Review Article

Vitamin D and extra-skeletal health: causality or consequence

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Abstract

Vitamin D deficiency /insufficiency is widely recognized as a global health problem that is likely to be involved in pathogenesis or progression of many acute and chronic health disorders. Its relation to skeletal health has been clearly demonstrated and thoroughly examined. This review aims to highlight the continuous debate about the relation between vitamin D and extra-skeletal health and whether it is a causality or just an association. Overall, the available evidence does not meet the criteria for establishing cause-and-effect relationships because of the limitations of observational studies to corroborate the causality due to many potential confounders. Moreover, the causal relationship couldn't be established in randomized studies or in many meta-analyses. This may reflect the fact that vitamin D level reduction is just a biomarker of ill health. The inflammatory processes involved in the disease occurrence and the functional limitations of the diseases would have a role in reducing serum 25-hydroxy vitamin D "25 (OH) D" level, which would explain why low vitamin D is reported in a wide range of disorders. This may underscore the possibility of harm instead of benefit of vitamin D supplementation when its exact role is not fully established, thus many guidelines and interest groups are still hesitant toward recommending replacement in extra-skeletal disease. Future directions entails the need for a large well-designed randomized control trials (RCTs) to resolve the active debate on the benefits of vitamin D replacement for extra-skeletal disease, and not only that, future studies should establish specific, clinically relevant effects of vitamin D repletion, provide cut-values for optimal serum levels of 25 (OH) D, and appropriate doses for non-skeletal health benefits.

Key words: Vitamin D; Diabetes; Cancer; immune system; cardiovascular disease

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Introduction

The discovery of the potential non-skeletal functions of vitamin D has received tremendous amount of attention with increasing reports of association between vitamin D deficiency and a wide range of health conditions. Over the last decades, the defined genome-wide map of vitamin D receptor (VDR) binding was recognized to potentially regulate the pleiotropic effects of the active metabolite to 1,25-dihydroxy vitamin D 3($1,25\text{-}(OH)_2D_3$). [1] The VDR and the alpha-hydroxylase enzyme are the key factors in the non-skeletal functions of the VDR-vitamin D endocrine system. Many tissues express the 1-alpha-hydroxylase enzyme including the skin, gastro intestinal tract, vessels, mammary epithelial cells, osteoblasts, osteoclasts and granulomatous tissues, and therefore can generate the active form in an auto or paracrine way. [2] The active form then binds to the VDR which is expressed in nearly all nucleated cells, then vitamin D with its VDR form a hetero dimer with retinoid X receptor which binds to genomic sequences (vitamin D response elements) to regulate gene expression. [1] Many reviews has explored the relationship between vitamin D and extra-skeletal health. [3-5] The objective of this review is neither to examine in depth all the available evidence exploring the relationship between vitamin D and extra-skeletal health, nor to look into the breakthroughs and molecular advances in vitamin D in relation to this subject. Rather it aims to highlight the results or conclusions of conflicting major trials that have explored this relationship to contribute further in this active debate of causality vs. consequence. It is more likely to end up with more questions in mind rather than finding answers by the end of the review.

Search Strategy

The review had intentionally focused on major RCTs that had conflicting conclusions to serve the aim of the intended debate. The literature review was conducted on PubMed, Google scholar and science direct search engine using the following search key words:

(Vitamin D, Diabetes, Cancer, immune system and cardiovascular disease). And some search filters were applied on and off such as (systematic review, meta-analysis, randomized control trials, observational study) with special focus on human studies and papers published in English.

