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 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, 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 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 catabolism and use of approximately 4,000 IU per day for adults⁴, consistent with the daily doses of 4,000-10,000 IU 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 induced nutritional deficiency to clearly articulate their position, its mechanisms, and to provide a risk-benefit ratio substantiating what otherwise is 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 Vancouver 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, M.D., is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (CholecalciferolCouncil.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.


Updates: The most complete version of this article is available at the following location [http://intjhumnutrunctmed.org/](http://intjhumnutrunctmed.org/)

Copyrights: Copyright © 2015 by author(s) and International College of Human Nutrition and Functional Medicine www.ICHNFM.org

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;3(2):1
**Background**

Vitamin D3 functions via the vitamin D receptor (VDR) to support innate and acquired immune responses via several mechanisms including: 1. regulating inflammation via mechanisms that include suppression of NFkB, 2. inhibiting viral replication and enhancing anti-viral defenses via elaboration of antimicrobial peptides (AMP), 3. via the AMP, enhancing innate immunity against cancer, bacteria, fungi and other microbEs, 4. 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 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 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 metabolites, which are promulgated in this model to be immunosuppressive]).\(^9,10\) I propose here that their position is easily deflated with minimal effort and that the arguments espoused by its proponents lack internal consistency. As an of the example, when they note that patients benefit from vitamin D supplementation, these proponents countermeasure not with fact but with additional unsupported 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 superstition 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 improved 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 (1000 IU)/d to attain" demonstrated clear authority of the literature and paved the way for our "paradigm shift" paper that followed after (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.

**Counterarguments against iatrogenic induction of vitamin D deficiency**

**Counter argument #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 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 immunomimpairment, 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 a favorable risk-to-benefit ratio for their intervention.

**Counter argument #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 microbial monkeywrench?

**Counter argument #3—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): "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." "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."

- **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." 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:** "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." "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."

**Counter argument #4—The Marshall Protocol claims 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 the Marshall Protocol's inclusion of 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 and therefore causal protective benefits of vitamin D supplementation.

- **Meta-analysis of randomized controlled trials:** Vitamin D supplementation and total mortality (Arch Intern Med. 2007 Sep): “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): 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, 95% CI 0.03-0.51, and irregular vs no supplementation 0.16, 0.04-0.74. 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 (1.0-9.0) 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 the fact that severe vitamin D deficiency rickets was associated with a 300% increased risk for diabetes.

- Estimated benefits in 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 (22,300-52,300 deaths), representing 16.1% (9.7-22.7%) of annual deaths and the economic burden by 6.9% (3.8-10.0%) or $14.4 billion ($8.0 billion-$20.1 billion) less the cost of the program. It is recommended that Canadian health policy leaders consider measures to increase serum 25(OH)D levels for all Canadians."

- Vitamin D reduces risk of multiple sclerosis: 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."

Invitation

Advocates for the "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 involved microbes and mechanisms along with risk:benefit analysis addressing the concerns described in this introduction and invitation.

<table>
<thead>
<tr>
<th>Proven benefits based on multiple studies of vitamin D3 supplementation include excellent risk:benefit in the prevention and treatment of many conditions*</th>
<th>Faults needing remediation in favor of &quot;iatrogenic induction of vitamin D deficiency as therapy against infections and infection-induced inflammatory disease&quot; per Marshall, Waterhouse, et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>0. Essentially nonexistent—molecular mechanisms weakly explained, many of their citations in their Ann N Y Acad Sci 2009 Sep paper 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.</td>
</tr>
<tr>
<td>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</td>
<td>0. No risk:benefit analysis provided in their proposal</td>
</tr>
<tr>
<td>3. Reduction of cardiovascular risk (modest)—mechanisms include reduction in inflammation and hypertension</td>
<td>0. Numerous inconsistencies in their model</td>
</tr>
<tr>
<td>4. Prevention/alleviation of nearly all autoimmune diseases (strong)—specifically multiple sclerosis, autoimmune diabetes, and rheumatoid arthritis</td>
<td>0. Benefit not shown to outweigh risks for nontreatment of conditions that respond to vitamin D supplementation</td>
</tr>
<tr>
<td>5. Reduction musculoskeletal pain (very strong)—back pain, migraine, limb pain, fibromyalgia-like presentations, opioid requirements</td>
<td>0. 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</td>
</tr>
<tr>
<td>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</td>
<td>*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 (cholecalciferol). Altern Ther Health Med 2004 Sep available at FunctionalInflammology.com/reprints</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

24. Mirzaei et al. Gestational vitamin D and the risk of multiple sclerosis in offspring.


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 www.InflammationMastery.com/reprints


14. "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


