nationwide vitamin D supplementation programs, which were completely ignored and never mentioned despite the fact that vitamin D has been proven effective against HPV infections via a variety of levels of evidence. Their concluding statement "The bivalent vaccine is confirmed as being highly effective vaccine and should greatly reduce the incidence of cervical cancer" is overzealous and is an epidemiologic error when they failed to consider any other interpretive options. Indeed, such considerations—controlling for other possible factors—is the defining characteristic of competent epidemiology. The authors followed their egregious overstatement (quoted previously) with a confirmatory understatement: "It is possible therefore that vaccine effectiveness was over-estimated." Neither the accompanying editorial nor the publications for the mass media mention of the probable overestimation of vaccine effectiveness. My rapid response to the original article is as follows:

Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HVP vaccination

In April 2019, Palmer et al [1] published a retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland, and the authors attributed a reduction in HPV prevalence among unvaccinated women with "herd protection." However, the authors did not mention Scotland's population-wide public health campaigns to address endemic vitamin D deficiency. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. Vitamin D deficiency results in impaired mucosal and immune defenses and correlates in a dose-dependent manner with increased cervicovaginal HPV infection [2]. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century with landmark publications such as Vieth's authoritative documentation of safety in 1999 [3], Zittermann's "Vitamin D in preventive medicine" in British Journal of Nutrition in 2003 [4], and Vasquez's "Clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers" in 2004 [5] followed by an important partial summary of vitamin D usage guidelines in British Medical Journal in 2005 [6]. These and similarly themed articles have contributed to increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral

infections and various types of cancer. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements to combat the high prevalence of vitamin D deficiency in Scotland [11].

Widespread vitamin D deficiency in Scotland was followed by widespread recommendations for vitamin D supplementation starting in 2006 and 2009. In 2006, Burleigh and Potter published in Scottish Medical Journal [12] stating that, "The prevalence of vitamin D deficiency is high in older outpatients in this geographical area." In 2007, Hyppönen and Power [13] showed that among British adults "Prevalence of hypovitaminosis D in the general population was alarmingly high during the winter and spring, which warrants action at a population level rather than at a risk group level." In 2008, Rhein [14] further specified that "Vitamin D deficiency is widespread in Scotland." In 2009, the Scottish Government acknowledged the need to educate its population about the importance of vitamin D3 supplementation [15]. From that time until the present, the Scottish Government, United Kingdom National Health Services, and various advocacy groups and programs (e.g., ScotsNeedVitaminD.com[16], Healthy Start, which provides vitamin D supplements to all children and pregnant women in Scotland [17]) continue assertive public health campaigns recommending vitamin D supplementation and increased vitamin D production via sun exposure via the "Shine on Scotland" program initiated in 2009 [18] for all of its citizens [19-23].

Vitamin D supplementation has been the subject of many clinical trials documenting anti-inflammatory, antiviral, and anticancer benefits. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (cervical intraepithelial neoplasia [CIN] 1-2): vaginal vitamin D treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they found that vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism and antioxidant status. In 2018, Vahedpoor and colleagues [39] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they observed, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially invalid and misleading, especially when the authors make no account whatsoever of the national program for vitamin D supplementation which started in the same timeframe. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

My reply makes quite obvious the shortcomings of their biased research publication. One should reasonably wonder why the BMJ would publish such a flawed report, and then pay for a "commissioned" "editorial" which was "not peer-reviewed." Then, the editors collectively stifled any further conversation regarding the antiviral action of vitamin D delivered to the same population in the same time-frame, despite its proof of clinical effectiveness. Such a compilation of errors could hardly seem accidental, although they would synergize fantastically for promoting sales and government mandates of the HPV vaccine.

 ISSN 0317-0209

And now for the silent treatment from BMJ editors: Reasonably anticipating that the BMJ would share my well-cited concerns with their readership via publication in a Letter to the Editor or Reply, I waited to hear from the Editors. When no response arrived by several weeks later, I emailed the Letters Editor and the Editor in Chief along with two other associate editors. The probability of none of them receiving my email nor noting my two posted rapid replies is essentially zero, and they have offered no response nor explanation for why their publications omitted this key data.

From: Dr Alex Vasquez
Date: Thu, May 9, 2019 at 4:34 PM
Subject: Re: Letters timeframe
To: Davies
Cc: Doshi, Godlee, Ludwig

Thank you for your earlier replies. I am following-up with interest in publishing the concerns raised in my rapid responses, because the original research appears to have looked at a chronological correlation without looking at the national health campaigns that started in the same time-frame. In particular, the public health campaign that I detailed has double-blind placebo-controlled evidence of clinical effectiveness, so it is worthy of consideration.

Of the two rapid responses posted (thank you), the second is a bit more refined and has (a few) better citations (I think I changed 2 of them).

1. Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends *https://www.bmj.com/content/365/bmj.l1375/rr-4*

2. Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination *https://www.bmj.com/content/365/bmj.l1161/rr-8*

As noted in my responses, vitamin D demonstrates antiinflammatory, microbiome-modifying, immune-supporting (eg, antimicrobial peptides, sIgA) and it specifically demonstrates effectiveness against HPV. I trust that we share the same goal of helping patients avoid HPV-related disorders, and cholecalciferol clearly shows benefit, safety, wide availability, and low cost.

[32] Moscarelli L, Annunziata F, Mjeshtri A, Paudice N, Tsalouchos A, Zanazzi M, Bertoni E. Successful treatment of refractory wart with a topical activated vitamin d in a renal transplant recipient. *Case Rep Transplant.* 2011;2011:368623. doi: 10.1155/2011/368623. Epub 2012 Jan 3.

[33] Aktaş H, Ergin C, Demir B, Ekiz Ö. Intralesional Vitamin D Injection May Be an Effective Treatment Option for Warts. *J Cutan Med Surg.* 2016 Mar-Apr;20(2):118-22. doi: 10.1177/1203475415602841. Epub 2015 Aug 20

[34] Raghukumar S, Ravikumar BC, Vinay KN, Suresh MR, Aggarwal A, Yashovardhana DP. Intralesional Vitamin D3 Injection in the Treatment of Recalcitrant Warts: A Novel Proposition. *J Cutan Med Surg*. 2017 Jul/Aug;21(4):320-324. doi: 10.1177/1203475417704180. Epub 2017 Apr 6.

