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MiniReview

Disputes on escalating proof of vitamin D's supplementation

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Abstract

Vitamin D supplementation appears to be potential for reducing risks of cancer, cardiovascular disease, and other chronic diseases, existing evidence on its benefits and risks is inadequate and debatable. Questions remain as to whether supplementation of Vitamin D playing any role in the above mentioned diseases. In the absence of compelling evidence for benefit, taking supplement is producing any risk or not. While sorting the various positive and negative claims for Vitamin D, it attracts an urgent need for further research and review on reports to answer fundamental questions about the risks and benefits of supplementation. There still remains a great need to advance our understanding regarding the effectiveness of Vitamin D. This review gives an overview on disputes of Vitamin D supplementation that is convincing and interventional regarding burning issues of Vitamin D therapy. Beyond its use to prevent osteomalacia or rickets, the evidence for other health effects of vitamin D supplementation in the general inhabitants is conflicting. It is a well known predictability that any effective substance also has unwanted side effects, so clear cut evidence regarding the safety is required before supplementing Vitamin D for pathological conditions and other health benefits.

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Introduction

Getting too much of vitamins is good or bad for health; the question is unanswerable in so many aspects. The health penalty of going overboard on vitamins and minerals are still in dispute. Nowadays, everything from bottled water to apple juice seems to have vitamins and minerals in it and that may sound like a way to cover body's nutritional requirements and consumption creating danger of getting too much of these and these overloads can hurt our health. According to basic knowledge regarding vitamins and minerals, more is not necessarily better, so avoid overdoing it is the best suggestion. Most people don't realize that there's no advantage of taking more than the recommended amounts of vitamins and minerals, and they don't recognize the disadvantages. The old saying of "You are what you eat." is true. There is one level of a body's metabolism is more important than any other aspect. Human beings need all vitamins and minerals, but not in excess. Based on the above aspects, this review mainly focuses on the convincing and interventional disputes on Vitamin D therapy.

Knowledge of new insights into clinical and biological significance of Vitamin D is essential in the field of medicine before supplementing it to the human beings. Scientists from different medical universities found that higher vitamin D levels in healthy individuals have a significant impact on the genes that are involved in several biologic pathways associated with illnesses, including cancer, autoimmune disease, cardiovascular disease and infectious diseases (Hosseinnezhad *et al*., 2013).

Vitamin D is a fat soluble vitamin that plays a vital role in the human body. Vitamin D has been used in the maintenance of several organ systems as well as the immune system. Because of its important functions, deficiency can lead to many health problems. Heart disease, arthritis, diabetes, high blood pressure, and even cancer have been associated with a lack of vitamin D (Michael and Tai, 2008). Additionally, new studies suggest that vitamin D may play a role in protecting against Alzheimer's and Parkinson's disease (Khanh *et al.*, 2012).

Vitamin D for humans is obtained from sun exposure, food and supplements. Vitamin D doses for infants vary according to country and seasons. Over the last few hundred years human lifestyle have changed. The industrial revolution resulted in more indoor work and less exposure to sunlight. Mankind ignored this truth and sometimes ridicule regarding exposure to sunlight. Based on the different conflicts and newsletter regarding Vitamin D and its use, this review article focused on the passion and dispassion of Vitamin D supplement for various diseases. This is a retrospective, systematic and comprehensive review article from secondary sources. It includes literatures, clinical trial reports that contain information and intervention under investigation. The main aim of this review is to figure out the controversies in

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Vitamin D supplementation and therapeutic effects and also to find an dependant and independent inverse association between reports already published, to find evidence that Vitamin D supplementation affects clinical outcome or not?

Vitamin D and the heart

Scientist's focal point on the role of Vitamin D in the heart is increasing alarmingly. The role of Vitamin D in cardiovascular disease (CVD) is relatively a novel field of interest. Heart and blood vessels are main target tissue for Vitamin D (Pilz *et al*., 2009). Heart collaborative group done the prospective study regarding the effect of Vitamin D in CVD's and reported that individuals with low serum concentrations of 25(OH) D were at increased risk for future CVD, in particular for heart failure and cerebrovascular events (Anderson *et al*., 2010). Clinical and mechanistic evidence on the effect of vitamin D status on cardiovascular risk factors was summarized by Stefan *et al.* (2011). Parathyroid hormone (PTH) suppression by vitamin D supplementation reduces cardiovascular risk and the proposed antihypertensive, antiinflammatory and antidiabetic actions play important scientific evidence for the biological significance of vitamin D (Stefan *et al.*, 2011). Heart failure patients have a poor vitamin D status and were confirmed by clinical studies, but whether vitamin D deficiency is only the consequence of heart failure or possibly contribute to myocardial diseases is unclear (Pilz *et al*., 2010).

