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REVIEW

Łukasz Szternel, Grażyna Odrowąż-Sypniewska

Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland

The association of vitamin D with common diseases — an appraisal of recent evidence

Corresponding author:

Łukasz Szternel
Department of Laboratory Medicine
Collegium Medicum,
Nicolaus Copernicus University
Sklodowskiej-Curie Street No. 9
85–094 Bydgoszcz, Poland
Phone: +48 52 585 40 46
Fax: +48 52 585 36 03
e-mail: lukaszszternel@wp.pl

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ABSTRACT

It has been several years since the discovery of the pleiotropic effects of vitamin D, and there is still hot debate as to the role of vitamin D and attempts to standardise methods of determining 25(OH)D concentrations as well as supplementation with vitamin D. Many studies, both observational and randomised controlled trials, have revealed a whole range of opportunities of active vitamin D metabolite contribution to the treatment of common diseases. A relationship between high concentrations of vitamin D and a low risk of incidence of colorectal cancer, cardiovascular diseases, hypertension, ischaemic stroke, depression, metabolic syndrome and type 2 diabetes has been suggested for a long time, although recently published meta-analyses have created some doubts. There is no consensus regarding vitamin D supplementation and the optimum concentration of serum 25(OH)D. The Institute of Medicine's 2011 report recommends achieving serum 25(OH)D concentration of 20 ng/mL as optimal, at a dosage of 600 IU of vitamin D per day. International recommendations suggest for individuals at risk a dosage of vitamin D of 2,000 IU per day. Polish experts advise that the optimal concentration of 25(OH)D should be greater than 30 ng/mL for adults.

Key words: vitamin D, protective effect, cancer, supplementation, recommendations

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Introduction

Numerous studies in recent years, related to the discovery of the 'nonclassical' effects of vitamin D, have resulted in immense interest in the possibility of multidirectional use of vitamin D measurement in the diagnosis and monitoring of the treatment of many common diseases. There are several illnesses such as Parkinson's disease, multiple sclerosis, some forms of cancers, rheumatoid arthritis, allergic asthma, diabetes and heart diseases, in which vitamin D deficiency can be identified [1].

Vitamin D status can be defined using static and dynamic parameters. The first group includes measurement of blood 25(OH)D concentration, which gives information on the amount of substrate available to form a biologically active metabolite- 1,25(OH)2D (1, 25-dihydroxyvitamin–calcitriol). The dynamic status of vitamin D is assessed by concentration of parathyroid hormone, bone turnover markers, optimisation of bone mass and muscle strength [2].

Standardisation of 25(OH)D assays

Reliable measurement of serum 25(OH)D can present some difficulties. The first problem is called the 'matrix effect'. It is connected with the structure of 25(OH)D, characterised by high hydrophobicity, which can result in interference with serum components. Another difficulty is the presence of vitamin D metabolites which differ in biological activity and affinity for liver enzymes, binding proteins and VDR (vitamin D receptor). The problem of reliably measuring 25(OH)D concentration also results from the presence of 3-epi-25(OH)D3 stereoisomer, especially in the samples from children [2, 3]. According to the current guidelines for manufacturers of diagnostic laboratory products, there is a need for simultaneous determination of both 25(OH) D2 and 25(OH) D3 concentrations in the blood. It is worth remembering that in some diseases, such as renal failure, it is recommended to define both forms of vitamin D, i.e. 25 (OH) D and 1,25-dihydroxyvitamin D, as the latter is formed in the kidneys. In tuberculosis

or sarcoidosis, the opposite situation occurs, namely excessive hydroxylation of 25(OH)D in macrophages and granulomas leads to an intense increase of calcitriol concentration, which can lead to hypercalcaemia [4].