[35] Naresh M. A Study of Effectiveness of Intralesional Vitamin D3 in Treatment of Multiple Cutaneous Warts. IOSR *Journal of Dental and Medical Sciences* (IOSR-JDMS) 2019:18(3),84-87

[36] Abdel Kareem IM, Ibrahim IM, Fahmy Mohammed SF, Ahmed AA. Effectiveness of intralesional vitamin D3 injection in the treatment of common warts: single-blinded placebo-controlled study. *Dermatol Ther.* 2019 Mar 28:e12882. doi: 10.1111/dth.12882

[37] Schulte-Uebbing C, Schlett S, Craiut I, Antal L, Olah H. Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment. *Dermatoendocrinol* 2014 Oct; 6:e27791. doi:10.4161/derm.27791

[38] Vahedpoor Z, Jamilian M, Bahmani F, Aghadavod E, Karamali M, Kashanian M, Asemi Z. Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia: a Randomized, Double-Blind, Placebo-Controlled Trial. *Horm Cancer.* 2017 Feb;8(1):58-67. doi: 10.1007/s12672-016-0278-x. Epub 2017 Jan 3

[39] Vahedpoor Z, Mahmoodi S, Samimi M, Gilasi HR, Bahmani F, Soltani A, Sharifi Esfahani M, Asemi Z. Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Nutr Metab.* 2018;72(2):151-160. doi: 10.1159/000487270. Epub 2018 Feb 21

Thank you,
Dr Alex Vasquez

Again expecting the journal's editors might value research accuracy, journalistic integrity, and the importance of ethical standards in clinical care and research, I was a bit surprised that these five BMJ Editors would collectively fail to reply to cited concerns about the quality of their publication. BMJ claims on its website that it hosts and/or represents an "international community of readers, authors, and editors" but apparently this sense of "community" does not apply to the questioning of publications that show obvious bias by ignoring other influences and funneling the results toward vaccine endorsement.

 ISSN 0317-0209

Basic components of research integrity: Tutorial articles published in journals as well as textbooks such as *The Lancet Handbook of Essential Concepts in Clinical Research*[11] can inform the implementation and evaluation of research. Ideally (but largely theoretically), research is performed honestly and competently, critically reviewed postproduction and prepublication by independent scientists/scholars, and then refereed by at least one expert-level Editor prior to publication and dissemination; the fourth component of research integrity is post-publication critique by readers and correspondence between such readers and the original authors. A fifth component of research integrity is the publication of article-specific editorials/commentaries that provide context and perspective for the new information presented; as with the original research, such Editorials should be independently peer-reviewed in a blinded manner by internal or external reviewers prior to publication.

Authorial and editorial bypassing of research integrity: A notorious pitfall in the publication of descriptive and retrospective studies such as the one by Palmer et al being discussed here is that of false attribution; that is, the erroneous assumption that because an intervention was followed by an observation that the former caused the latter. This error is intellectually grave as it can lead to erroneous conclusions about cause-and-effect relationships, thereby misleading government policy and clinical care. This error is also described as overstepping the data, erroneous inference, and—in Latin—post hoc ergo propter hoc which translates to "after this, therefore because of this", also known as the post hoc fallacy. In truth, causal relationships can only be established in appropriately conducted clinical trials; non-interventional retrospective population studies such as this one lead by Palmer can add only accessory information but are incapable of establishing or refuting causality, especially when the study itself fails to control for other variables and considerations.

"Errors" in study design may be accidental or intentional. In addition to the failure to consider other causes for an observed outcome, investigators can also accidentally or intentionally "stack the deck" in order to make a certain conclusion more or less likely. Strategically or innocently, researchers can select patients that may have covariables that are of major importance to the outcome being studied. Indeed, the authors noted that "partial immunization was associated with increased deprivation, having left school, and increasing age" but they failed to follow-up on these considerations and their HPV-relevant implications. Co-variables that correlate with more vaccination are better financial status, better healthcare insurance coverage, better nutrition, less sexual promiscuity and less social inequality/defeat stress. Improved nutrition obviously provides an anti-viral effect by reducing inflammation-promoted viral replication and also by enhancing immune defenses; wealthier and better educated persons are known to consume more nutritional supplements. A reduced number of sexual exposures would obviously affect the prevalence of a sexually transmitted diseases (STD). Less socioeconomic stress would lead to a relative improvement in immune function compared to a group with stress-induced immunodysfunction and immunosuppression. Obviously—and completely ignored by all of the authors and editors of this BMJ publication—is the fact that the act of vaccination itself with its attendant information (ie, behavior-changing education) regarding the risks of sexual behavior (ie, promiscuity verses abstinence) and the value of STD-blocking barrier methods (e.g., condoms) would be clearly expected to reduce HPV-related disease. As noted in *The Lancet Handbook of Essential Concepts in Clinical Research* (page 35), "When selection bias or information bias exists in a study, irreparable damage results. Internal validity is doomed." Also (page 46), "Although assessment of many outcomes is often cited as a positive attribute of cohort studies, this feature can be abused. For example, testing the associations between exposure and many outcomes, but only reporting the significant ones, represents misleading science."

In this case, the authors quite obviously failed to consider anything other than their chosen vaccine program, and then they assumed that the vaccine program was responsible for the observation that cervical disease was decreased in the vaccinated group. How these researchers were able to remain ignorant of a well-publicized government-endorsed nationwide public health campaign emphasizing improved nutrition and vitamin D supplementation[12] (which is proven with a variety of clinical research to reduce the burden of HPV infections, to improve general immunity, and to reduce inflammation) is unclear; one can only reasonably speculate why the journal's editors would fail to publish commentary and consideration in this regard.

Bizarrely, BMJ allowed the study's lead author to post additional commentary on his own research, as if the publication needed any additional biased aggrandizement. Not surprisingly, Palmer[13] agreed with his own perspective and endorsed the greatness of his research, stating that his research revealed "a veritable triumph for medicine" and that the intervention he endorses is "the only feasible solution" to preventing HPV-related cervical cancer. As would be expected in one of the "mainstream medical journals", zero mention was made of nutritional immunorestoration, microbiome modification, nor antiviral nutrition strategies—all of which have a clear role in the prevention of HPV-related cervical disease. Clearly, if the only intervention considered is vaccination, and all other social and biological interventions are ignored, then the only possible solution will appear to be vaccination, regardless of the lack of merit of this conclusion. Whether or not one "believes in" the common oversimplified model of HPV-induced cervical disease and/or the promul-

gated "value" of vaccination, we should all want the research to be accurate and for all variables and treatment options to be considered for this condition, especially when the promoted vaccine appears responsible for a large number of injuries and deaths.[14] As noted recently (2018) by former BMJ Editor Richard Smith, the BMJ and its publishing group sells millions of dollars/pounds/euros worth of "product advertising" (e.g., £2.7m) and article reprints (£1.98m or $2,497,770 United States dollars); most of these advertisements and article preprints are purchased by the medical device and drug (including vaccine) industry to promote sales of their products.[15]

The case for postpublication retraction: According to the Committee on Publication Ethics,[16] journal editors should strongly consider retracting a publication if any of the following occur: 1) evidence that the findings are unreliable, either as a result of misconduct [e.g. data fabrication] or honest error [e.g. miscalculation or experimental error], 2) redundant publication, 3) plagiarism, 4) unethical research. In my opinion, any legitimate critical reading of this article would have easily led to its pre-publication rejection or its post-publication retraction, but because the article has financial value by promoting a multibillion dollar vaccine paradigm and up to thousands/millions of dollars in article reprints and pharmaceutical advertising, it was published, editorially praised, and then publicly glorified without (to my knowledge) any scientific criticism. In the irony of ironies, lead author Palmer was quoted by Medscape (op cit) as stating: "One of the things this study really does hammer home is that the anti-vaccine lobby are actually peddling falsehoods."