Direct protective role of vitamin D against heart failure include effects on myocardial contractile function, regulation of natriuretic hormone secretion, effects on extracellular matrix remodeling, reduced left ventricular hypertrophy, and the regulation of inflammatory cytokines (Weishaar *et al*., 1990; Trivedi *et al*., 2003; Tishkoff *et al.*, 2008; Szabo *et al*., 2009). Low Vitamin D levels were coupled with poor outcomes in patients with end-stage heart failure in anticipation of heart transplantation (Zittermann *et al*., 2008) and it supports the importance of Vitamin D. Hemodialysis patients with secondary hyperparathyroidism when treated with intravenous vitamin D showed significant reductions in left ventricular wall thickness and left ventricular mass index (Park *et al.*, 1999). Like these evidence are accumulating in the recent years regarding the role of Vitamin D in CVD.

In spite of all the above scientific evidences, there is an ongoing debate that administration of vitamin D actually increases cardiovascular risk or not? In the initial analysis of the Women's Health Initiative (WHI) study no detrimental effect of vitamin D could be detected in CVD. Treatment with moderate doses of calcium plus vitamin D did not seem to alter coronary artery calcified plaque burden among postmenopausal women (Manson *et al.*, 2010). However, a recent re analysis of the WHI trial (Bolland *et al*., 2011) reported that application of calcium (with or without vitamin D) modestly increase the risk of cardiovascular disease. This finding shakes an old medical paradigm to the core. Meta analysis reported that oral calcium and vitamin D supplement are safe (Wang *et al*., 2012). In a clinical trial (NCT01018849) participants in one group were given 150,000 IU of vitamin D3 every two months and the other group with placebo over one year but the results were unsatisfactory and inconclusive (Bolland *et al.*, 2011). Despite of the accumulating data suggesting that a sufficient vitamin D status may protect against CVD, we still must wait for results and confirmation before raising general recommendations for vitamin D in the prevention and treatment of CVD. Overview on open issues and unanswered questions regarding vitamin therapy in cardiovascular disease is depicted in the Figure 1(Vincent *et al*., 2012).

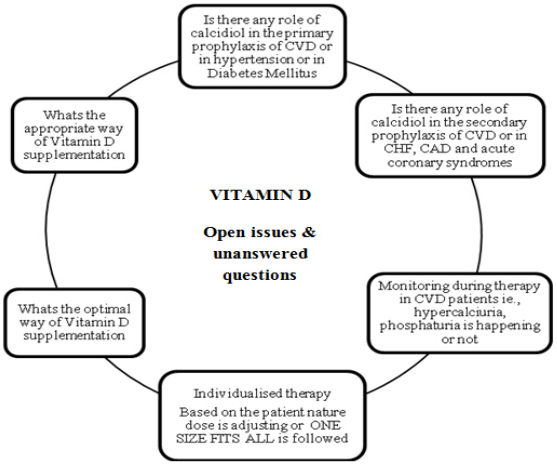

Figure 1. Open issues and unanswered questions regarding vitamin therapy in cardiovascular disease

Vitamin D in cancer

Scientist's evaluated the role of Vitamin D in cancer and reported positive and negative correlation (Tang *et al*., 2012). Numerous mechanisms and methodologies are projected for the anticancer activity of Vitamin D (Figure 2). The exact molecular mechanism behind the pharmacological action of Vitamin D is still an issue. *In vivo* and *in vitro* studies reported that dairy products, calcium, and dietary vitamin D inhibit the development of colorectal cancer (CRC) (Huncharek *et al.*, 2008). Evidence indicates that food containing folates, selenium, Vitamin D, dietary fiber, garlic, milk, calcium, spices, vegetables, and fruits are protective against CRC in humans

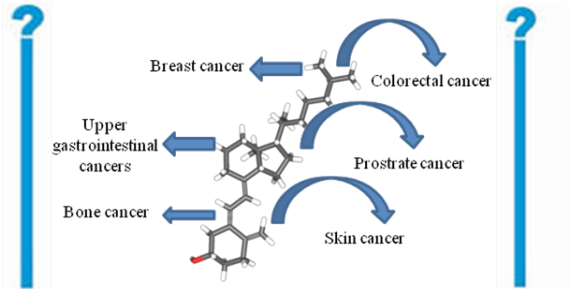

Figure 2. Role of Vitamin D in cancer

(Aggarwal *et al.*, 2013). Survival rate of patients with CRC has been associated with the levels of 25(OH) D levels. Vitamin D detoxifies a carcinogenic bile acid-lithocholic acid, and can reduce polyps in the colon which often ultimately turn into cancer tumours (Ng *et al*., 2009). Further study is still warranted in this report.

