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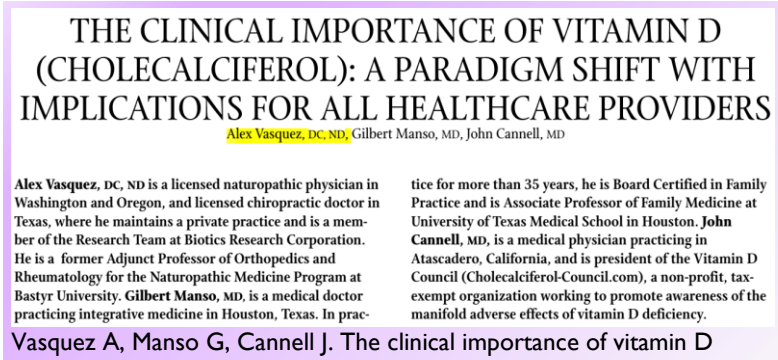
Iatrogenic Induction of Vitamin D Deficiency: The Position Against This Potentially Harmful Practice and Open Invitation for Its Proponents to Articulate Substantiation

Alex Vasquez DC ND DO FACN

Introduction

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

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



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

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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 http://ow.ly/LkBoK

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)[9]; the scientific rationale for this protocol and its means of implementation remain unclear, inserting doubt and promoting unnecessary clinical inertia among clinicians.[10] 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[11] 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[12] 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[13,14,15]): 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."[16] 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."[17]
- 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."[18] *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."[19] 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."[20]

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[21]): "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[22]): 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[23]): "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."[24] ❷ "METHODS: 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."[25]

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 in this introduction and invitation, 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 to professional forums 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 10 Apr 2015; if any changes, corrections, withdrawals are made or rebuttals/replies posted, these will be made freely available at www.ICHNFM.org and www.IntJHumNutrFunctMed.org.

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

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

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