The importance of nutritional expertise and independent publications in the post-truth and pro-pharmaceutical era: The international community has been living in the post-truth era—defined as being dominated by utter disregard for truth in the service of financial and political power—now for many years.[17] Given that nutritional education is generally excluded from medical education and post-graduate training, the only way for clinicians to learn about the clinical use of vitamins and minerals to prevent and treat a wide range of diseases—including but not limited to HPV-related diseases—is to access independent publications such as *Journal of Orthomolecular Medicine*,[18] expert-level textbooks,[19] nutrition-inclusive conferences and online courses. A clinician will likely never learn that HPV diseases can be prevented and treated by nutritional interventions by reading and following the mainstream medical journals and mass media. But from the orthomolecular perspective, the rationale supporting such interventions is quite obvious and strongly grounded in legitimate science, biological plausibility, and clinical trials (e.g., antiviral nutrition strategies).[20]

Author information: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, human microbiome and immunonutrition. Dr Vasquez has served as a consultant to Biotics Research Corporation. Dr Vasquez has archived the PDF versions of the herein-discussed rapid replies in free-access depositories, specifically https://ichnfm.academia.edu/AlexVasquez and https://www.researchgate.net/profile/Alex_Vasquez2.

Citations

1. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *BMJ.* 2019 Apr 3;365:l1161. doi: 10.1136/bmj.l1161
2. Brotherton JML.The remarkable impact of bivalent HPV vaccine in Scotland. *BMJ* 2019;365:l1375 https://doi.org/10.1136/bmj.l1375
3. Wallace D. UK's HPV vaccination program 'dramatically' reduces risk of cervical cancer, study shows https://www.foxnews.com/health/u-k-hpv-vaccination-program-dramatically-reduces-risk-of-cervical-cancer-study-shows Published 5 April 2019 and accessed May 2019
4. Russell P. HPV Vaccine Linked to 'Dramatic' Decrease in Cervical Disease. *https://www.medscape.com/viewarticle/911346* April 04, 2019
5. Vasquez A. Critique of "Prescription-strength omega-3 fatty acids to prevent heart disease" by Harvard Medical School 2019 Feb https://www.academia.edu/38289348 and video *https://vimeo.com/314997927*
6. Vasquez A, Pizzorno J. Concerns About the Integrity of The Scientific Research Process—Focus On Recent Negative Publications Regarding Nutrition, Multivitamins, Fish Oil And Cardiovascular Disease. Integrative Medicine 2019 Feb; 8-15 Externally archived at *https://www.ichnfm.org/public*
7. Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. Comment on Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. 2005 Jul 9;331(7508):108-9 PMID: 16002891 PMCID: PMC558659 DOI: 10.1136/bmj.331.7508.108-b
8. Smith R. Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies. PLoS Med. 2005 May; 2(5): e138 Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1140949/ and *https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0020138*
9. "VISION: To prevent cancer and infectious diseases through excellence in the PROVISION OF public health services supporting screening and vaccination." vcs.org.au/about-us/strategic-plan/. Also noted and of importance: Impact of HPV vaccination: Achievements and future challenges. Papillomavirus Research (2019), The

remarkable impact of bivalent HPV vaccine in Scotland. BMJ 2019; 365 :l1375. *https://www.vcs.org.au/our-impact/scientific-publications/* Accessed 2019 May 16
10. Vasquez A. Pharma Echo Chamber, Sociopolitical Matrix, and Power Vortex: A Diagram-Centric Conceptualization. Int J Hum Nutr Funct Med 2019;7:2 Externally archived at *https://www.academia.edu/38476348*
11. Schultz KF, Grimes DA. The Lancet Handbook of Essential Concepts in Clinical Research. London, Elsevier. 2006
12. "The proportion of adults who report taking dietary supplements (such as vitamins, fish oils, minerals etc) has increased slightly since 1998 (there was no change between 1995 and 1998). In 1998, 15% of men and 16% of women aged 16-64 took some form of dietary supplement, which increased to 20% and 26%, respectively, in 2003." The Scottish Health Survey 2003. Chapter 3 Fruit and Vegetable Consumption and Eating Habits. *https://www.webarchive.org.uk/wayback/archive/20180602183443*. "Therefore, routine vitamin D supplementation is recommended for all children over 1 year of age and should be continued until 5 years unless the diet is diverse and plentiful." Scottish Government. Nutritional Guidance for Early Years: food choices for children aged 1-5 years in early education and childcare settings. Published: 23 Jan 2006. *https://www.gov.scot/publications/nutritional-guidance-early-years-food*. Boy wins NHS backing in vitamin D campaign. T*he Scotsman 2009 December https://www.scotsman.com/news/boy-wins-nhs-backing-in-vitamin-d-campaign*. "At scotsneedvitamind.com, we believe the people of Scotland would see health improvements by taking a regular Vitamin D supplement. We think there is enough evidence currently available to make all of us take action, from health care professionals to parents and teachers." *https://scotsneedvitamind.com/about-us/.* "The United Kingdom National Health Services created a program called Healthy Start, which offers vouchers for free vitamin D supplements to qualifying pregnant women, women with a baby under one year old and children under the age of five years located in Scotland, Northern Ireland, England and Wales. In April of 2017, the Scottish government partnered with the Healthy Start program to offer free vitamin D supplements to all Scottish pregnant women, regardless of whether they qualify for vouchers. This joint effort was created to decrease the risk of rickets and other health complications caused by vitamin D deficiency. Scotland offers free vitamin D supplements for all pregnant residents. Posted on: November 28, 2017 by Missy Sturges and John Cannell, MD. *https://www.vitamindcouncil.org/scotland-offers-free-vitamin-d-supplementation.* See also: National Health Services Scotland. Vitamin D. https://www2.gov.scot/resource/0038/00386784.pdf Scottish warning over vitamin D levels. 19 September 2010 https://www.bbc.com/news/uk-scotland-11355810 "Following recommendations from the Scientific Advisory Committee on Nutrition (SACN), Scottish Government advice on vitamin D for all age groups has been updated as follows: Everyone age 5 years and above should consider taking a daily supplement of 10 micrograms vitamin D, particularly during the winter months (October – March)." Scottish Government. Vitamin D. *https://www2.gov.scot/Topics/Health/Healthy-Living/Food-Health/vitaminD* Scottish Government. Vitamin D information for health professionals in Scotland. November 2017 https://www.gov.scot/binaries/content/documents/govscot/publications/pub... "Scots should consider taking vitamin D supplements all-year round, but particularly in autumn and winter, according to new health advice." All Scots advised to take vitamin D says new health guidance. 21 July 2016. *https://www.bbc.com/news/uk-scotland-36856176* "International experts are calling for food in Scotland to be fortified with vitamin D, in an attempt to cut the large numbers of people who develop multiple sclerosis at sunshine-deprived northern latitudes." Add vitamin D to Scotland's food – experts: Dosing whole population would help cut levels of multiple sclerosis, say scientists. 23 Dec 2011 *https://www.theguardian.com/uk/2011/dec/23/vitamin-d-scotland-food-multi*. All Scottish babies should have vitamin D supplement, CMO says. The Pharmaceutical Journal 2017 Nov 30. *https://www.pharmaceutical-journal.com/news-and-analysis/news/all-scotti...* Accessed April 2019
13. Palmer T. Bivalent HPV vaccine in Scotland is having a considerable and sustained effect. *https://blogs.bmj.com/bmj/2019/04/03/tim-palmer-bivalent-hpv-vaccine-in-scotland-is-having-a-considerable-and-sustained-effect/* Posted April 3, 2019 and accessed May 2019
14. See HPV vaccine danger-related rapid responses to the article online https://www.bmj.com/content/365/bmj.l1161/rapid-responses, especially from Noel Thomas (*https://www.bmj.com/content/365/bmj.l1161/rr-6* posted 10 April 2019) "When Steve Hinks drew attention to the totals for the HPV vaccine in 2017, there were over 300,000 adverse events recorded, and more than 400 deaths, following HPV vaccination. (2,3) ... However, a Freedom of Information request to the MHRA last year, revealed that in the period May 2006- -Feb 2018, in the UK, adverse event reports for the HPV vaccine totaled 3194, total reactions 12,783, fatal outcome reports, 8. (4)" See also the following:
15. Smith R. The hypocrisy of medical journals over transparency. *https://blogs.bmj.com/bmj/2018/01/24/richard-smith-the-hypocrisy-of-medical-journals-over-transparency/* Posted January 24, 2018 accessed May 2019
16. Committee on Publication Ethics. Retraction Guidelines. *http://publicationethics.org/files/retraction%20guidelines*.pdf Accessed May 2019