Immune Mediated Diseases

The field of vitamin D immunology has revolutionized long time back by the findings that monocytes, macrophages, dendritic cells and activated T and B cells express the specific high-affinity VDR and 1α-hydroxylase activities. [6] Existing animal and human data indicate that $1,25\text{-}(OH)_2D_3$ could modulate immune system in the direction of immune regulation and anti-inflammation through inhibition of the acquired autoimmunity, this has been thoroughly reviewed by Ponsonby et. al. [7] and through activation of the innate immune system. [8] The mechanism of action of vitamin D on mycobacterium tuberculosis (TB) infection for example, became clearer when scientists reported the effect of activation of toll-like receptors (TLR) of the macrophages by innate immune response, in humans infected with TB, on the up-regulation of VDR expression. [9] Activation of these receptors also leads to generation of intra cellular active form of vitamin D and eventually leading to the production of an antimicrobial peptides such as "Cathelicidin." [9,10] Both cathelicidin and β-defensin play a major role in the immune defense especially in respiratory tract infection via inactivating viral pathogens [11] as well as recruiting phagocytes. [12] VDR polymorphism is common and could be associated with defects in gene activation which can explain the increasing risk for developing auto immune diseases in some patients. [13] However, little research addressed the relevance of VDR gene polymorphism to immune regulation or auto immune disease. [14] Pre-treatment with $1,25\text{-}(OH)_2D_3$ in animal models inhibits the progression of most common auto immune diseases, including multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease. [15-17] The efficacy and/ or safety of vitamin D supplementation in preventing auto immune disease in human are not well studied with few clinical trials suggesting a beneficial effects. [18] However, there is growing possibility that persistent bacteria drive chronic autoimmune/ inflammatory diseases and the use of vitamin D (asecosteroid) may improves symptoms, but allows chronic pathogens to proliferate over time. [6]

Infectious Diseases

Epidemiologic studies have demonstrated a strong association between seasonal variations in vitamin D concentrations and seasonal epidemic outbreaks, morbidity and mortality of viral infections. [20] Trial of vitamin D supplementation in infection revealed conflicting results ranging from lower risk in children with severe vitamin D deficiency in one RCT [21] to no role in reducing the incidence of upper respiratory infections in other RCTs. [22, 23] One systemic review of 13 RCTs found mixed results, with some trials reported that adequate vitamin D concentrations may decrease all-cause infection rates. [24] However, the beneficial clinical effects of vitamin D; as supplementary treatment in patients with tuberculosis, was not detected in RCTs. [25, 26] And a systematic review concluded that there is no sufficient evidence to recommend any nutritional supplements for treating patients with active tuberculosis. [27]

Cell proliferation and Cancer

Vitamin D inhibits cellular proliferation and angiogenesis, reduces inflammation, promotes differentiation and apoptosis. [28] An extensive review of the relationship of vitamin D and cancer concluded that living at a high latitude may expose people to cancer, associating this with ultraviolet B exposure and vitamin D synthesis. [29] Initial human studies reported a possible association between vitamin D status and the risk of almost all cancer types with the greatest risk in association with colon cancer. [28] In a nested case-control study; in 2496 European participants, a higher incidence rate ratio of colon cancer (1.28) was reported in participants with serum 25(OH)D levels between 10 and 20 ng/mL (25 to 50 nmol/L) compared with those with 20 to 30 ng/mL (50 to 75 nmol/L) serum levels. [30] One recent study found an inverse association between colorectal cancer and higher versus lower vitamin D level (OR, 0.60, 95% CI; 0.38–0.94) but not with the vitamin binding protein. [31] In a meta-analysis of 9 case-control studies, a 6% (95% CI; 3-9 %) reduction in the risk of colon cancer for each 4 ng/mL (10 nmol/L) increase in basal serum 25 (OH) D concentration was detected. [32] For prostate cancer, 3 meta-analyses of prospective studies found no relationship with circulating 25 (OH) D, [33-35] but on the contrary, a significantly increased risk was reported in men with higher serum 25 (OH) D concentrations. [36] For pancreatic cancer, higher vitamin D concentrations (>100nmol/L) were associated with a 3-fold increased risk (OR,2.92, 95% CI; 1.56-5.48) in one study [37] this association has been explored further in the overview of the cohort consortium of Vitamin D Pooling Project of Rarer Cancers (VDPP) which had similar conclusion. [38]