Dietary intake of Vitamin D is not related with prostate cancer and reports regarding the role of Vitamin D are controversial (Huncharek *et al*., 2009). Black people, who cannot photosynthesize vitamin D under their pigmented skins, are more prone to develop prostate cancers. Research studies reported that Vitamin D plays a protective task in a variety of internal malignancies whereas epidemiologic and laboratory studies suggest that Vitamin D may have a comparable shielding effect on skin cancer (Tang *et al.*, 2012). Epidemiology studies argued that the levels of sunlight and cancer are inversely proportional.

While coming to breast cancer, Stearns and Visvanathan (2013) reported that vitamin D reduces the risk of breast cancer development. Vitamin D receptor (VDR) gene polymorphisms have been reported to influence the susceptibility to breast cancer. However, published findings on the association between VDR Cdx2 polymorphism and breast cancer susceptibility were conflicting (Zhou *et al*., 2013). Decisive study of the current evidence indicates that there is no consistent relationship between serum vitamin D levels or a surrogate and upper gastrointestinal cancers (Trowbridge *et al.*, 2013).

In all the above mentioned reports the underlying molecular mechanism related to Vitamin D has not been illuminated. There are no reported contraindications with cancer drugs or cancer treatments in fact, exactly the opposite seems true. Most of the studies reported positive correlation and some studies reported negative correlation and some indicate no correlation between Vitamin D and anticancer effect. Lack of unswerving relationship is an outcome of inaccurate and imprecise assessment of Vitamin D role and its importance (Trowbridge *et al*., 2013).

The novel exhilaration is the discovery that cells contain large numbers of receptor sites for vitamin D. Of course, various medical directives and news which give the impression based on out of date research and/or subjectivity not science, and these seem bent on cutting for vitamins and supplements by the humans. In case of vitamin D, recommended daily allowance (RDA) levels are much lower. Recent research on vitamin D merely highlights the conflict and at the same time the bureaucrats are clamping down, the scientists are just discovering how these essential ingredients really work. At last, the state-of-the-art, research reserve on how to fabricate a diet of Vitamin D to beat cancer and how it will work out?

Vitamin D in hypertension

Hypertension is one of the most burning health problems in the world. Numerous observation data support the concept that vitamin D is involved in pathogenesis of hypertension and display positive effect (Pavlovi *et al*., 2011). Few prospective and cross sectional studies have been conducted to correlate vitamin D levels with blood pressure but the results are conflicting (Pilz *et al*., 2009; Ullah *et al.*, 2010). A significant inverse correlation between blood pressure, pulse pressure and vitamin D level was observed (Scragg *et al*., 2007). An increased prevalence of hypertension in patients with low calcidiol level was observed (Judde *et al.*, 2008) and was inversely associated (Burgaz *et al.*, 2011). There are studies showing no relationship between calcidiol level and hypertension (Pavlovi *et al.*, 2011). Reduced blood pressure has been observed in people taking oral vitamin D (Kunes *et al*., 1991). Despite these contradictory findings, majority of the cross-sectional studies reported an inverse relationship between calcidiol levels and blood pressure (Pavlovi *et al*., 2011). Unfortunately, not enough studies have been conducted to investigate the effect of calcidiol and calcitriol as an antihypertensive agent. Studies are not very promising but for scientific knowledge we need more reliable information and proof about vitamin D as an antihypertensive agent (Pavlovi *et al.*, 2011).

Treatment of patients with hypertension is still a challenge for physicians (Pavlovi *et al.*, 2011). There are some plausible biological mechanisms. Patients with hypertension and vitamin D deficiency could benefit from vitamin D supplementation or calcitriol treatment, particularly patients with chronic kidney disease (Pavlovi *et al*., 2006). Blood pressure has been shown to vary inversely with UVB light availability and have a high prevalence of low circulating levels of 25-hydroxyvitamin D3 (25(OH)D3), it has seemed

reasonable to speculate that vitamin D deficiency may contribute to their increased prevalence of hypertension (Nesby *et al.*, 2002; Scragg *et al.*, 2007). In humans, skin exposure to UVB, which is the major source of vitamin D formation, has been linked with lower blood pressure (Woodhouse *et al.*, 1993; Krause *et al.*, 1998).

Studies have shown that VDR activation can improve pathogenetic factors contributing to vascular disease and improvement in BP has not been consistently found (Forman *et al.*, 2005), raising questions about the efficacy and the importance of vitamin D deficiency in hypertension (Stephen *et al.*, 2010).