 ISSN 0317-0209

17. The challenge of the post-truth era. Nat Cell Biol. 2018 Nov;20(11):1231. doi: 10.1038/s41556-018-0231-z. See also: Talton J. In our post-truth era, how we view reality is more important than ever. Seattle Times January 3, 2019 https://www.seattletimes.com/pacific-nw-magazine/in-our-new-post-truth-era-the-way-we-view-reality-is-more-important-than-ever/. See also: Harari YH. Are we living in a post-truth era? Yes, but that's because we're a post-truth species. Sep 7, 2018 *https://ideas.ted.com/are-we-living-in-a-p ost-truth-era-yes-but-thats-because-were-a-post-truth-species/*
18. Vasquez A. Orthomolecular Medicine, Catalytic Creativity, and the Psychosocial Ecosystem. Journal of Orthomolecular Medicine. 2018 Dec *https://isom.ca/article/orthomolecular-medicine-catalytic-creativity-and-the-psychosocial-ecosystem/*
19. Vasquez. Textbook of Clinical Nutrition and Functional Medicine. Barcelona; International College of Human Nutrition and Functional Medicine, 2016
20. Vasquez. Antiviral Nutrition (ebook; *https://www.amazon.com/dp/B00OPDQG4W*) also published as Antiviral Strategies and Immune Nutrition (paperback; https://www.amazon.com/dp/1502894890). CreateSpace Independent Publishing Platform; 2014

 ISSN 0317-0209

THE PATH AHEAD

Concerns About The Integrity of The Scientific Research Process—Focus On Recent Negative Publications Regarding Nutrition, Multivitamins, Fish Oil And Cardiovascular Disease

Alex Vasquez, DC, ND, DO; Joseph Pizzorno, ND, Editor in Chief

Abstract

The next step in reestablishing credibility seems to us honesty and recognizing we all share a common goal of the health and wellness of the human community and the planet. Everyone agrees that the current healthcare system, despite its many incredible successes, is also showing its limitations and is no longer sustainable. We believe the solution starts with us the researchers and editors. A good first step might be formally recognizing the errors and showing how we can and *intend* to get better.

Evidence-based medicine—by definition—requires objective, reliable and accurate research and reviews from which to make the best decisions in patient care and public policy. The causes of inaccurate information, ranging from presumably innocent mistakes all the way to apparently intentional fraud, affect all scientific and biomedical disciplines.[1] While these accidental and intentional errors can derail our understanding of diseases and impact tens of thousands of affected patients, such inaccuracies in the field of nutrition c… worldwide.[2] While… a specific disease… human populatio… nutrition researcl… particularly conte… nutrition researcl… healthcare profess… nutrition. Clinical… vast majority of … medical training p… are obviously i… gastroenterology[7]… training in clini… proclaims itself a… including the entire territory of clinical nutrition.[10] A major and serious problem arises when unskilled and invalid research is published by authors (including nonphysician journalists[11]) in major journals which mischaracterizes the validity of nutrition interventions (e.g., essentially always concluding that nutritional interventions are inefficacious or potentially hazardous) and then such research is used politically and in the media to disparage, restrict and regulate practitoners and nutrition supplement industry[12] to the detriment of human health.

Several factors disrupting the integrity of nutrition research are commonly found in studies published by "elite" universities in "top-tier" journals, which are then republished and distributed as "headlining news" in newspapers, magazines, and television via which they …ent policy and …ons of people. … examples of …lications, lists …sed solutions. …pendent upon …stigative and …s of clinical …rovements are … ignorance in …

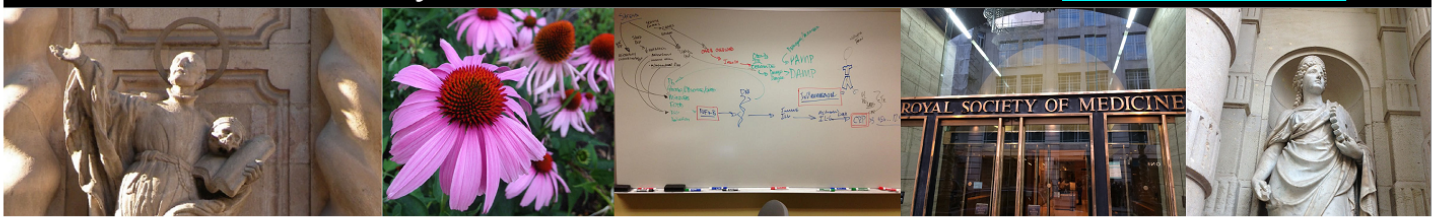
…tion

…eview recent examples of questionable or inaccurate publications related to nutrition. Perceived shortcomings are documented with both citations here and links to more detailed and authoritative reviews and video presentations. In some instances, speculations regarding the cause and consequences of identified errors are provided.