In a meta-analysis of prospective studies, the risk of post-menopausal breast cancer decreased with 25 (OH) D levels between 27 and <35ng/mL (67to<87nmol/L), with no further reduction for levels above 35ng/mL. [39] The same meta-analysis also reported a significant inverse association between vitamin D level and the risk of post-menopausal breast cancer but not pre-menopausal cancer. [39]

Unfortunately, the results of RCTs on *protective effect of vitamin D* on cancer risk are inconsistent. One small clinical trial of vitamin D and calcium supplementation found more than 60% reduced overall risk of all cancers in post-menopausal women who received calcium with and without vitamin D. [40] However, in the famous Women's Health Initiative trial, there was no effect on the incidence of colorectal cancer using vitamin D3 (400units/day) and calcium (1000mg/day). [41] In a comprehensive review and meta-analysis of twenty papers examining vitamin D blood levels or the dietary intake of vitamin D in relation to skin cancer (melanoma and none melanoma skin cancer) has concluded that vitamin D intake (diet and/or supplements) doesn't seem to have any protective effect against the development of skin cancer. [42]

Hypertension

The geographic and racial variation in blood pressure (BP) could be partly explained by the exposure to sunlight and subsequent vitamin D synthesis. [43] Animal studies showed that the active form of vitamin D takes parts in regulation of the renin-angiotens in system with a resultant anti-hypertensive and vascular protective effects. [44] Mice with in born deficiency of the 1-alpha-hydroxylase gene develop high renin hypertension and cardiac hypertrophy. [44] Epidemiological studies suggested that vitamin D deficiency may be an independent risk factor for arterial

hypertension. In the Third National Health and Nutrition Examination Survey (NHANESIII) the mean systolic BP was about 3 mm Hg lower in those with the highest quintile of serum 25 (OH) D levels in comparison with those in the lowest quintile. [45] Another meta-analysis of 18 studies reported a pooled odds ratio (OR) of hypertension of 1.37 (95% CI; 1.19 – 1.59) for the lowest versus the highest vitamin D levels. [46] In a meta-analysis of 11 RCTs, a significant reduction in diastolic BP of −3.1 mm Hg (−5.5 – −0.6) with vitamin D therapy was found only in hypertensive patients. [47] Another meta-analysis [48] of 4 RCTs found that vitamin D administration reduced systolic BP by 2.44mm Hg (−4.86–−0.02) irrespective to the dose, duration, or intervention. However, in another meta-analysis of 10 trials reported no significant overall effect of vitamin D supplementation on BP except in trials using higher doses of vitamin D (>1000 IU per day) where a significant lowering of diastolic BP was reported (−1.5 mm Hg). [49]