Patients with hypertension were exposed to UVB radiation three times a week for 3 months and the results showed 25-hydroxyvitamin D levels increased by approximately 180%, and both systolic and diastolic blood pressure reduced by 6 mm Hg (Kunes *et al.*, 1991). In contrast, a large prospective study of men and women found no association between intake of vitamin D from diet or supplements and hypertension incidents (Krause *et al.*, 1998; Forman *et al.*, 2005). Vitamin D could have certain impacts on hypertension treatment (Ran and Declan, 2010) but to prove that, researchers need more prospective studies.

Vitamin D supplementation provides a rationale for well-performed prospective large randomized clinical trials addressing efficacy and safety of vitamin D in patients with cardiovascular disease, particularly hypertension. These trials need to answer the question of potential differences between short-versus long-term effects of normal and high-dose vitamin D supplementation on blood pressure, vascular function, and cardiovascular outcome (Forman *et al.*, 2005).

Vitamin D supplementation as an effective strategy to lower blood pressure and prevent hypertension remains unclear. Jorde *et al.* (2010) indicated that clinical study should have sufficient statistical power to examine whether high-dose, long-term vitamin D supplementation can reduce the incidence of hypertension or not. Majority of the clinical trials reported that lower levels of vitamin D may be related with higher blood pressure and higher risk of developing hypertension but conflicting studies exist (Anand and John, 2010). Thus controlled trials have failed to confirm the effect of vitamin D supplementation in blood pressure. Additional evidence is required before recommending vitamin D supplementation to treat blood pressure or prevent hypertension.

Vitamin D and bone health

Vitamin D deficiency results in an abnormal calcium-phosphorus product leading to diminished mineralization of the collagen matrix, causing rickets in children and osteomalacia, osteoporosis, and an increased fracture risk in adults (Holick *et al.*, 2007). Vitamin D is primarily responsible for regulating the efficiency of intestinal calcium absorption. In a low vitamin D state, the small intestine can absorb approximately 10% to 15% of dietary calcium. Gaugris *et al.* (2005) identified that the prevalence of inadequate 25(OH) D levels appears to be greatest in postmenopausal women and especially those with osteoporosis and a history of fracture. Much debate has taken place over the definition of vitamin D deficiency. Most agree that a 25(OH) D concentrationv<50 nmol/L, or 20 ng/mL, is an indication of vitamin D deficiency, whereas a 25(OH) D concentration of 51-74 nmol/L, or 21-29 ng/mL, is considered to indicate insufficiency; concentrations <30 ng/mL are considered to be sufficient (Heaney *et al.*, 2003). Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter) (Holick, 2004). Vitamin D levels have been suggested to be the best predictor of fracture risk (Malavolta *et al.*, 2005). In a study of more than 500 individuals with hip fractures, 95% were found to be vitamin D deficient (Gallacher *et al*., 2005). Although cutaneous vitamin D production exists with ultraviolet exposure, its synthesis varies with factors other than time spent outdoors, such as level of skin pigmentation, season, latitude, body mass, cloud coverage, air pollution, age, and the amount of skin exposure. Therefore, it might be overly simplistic to recommend a universal time frame for adequate vitamin D synthesis, without considering all of the above variables and negative effects of ultraviolet radiation (Sollitto *et al.*, 1997). Evidence has shown that supplementation can correct both vitamin D deficiency and insufficiency, except in those with gastrointestinal malabsorption (Wolpowitz and Gilchrest, 2006).

Rickets attributable to vitamin D deficiency is known to be a condition that is preventable with adequate nutritional intake of vitamin D (Mc Collum *et al*., 1922). Rickets, however, is not limited to infancy and early childhood, as evidenced by cases of rickets caused by nutritional vitamin D deficiency (Schnadower *et al*., 2006). To prevent rickets and vitamin D deficiency in healthy infants, children, and adolescents, an intake of at least 400 IU/day of

vitamin D is recommended (Carol *et al.*, 2008).

Epidemiologic, clinical, and laboratory evidence suggest a direct effect of vitamin D on muscle strength. Lower 25-OHD levels and higher PTH levels increase the risk of sarcopenia in older men and women (Marjolein *et al.*, 2003). Vitamin D supplementation preserves muscle strength and functional ability in high-risk groups, eg, frail, mostly homebound elderly people, but need to be researched well by controlled randomized trials (Hennie *et al*., 2002).

Conclusion

By reviewing most of the reported clinical trials and documents, the scientific question to supplement Vitamin D or not to supplement is still unanswerable. Report adds to many conflicting messages about the benefits and risks of vitamin D and calcium supplements. For years, experts have been touting the health benefits of these nutrients. "It's a more complex picture than they're painting. The conclusion of the present survey indicating that all the reports regarding Vitamin D are little baffling.

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