PDF articles: Full-text archives of the author's articles are available per the following:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.ichnfm.org/public
- **VIDEO**: BRIEF Critique of "Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" https://vimeo.com/287650812
- **VIDEO:** Bad Science in Medical Nutrition: Politics of Fish Oil https://vimeo.com/314997927

International Journal of Human Nutrition and Functional Medicine www.ICHNFM.ORG



Perspective, Opinion, Editorial • Education • Academia • Wage Theft • Corruption

Ending the Exploitation of Experts Begins with Educating Them about Employment, Curbing Enthusiasm to Preserve Enthusiasm

Alex Vasquez DC ND DO FACN

My own paths toward and perspectives on Education

My passion for teaching and education began "formally" when I was about 9 years of age, sitting on the floor of Ms Hall's 4th grade classroom; from that vantage as I sat somewhat near my best friend Robert, I saw the destructive power of bad teaching and discrimination, and from that day I started analyzing teachers, teaching methods, educational and social structures, and ways to convey knowledge and inspire students. Additionally inspired by my teacher of English and Literature in my final years at Riverside Military Academy, I began college with the plan of eventually teaching "something—most likely English and Literature" because I appreciated and valued teaching, proper grammatical structure, and nuanced use of language; I later developed and interconnected my interests in teaching, writing, language, physiology, medicine, and nutrition to complete three doctorate degrees in the health sciences and publish more than 120 articles, letters, rebuttals, monographs, and books on a wide range of topics, with those publications ranging from dense 1-page Letters and Responses to published research up to single-author textbooks of more than 1,180 pages. I have taught at various colleges and universities at the undergraduate, graduate/Masters, and Doctorate levels and have lectured internationally for post-graduate medical education. I see teaching not simply as effective transferal of information, but also as a means to interconnect and inspire generations of people, notably in a reciprocal manner. At its best, teaching and learning are activities that reflect and support love for life itself.

Oh, the stories I could tell you about the innards of Academia, "nonprofits", and "accredited" schools

I would be happiest to tell you that Academics and Administrators are vanguards
support for fellow Professors, and
commitment is to truth and realit
setting ablaze the passions of the
they teach, lead, and supervise; I'
in flower fields like a professoria
singing a rhythmical rendition of "*The Hills are Alive…with the…Passions of Education and Intellectual Integrity*." But a pollyannic representation of my observations would be a misrepresentation of the realities I have seen and experienced. I have seen university presidents lie to their students, expel experts for the sake of maintaining their own petty powers and preferences, and I have seen entire academic administrations lie (misrepresent) in unison to their boards of trustees and their accreditation commissions. I have seen stand-alone academic programs make millions of dollars in profit, while its administrators refuse to pay a living wage to doctorate-level infrastructure and while allowing themselves 6-week European vacations during major institutional initiatives. I have seen administrators lie to accreditors and allow students to cheat their way through graduate programs (by bypassing faulty examination software in online programs), and I have seen accreditors turn a blind eye to obvious university corruption, made worse when the accreditation commission is infiltrated by university administrators—thus did "accreditation" come to lose its value. I have seen "nonprofit educational institutions" underpay their faculty, plagiarize from their faculty, resell the work of other professionals without notice or compensation, and then pay their upper administrators in excess of US$160,000 for less than part-time work—thus did "nonprofit organization" come to lose its value. I have seen schools blackmail excellent professors and leaders in education with gag orders, legal threats, and financial bribery (range US$25,000 up to $250,000) to buy their silence about institutional corruption. I have corresponded with employment attorneys, State Attorneys General, and US Department of Education, most of whom shrugged their shoulders and said, "That's the way it is in academia." Sorry

PDF articles: Full-text archives of the author's articles are available:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.inflammationmastery.com/reprints
- https://www.ichnfm.org/public

Updates: The most complete version of
Functional Medicine ® ISSN 2378-4881

Citation: Vasquez A. Ending the Exploitation of Experts Begins with Educating Them about Employment, Curbing Enthusiasm to Preserve Enthusiasm. *Int J Hum Nutr Funct Med* 2016; epub in press

International Journal of Human Nutrition and Functional Medicine (ISSN 2378-4881) ICHNFM.ORG/journal

Barceloneta sunset © 2019 by Dr Vasquez

Tutorial & Editorial • Scientific Writing • Journal Editing • Professional Experience • Video

How to Improve Scientific Writing and Journal Editing: A Short Narrative-Video Guide, Part I

Alex Vasquez DO ND DC FACN

Introduction

"Hello everyone, Dr. Alex Vasquez here, and today I'm going to start a different series of videos, and this time the conversation is going to focus around journal editing and writing. I'm calling this "*Editing and Writing Tips #1*", and I'm going to start with a few of my own perspectives and experiences, then I'll talk about a few basics, and a few influential ideas. In later videos, I will talk about some more specific examples, and then perhaps at some point we will have a review and conclusion.

Early Experiences and Influences

Very briefly I'll talk about some of my own experiences, and the reason for my doing this is to share with you and segue into some examples that I think are very important. Basic though they might be, a lot of our success in various fields of life actually comes from respecting and appreciating and utilizing those basic concepts.

Let us start here with some of my initial experiences. I started becoming aware of language and the fact that I had some facility for it, first, when I was about 12 years old. I remember writing a poem in class, and again this is somewhat peripheral to the main topic of today, but I do remember that e
kind of my entryway, I think, i
that our assignment was to wr
remember writing this poem in cl
on and on, and—compared with s
I just realized that writing for me

Then again, when I wa
military school, I remember in ou

being asked questions, and I remember just how the answers to understanding grammar and language just came very easy to me, and I do remember feeling like I had some facility for the structure of language.

Another influential experience I had when I was about 11 years old, totally unrelated to language, is that we took, in the late 1970s or early '80s, a Computer Science class in our elementary school, and I remember that class also specifically having some influence on me, in terms of structuring logic. We basically had to write our own computer programs and this was back when computers were very new. Obviously today everybody has computers; back in the late '70s, computers were a novelty. I consider myself lucky to have taken this Computer Science class; it was obviously extremely basic, but we did have to write some code and what I remember from that is just the sequential manner in which communication has to take place in order to be successful. In this case, we were writing programs for computers and doing basic

> "Writing comes from the entirety of one's experience."
> Dr Alex Vasquez

PDF articles: Full-text archives of the author's articles are available:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.inflammationmastery.com/reprints
- https://www.ichnfm.org/public
- See original video here: https://vimeo.com/318326979

Citation: Vasquez A. How to Improve Scientific Writing and Journal Editing: A Short Narrative-Video Guide, Part 1. *Int J Hum Nutr Funct Med* 2019;7:1 https://www.ichnfm.org/journal2019a Externally archived at https://www.academia.edu/38426918

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 34, NUMBER 1
PUBLISHED: MARCH 2019

Editorial

Misrepresentations of Clinical Nutrition in Mainstream Medical Media: Growing Importance of Legitimate Expertise in Independent Peer-Reviewed Publications - Part 1

2018 As a Milestone in the Post-Truth Era

Among the various topics that have either interested or fascinated me throughout my youth and well into my adult years, Nutrition has certainly reigned supreme. My personal routine has been to read as much as reasonably and practically possible on the topic, while not doing so to the exclusion of other topics in biomedicine, psychosociology and philosophy. Thus, with roughly 30 years of experience in reading books and primary research in the field of Nutrition, I could not help but notice the radical departures that occurred in 2018 from the previous norms to which I had grown accustomed.