Cardiovascular Disease (CVD) and Cardiovascular Mortality

Observational studies found that the prevalence of vitamin D deficiency, CVD, diabetes, and hypertension increases with increasing distance from the equator and suggested a role of ultra violet light exposure and vitamin D synthesis in the geographic and racial differences. [43] Data analysis from the NHANES III revealed an inverse relation between serum levels of 25 (OH) D and major cardiovascular risk factors including hypertension, diabetes mellitus, hypertriglyceridemia, and obesity in 15,088 subjects from United States with increased OR for cardiovascular events (1.24), heart failure (2.10), and peripheral arterial diseases (1.82) in adults with 25 (OH) D levels <20 ng/mL. [50] The Framingham offspring study followed 1,739 participants for a mean of 5.4 years and found 53% to 80% higher rates of a composite CV end point (fatal or nonfatal MI, ischemia, stroke, or heart failure) in people with low vitamin D levels with 1.62 hazard ratio of the first cardiovascular event in persons with 25 (OH) D value below 15 ng/mL than those with higher values. [51] In a large meta-analysis which included 19 prospective studies with 65,994 participants reported a relative risk (RR) of CVD of 1.03 (95% CI; 1.00-1.60) per 10 ng/mL (25 nmol/L) decrement in serum 25 (OH) D). [52] In a meta-analysis of good quality studies the RR of increased CV events associated with hypovitaminosis D was 1.27 (95% CI; 1.04-1.56). [53] The reported beneficial actions of vitamin D on CVD include modulation of classic cardio vascular risk factors, [50, 54] and modulation of endothelial dysfunction. [54] Moreover, secondary hyper parathyroidism in patients with chronic low vitamin D is associated with increased risk of CVD and mortality. [55] A meta-analysis of prospective studies found an inverse association with cardiovascular events and mortality. [56] Deficient or insufficient serum 25 (OH) D levels have been documented also to predict heart failure, [57] peripheral arterial disease, [58] stroke, [59] and cardio vascular mortality. [58] Unfortunately, the results of vitamin D supplementation and the incidence of vascular diseases are not encouraging. In an extensive meta-analysis of 51 RCTs, vitamin D supplementation showed no significant effects on death (RR 0.96), myocardial infarction (RR 1.02), or stroke (RR 1.05). [60] In another systematic review of vitamin D and cardio metabolic outcomes, 4 trials found no effect of supplementation on cardiovascular outcomes. [54]

Diabetes Mellitus (DM)

While it's not well understood how vitamin D acts on glucose homeostasis, postulated mechanisms include immune modulation, anti-inflammation, insulin synthesis and secretion, and insulin sensitivity. [61] Moreover, VDR gene polymorphisms may influence pancreatic secretion of insulin and glucagon with development of type 1 DM in some populations, and a link between low vitamin D and type 1 DM has been suggested in some observational studies. [62] However, a 13-year nationwide Danish study found no difference in Vitamin D levels between children newly diagnosed with type 1 diabetes and their healthy siblings. [63] Another interesting study found that severe vitamin D deficiency is an independent predictor of all-cause mortality but not retinopathy or nephropathy in patients with type 1 DM. [64] On the other hand one birth-cohort study of 10,366 Finnish children found a significantly reduced risk of 0.22 for type 1 DM with high-dose vitamin D supplementation. [65] A European Community Concerted Action

Program in Diabetes subgroup multicentre study found a significantly reduced risk for type 1 DM in countries with vitamin D supplementation. [66] These results are supported by a meta-analysis of 5 studies. [67] However, still there is no enough evidence to support vitamin D supplementation to prevent diabetes type one in susceptible children. On the other hand, many studies have linked low vitamin D status with the development of metabolic syndrome [68] and diabetes type 2. [69-71] The postulated mechanisms are not completely clarified including VDR-mediated insulin synthesis and secretion [62] and vitamin Dup-regulation of lipoprotein lipase enzyme. [69] In a meta-analysis of prospective studies; low vitamin D concentrations have been associated with an increased risk of development of type 2 DM in the general population. [70] In another meta-analysis of 21 prospective studies, the summary RR for type 2 diabetes was 0.62 for patients with the highest versus lowest category of 25(OH) D values. [71] A meta-analysis showed that the highest prevalence of type 2 DM (0.36) was associated with the lowest blood levels of 25 (OH) D in non-black individuals and the prevalence of metabolic syndrome (0.71) was highest among those with the lowest dairy intake. [72] Many trials addressed the prevention of incident type 2 diabetes by vitamin D supplementation. In the large Women's Health Initiative study, the combined use of vitamin D and calcium was found to lower the risk of incident type 2 DM. [73] In the Nurses' Health Study, 83,779 women were followed for 20 years and found no association between total vitamin D intake and type 2 diabetes but when the highest and the lowest category of vitamin D intake were compared, the RR of type 2 diabetes was 0.87 (95% CI; 0.75-1.00). [74] One systematic review of interventional trials of vitamin D found that prevention of incident type 2 DM by the combined use of vitamin D and calcium supplementation may occur only in patients with glucose intolerance. [72] Interventional studies of vitamin D supplementation specifically designed for metabolic control of type 2 DM or diabetic complications are very few. One meta-analysis of 15 RCTs found that vitamin D supplementation did not exert any significant effect on fasting glucose, glycated hemoglobin or insulin resistance in diabetic patients. [75] Similar results were obtained from another meta-analysis [76] of 35 trials.