Of course, 2018 was not the first year during which "bad research" was published in mainstream medical journals and then replicated throughout the echo chamber of mass media; one could observe this periodically occurring throughout the past 50 years, starting not at least with the demonization of dietary cholesterol and the glorification of processed foods, especially refined grains and so-called vegetable oils. But in 2018 what many of us observed was not simply poorly performed research but, in s
es, radical departures from any attempt to pre
descriptions that could be considered "reason
previous standard.[1] Especially related to the
trition, mainstream medical journals and the
which parrots their conclusions have begun
overt misrepresentations of Nutrition with re
gard for science, logic, biomedical history and

One has to be aware of a few key ironies
terize mainstream medical discussions of nutri
that 1) medical physicians receive essentially
in clinical nutrition in their graduate school e
in their post-graduate residency training[2], 2)
sicians and organizations publish "research"
commentaries (both of which commonly conc
tritional interventions are inefficacious or unsafe), despite their lack of formal education on the topic, and then 3) mainstream medical voices consistently call for "regulating the nutrition supplement industry" despite their lack of training on the topic and because of negative conclusions based on their own poorly conducted research and self-serving conclusions. As such, not only are the map-makers blind, but they mislead their blind followers, and then both groups promote themselves as expert cartographers and guides when advising the public on an area that none of them have studied or understood. We should have no surprise whatsoever when the "medical community" publishes poorly conducted and self-serving "research" on the topic of nutrition, to reach their desired conclusion that nutrition is unsafe and inefficacious, and that the profitable market needs to be managed of course by the selfsame "medical community" that is never received a decent 15 minutes on the topic of therapeutic nutrition. Pervasive and persistent ignorance on the topic of nutrition among medical physicians must be understood as intentional and strategic, because otherwise this problem would have been solved 30 years ago when it was first discussed during what was called at the time the "golden age of nutrition."[3] The easiest way to manipulate people and to keep them in a perpetual state of confusion, ineffectiveness, and dependency is to

PDF articles: Full-text archives of the author's articles are available per the following:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.ichnfm.org/public
- VIDEO: BRIEF Critique of "Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" https://vimeo.com/287650812
- VIDEO: Bad Science in Medical Nutrition: Politics of Fish Oil https://vimeo.com/314997927

when pondering the probable future of intellectual integrity and the products of education.

 ISSN 0317-0209

Mitochondrial Medicine Arrives to Prime Time in Clinical Care: Nutritional Biochemistry and Mitochondrial Hyperpermeability ("Leaky Mitochondria") Meet Disease Pathogenesis and Clinical Interventions

Alex Vasquez, DC, ND, DO, FACN

Alex Vasquez, DC, ND, DO, FACN, is director of programs at the International College of Human Nutrition and Functional Medicine in Barcelona, Spain and online at ICHNFM.org. (*Altern Ther Health Med.* 2014;20(suppl 1):26-30.)

Corresponding author: Alex Vasquez, DC, ND, DO, FACN
E-mail address: avasquez@ichnfm.org

MITOCHONDRIAL MEDICINE ARRIVES TO GENERAL PRACTICE AND ROUTINE PATIENT CARE

Mitochondrial disorders were once relegated to "orphan" status as topics for small paragraphs in pathology textbooks and the hospital-based practices of subspecialists. With the increasing appreciation of the high frequency and ease of treatment of mitochondrial dysfunction, this common cause and consequence of many conditions seen in both primary and specialty care deserves the attention of all practicing clinicians.

We all know that mitochondria are the intracellular organelles responsible for the production of the currency of cellular energy in the form of the molecule adenosine triphosphate (ATP); by this time, contemporary clinicians should be developing an awareness of the other roles that mitochondria play in (patho)physiology and clinical practice. Beyond being simple organelles that make ATP, mitochondria play clini… ce—contains inflammati… kinase and disease such… omparatively disorders su… n) and—like stated durin… h active and Nutrition a… that need to September … to appreciate mitochond… the highest mitochondrial dysfunction to clinical diseases must be considered on a routine basis in clinical practice. *Mitochondrial medicine* is no longer an orphan topic, nor is it a superfluous consideration relegated to boutique practices. Mitochondrial medicine is ready for prime time—now—both in the general practice of primary care as well as in specialty and subspecialty medicine. What I describe here as the "new" mitochondrial medicine is the application of assessments and treatments to routine clinical practice primarily for the treatment of secondary/acquired forms of mitochondrial impairment that contribute to common conditions such as fatigue, depression, fibromyalgia, diabetes mellitus, hypertension, neuropsychiatric and neurodegenerative conditions, and other inflammatory and dysmetabolic conditions such as allergy and autoimmunity.

BEYOND BIOCHEMISTRY

Structure and function are of course intimately related and must be appreciated before clinical implications can be understood and interventions thereafter applied with practical precision. The 4 main structures and spaces of the mitochondria are (1) intramitochondrial matrix—the innermost/interior aspect of the mitochondria containing various proteins, enzymes of the Krebs cycle, and mitochondrial DNA; (2) inner membrane—the largely impermeable lipid-rich convoluted/invaginated membrane that envelopes and defines the matrix and which is the structural home of many enzymes, transport systems, and important structures such as cardiolipin and the electron

importance; just as we have come to appreciate the

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 33, NUMBER 6
PUBLISHED: DECEMBER 2018

Editorial

Orthomolecular Medicine, Catalytic Creativity, and the Psychosocial Ecosystem

Transitioning From One Year to the Next

Various cultures since time immemorial have marked and celebrated the winter solstice with celebrations, meals with friends and family, and time away from work; transitioning from one calendar year to the next has given people pause and a moment to reflect on the events that happened in the past year and what might be anticipated in the next. Reflection with anticipation along with the realization that the future is somewhat malleable inclines people to imagine how the future might be shaped by the exertion of some modicum of creativity and effort. Any realistic conception of how we might improve the near future must segue from our recent past; we must have an awareness of what is going on around us as we look toward the future to visualize ourselves living within it and also acting upon it. What is going on in the world and how might I act upon that trend and flow in order to improve both its transition and its destination? What should each of us do on a personal level to (in the words of Mahatma Gandhi) be, embody, and materialize the change(s) that we want to see in the world?

Salutation and Introduction From the Journal's New Editor

Over the past few years I have reflected on several occasions how much I enjoy editing, and so I was correspondingly surprised and pleased when I was offered the opportunity to be the next Editor for the *Journal of Orthomolecular Medicine.* I began studying nutrition and orthomolecular concepts in my teen years and more diligently as I entered graduate school in the early 199 trition" book that I reac *Your Nerves* (1975) by this was followed imm tures of Jonathan V Wr of whom would later b University. By the mid- Jeffrey Bland PhD had tional medicine, which and personal[3] reasons. By this time my own personal library contained several hundred books, mostly dedicated to nutrition and health with another large section on philosophy and psychology. In 1994, I joined the Review Staff of the *Journal of Naturopathic Medicine,* and I started publishing nutrition articles, perhaps most of which might be seen as practice in preparation of an important letter published in 1996 by the American College of Rheumatology in their journal *Arthritis and Rheumatism.* Since those early years and during the course of three doctorate degrees and teaching thousands of students/attendees internationally, I have reviewed for[4] and published in[5] a wide range of refereed journals in addition to publishing commissioned books, chapters, and independent publications and videos. Being an author and reviewer for many different publications—along with my experiences teaching internationally, treating patients in various settings, designing and directing academic programs, and producing educational videos—has given me a wide range of experiences and insights that I hope to bring to the benefit of the *Journal of Orthomolecular Medicine.*

We Must Work Together if We Are Going to Succeed

I have to start this conversation with a few hopes, assumptions, and beliefs, namely that you (the reader) and I (the author and new Editor) have a few things in common. On a professional level, by virtue of the fact that you are reading this essay, I will assume that you are interested or actively engaged in healthcare, medicine, nutrition, research and/or public health. I might also imagine that some smaller percentage of our new and established readers are perhaps less inclined toward the mechanisms and more drawn to the *Journal of Orthomolecular Medicine* for its potential humanistic insights and social contributions; we can reasonably competent healthcare ate nutrition) are basic mit a counterargument of my assertions, they more to the point, my rdless of personal po- share some common the following:

- We each want to receive and deliver the best healthcare possible: If we have a problem, then we each want the best possible solution. Efficiency of time or money is not the top priority when we are seeking solutions

International Journal of Human Nutrition and Functional Medicine www.ICHNFM.org

Photos © by Dr Vasquez, 2013-2015

Mini-Review • Continuing Education • Microbiome • Dysbiosis • Infectious Disease

Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts

Alex Vasquez DC ND DO FACN

Experience and Perspectives

Many years ago when I published my first books[1,2] and articles[3] detailing "dysbiosis", the word could hardly be found in the Medline index, the topic was controversial at best and ethereal at worst, the term "microbiome" (first published in French in 1949 and in English in 1988) was virtually unknown, and I spent most of the time and space in my lectures and articles substantiating and defending the condition's existence. These days, everyone is talking about microbiome, dysbiosis, "leaky gut" (thanks largely to Leo Galland MD), and my 1996 article on "Silent Infections and Gastrointestinal Dysbiosis" has been downloaded at least 4,000 times and is one of the top 1% most popular articles on Academia.edu.[4] In the preparation of my dysbiosis lecture at a major functional medicine conference in 2010, I found that only 180 Medline articles indexed the term "dysbiosis", and now—slightly less than five years later—more than 1,200 articles index that term. Obviously, the dysbiosis concept has

"Dysbiosis" is an important concept, but doctors cannot treat concepts.

We have to define, describe, and deconstruct the microbes, molecules, and mechanisms into their components, then rebuild a conceptual scaffold and intellectual structure that becomes a useful tool that, with study and experience, can be used in a clinical setting to effective benefit.

practical application is a bit indelicate and cumbersome beyond the most commonly repeated advice of advocating probiotics, avoiding antibiotics, perhaps delving into using botanical antimicrobials and laboratory testing. Breath testing (an insensitive test for only one subtype of gastrointestinal dysbiosis) and microbiologic testing have become popular to the point of overuse as doctors grapple for clinical clues. (Noteworthy in the conversation on functional laboratory testing is that one functional medicine laboratory in particular used inaccurate proprietary microbe-identification methods to extract

ney only to
uffering and
to do with it
Medicine
microbiota
the comple
Project, the
that live in
to anxiety
tantalizing
therapeutic
being integ

PDF articles: Full-text archives of the author's articles are available:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.inflammationmastery.com/reprints
- https://www.ichnfm.org/public
- **See various videos and course excerpts here: https://www.ichnfm.org/image-gallery-dysbiosis-course**

M
uman
edicine
uch

Citation: Vasquez A. Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts. *Int J Hum Nutr Funct Med* 2015;v3(q2):p1

CME
CONTINUING MEDICAL EDUCATION

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

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. **Gilbert Manso, MD**, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. **John Cannell, MD**, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 2 hours.

OBJECTIVES

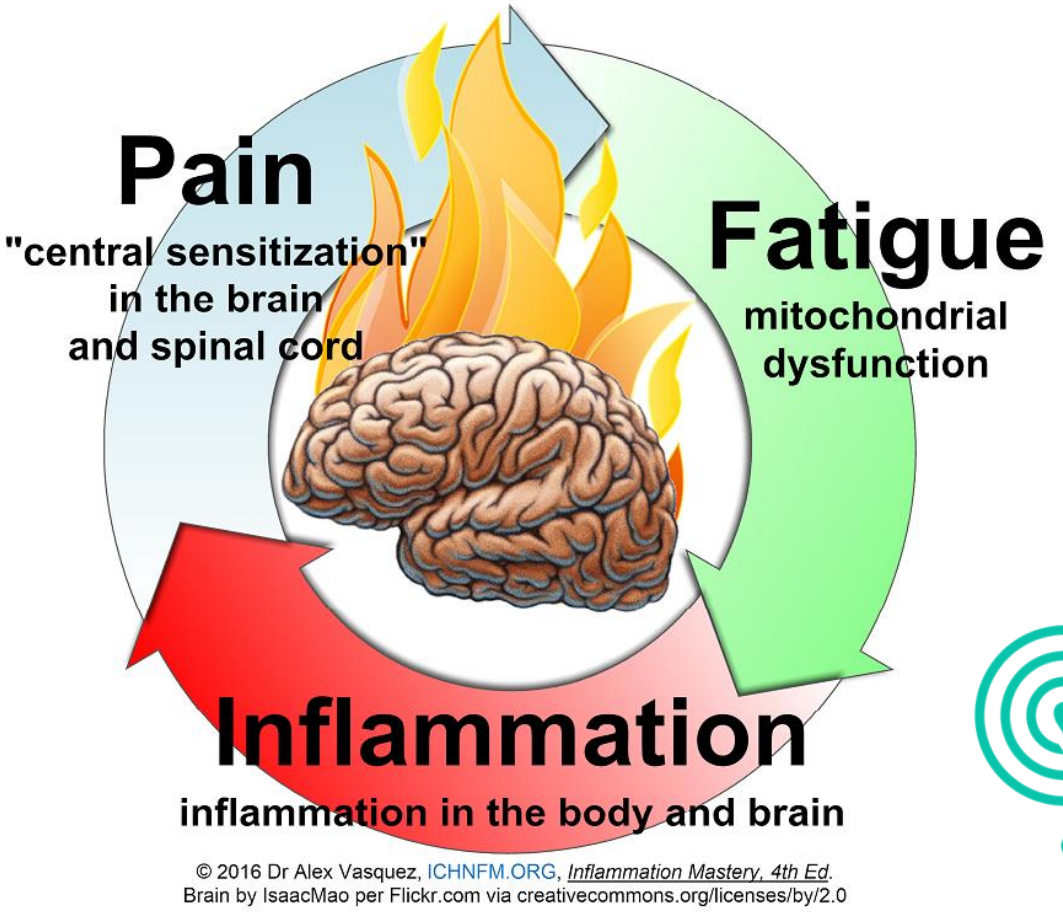
Upon completion of this article, participants should be able to do the following:

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 imple
proper doses and wi

*Reprint requests: InnoVision Communica
phone, (760) 633-3910 or (866) 828-296
innerdoorway.com. Or visit our online C
-therapies.com and selecting the Continu*

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

Brain Inflammation
in Chronic Pain, Migraine and Fibromyalgia
The Paradigm-Shifting Guide for Doctors and Patients Dealing with Chronic Pain



Alex Vasquez, D.C., N.D., D.O., F.A.C.N.