Conclusion and Future Directions

Consistently, observational studies have suggested an inverse association between low vitamin D concentrations and development of some extra-skeletal diseases. Some studies suggested that the association between serum 25 (OH) D levels and some illnesses as cancer, and mortality is a curvilinear indicating higher risk at both low and high serum levels. In contrast to observational studies, the results of RCTs using vitamin D supplementation in preventing or ameliorating these extra-skeletal diseases were disappointing. Results showed inconsistent reduction in the risk with supplementation even if the basal serum level was low and was raised to optimal levels. Some RCTs did not find a dose response relationship between serum 25 (OH) D and reported outcomes. Failure to show benefits of vitamin D supplementation on different health outcomes may be explained by possible methodology flaws like low power, inadequate supplementation, or insufficient follow-up, in addition to variability in basal vitamin D levels, dietary and sun exposure habits, and final 25 (OH) D levels between participants. Moreover, most RCTs have measured the 25 (OH) D levels with variable precision and did not ensure adequacy of supplementation by raising the 25 OHD levels to or above 30ng/ml. Most importantly, many published RCTs were performed in general populations (not vitamin D-deficient populations), not designed to primarily assess a vitamin D specific outcome variable, and with poorly defined treatment end points. One important confounding factor was the combined use of calcium supplementation, which can influence outcomes irrespective to vitamin D supplementation. Moreover, inter-individual variation in vitamin D status, host genes encoding vitamin D-responsive elements could affect the efficiency of vitamin D3 supplementation as seen in studies of VDR polymorphisms.

Overall, the available evidence does not meet criteria for establishing cause-and-effect relationships because of the limitations of observational studies to corroborate the causality due to many potential confounders (age, smoking, diet, time of sun exposure, latitude, physical activity, body mass index,

vitamin D-binding protein). Theodoratou et al has summarized most of the available evidence derived from systematic reviews and meta-analyses in their review, [77] it included 107 systematic reviews and 74 meta-analyses of observational studies and 87 meta-analyses of RCTs with 137 outcomes. It concluded that there is no strong evidence supporting vitamin D replacement efficacy in any outcome, but pointed that associations with a selection of outcomes are probable.

The discrepancy between observational and interventional studies should attract attention that vitamin D level in ill health can be just a biomarker of inflammation or ill health. The inflammatory processes involved in the disease occurrence and the functional limitations of the diseases would have a role in reducing the serum of 25 (OH) D bio availability, which would explain why low vitamin D status is reported in a wide range of disorders. Interestingly, the available data may underscore the hazard of supplementation when its exact role is not fully established in prevention or treatment of extra-skeletal diseases. Thus, unless more evidence of clinically meaningful effects of supplementation is available, it may be too early to recommend for or against vitamin D supplementation for maintenance of extra-skeletal health and prevention of disease, beyond the daily requirements for calcium homeostasis and skeletal benefits.

Future directions entails the need for large well-designed RCTs to solve the active debate on extra-skeletal effects of vitamin D supplementation, find specific and clinically relevant effects of vitamin D repletion, provide cut-values for optimal serum levels of 25 (OH) D, and appropriate doses for non-skeletal health benefits. A large ongoing trial, which is expected to find a bit more definitive answers, is the Australian D-Health study. The results of this study might clarify some of the current conflicting results and come out with more clear advice regarding replacement for extra-skeletal health.

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