ICHNFM.ORG • InflammationMastery.com/pain

DOWNLOAD FREE SAMPLE: https://www.amazon.com/Dr-Alex-Vasquez/e/B00AT5764Y

- **VARIOUS VIDEOS AND BLOGS**: https://www.ichnfm.org/braininflammation
- **INFO**: https://www.inflammationmastery.com/fibromyalgia
- **INFO**: https://www.inflammationmastery.com/migraine
- From ***Inflammation Mastery, chapter 5***, the two sections specific to migraine and fibromyalgia were also published separately as ***Pain Revolution*** (full-color printing; https://www.amazon.com/dp/B01AR3NX0S) and ***Brain Inflammation in Chronic Pain, Migraine and Fibromyalgia: The Paradigm-Shifting Guide for Doctors and Patients Dealing with Chronic Pain*** (black-and-white printing; https://www.amazon.com/dp/B01EQ9KMH6/); both versions are also available in digital ebook format for phone, computer, iPad via the free Kindle software

The New York Academy of Sciences 200 Years

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Annals *Reports*
COMMENTARY

Biological plausibility of the gut–brain axis in autism

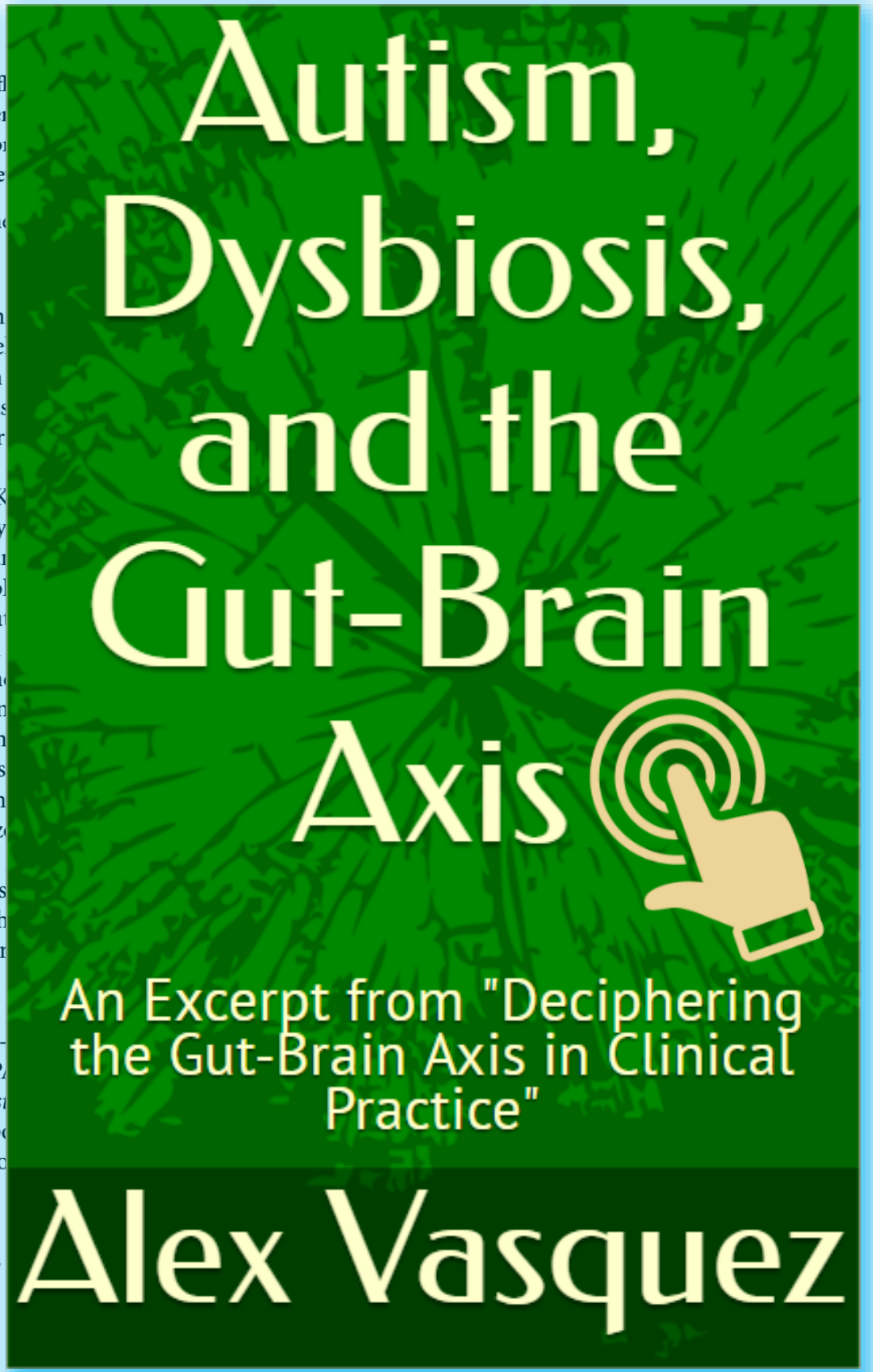
Alex Vasquez

**Organic abnormalities with neuroinfl
purine metabolism, neurotransmitte
noted in autism, and many of these ab
metabolites, and heightened serum le**

Keywords: gut–brain axis; autism; m

In their recent review, Sherwin
among many other issues, the re
gut microbiome–brain axis with
section subtitled "Microbiota-bas
the treatment of autism: hype or
et al.[1] largely discuss preclinical
the 2017 open-label study by K
used a sequence of oral vancomy
polyethylene glycol laxative, a
human fecal microbiota transpl
clinical benefit in subjects with au

Readers will likely benefit from
tional relevant clinical studies, in
lication by Sandler *et al.*[3] showin
of autistic manifestations followin
oral vancomycin, as well as cas
ing positive impact of various an
apies (metronidazole, ketoconaz
cillin) in patients with autism.[4,5]
have been shown to have gut dys
as well as *Clostridia* species,[6] th
group of bacteria noted for their pr
rotoxic substances. International
consistently demonstrated that
have heighted production of 3-(3-
3-hydroxypropionic acid (HPHP
phenylalanine metabolite of *Clos*
trointestinal tract.[7,8] HPHPA rep
with the conversion of dopamine to



doi: 10.1111/nyas.13516
Ann. N.Y. Acad. Sci. 0 (2017) 1–2 © 2017 New