The 'gold standard' of 25(OH)D determination are direct methods such as high performance liquid chromatography (HPLC) and tandem mass spectrometry coupled with liquid chromatography (LC-MS/MS) allowing at least separate measurements of metabolites such as 25(OH)D2, 25(OH)D3 and 3-epi-25(OH)D3. Chemiluminescence is the main method used in automatic platforms where specific antibodies or labelled proteins bind vitamin D molecules [3].

Different methods used for the determination of vitamin D (and its metabolites) sometimes produce inconsistent results from the same patient specimen. These differences in test results can misclassify patients as having a sufficient or an insufficient vitamin D level. In order to standardise vitamin D assays and thus ensure the safety of patients' health, in 2010 the National Institutes of Health Office of Dietary Supplements (NIHODS) established the VDSP (Vitamin D Standardisation Programme). Within the framework of standardisation, 25 experts from various fields recommended assays which determine concentration of 25(OH)D2 and 25(OH)D3.

One of the main problems which affect the quality of vitamin D assays is the reference material used to set the calibration curve. *In vitro* diagnostic manufacturers use their own reference material, which may result in significant differences in outcomes. In order to minimise differences in results and unify assay methods, there is a need for comparable reference material which could help standardise methods and harmonise results obtained from different laboratories [1]. A standardisation programme for analysing hormones — HOST (Hormone Standardisation Programme) recently qualified vitamin D as another hormone. In the first phase of the HOST programme, 40 selected native patient samples were analysed using the 'gold standard', which in this case is LC-MS/MS. Using the outcomes, manufacturers were obliged to correct their internal reference materials. In the absence of a standard, manufacturers are required to use reference material prepared by NIST (National Institute for Standards and Technology). An additional means of helping to unify results of vitamin D assays is an external quality control programme DEQAS (The International External Quality Assessment Scheme for Vitamin D Metabolites) available in Europe. Researchers from NIST work to create reference material which could help to improve the precision of vitamin D assays from different manufacturers.

Laboratories which perform vitamin D assays should participate in quality control programmes such as the Vitamin D Metabolities Quality Assurance Programme (VitDQAP), the College of American Pathologists (CAP), or in Europe — DEQAS. These programmes are an excellent help in assessing the improvement of quality of measurement of 25(OH)D and its metabolites [1].

Supplementation with vitamin D

Reliable and reproducible measurements of serum 25(OH)D gain an extra dimension in view of the parallel incorporation of vitamin D into standard therapy of such diseases as atopic dermatitis, multiple sclerosis, epilepsy, osteoporosis, kidney failure as well as infectious diseases. Recent reports have shown that vitamin D supplementation supports basic therapy in the treatment of tuberculosis, influenza and infections of the upper and lower airways.

It has been observed that patients suffering from hepatitis C display a significant decrease in serum 25(OH)D levels, below 20 ng/mL. In the study by Lange, a beneficial influence of calcitriol administration has been suggested, which has the effect of amplifying standard HCV therapy [5, 6]. Leis et al. documented that children under five years of age, whose daily intake of vitamin D does not exceed 80 IU/kg, were characterised by a four-fold greater degree of incidence of diseases associated with acute lower respiratory tract infections. Leis's studies suggest that optimal supplementation with vitamin D could prevent bronchiolitis and pneumonia [5, 7].

A Polish intervention study on patients with atopic dermatitis who had received treatment with vitamin D supplementation in an amount of 2,000 IU/daily for three months (in patients with vitamin D deficiency < 20 ng/mL), revealed a two-fold increase in serum 25(OH)D levels, accompanied by a two-fold decrease in symptoms of atopic dermatitis [8]. Uncontrolled observational studies conducted by Pierrot-Deseilligny concerned the impact of vitamin D supplementation, used in parallel with primary therapy, on remission and relapses of multiple sclerosis. It was observed that the rate of recurrence of multiple sclerosis decreased (13.7%) with increasing concentration of 25(OH)D for every 4 ng/mL (10 nmol/L) [9].

Shroff et al. supported the hypothesis concerning a positive impact of ergocalciferol (vitamin D2) supplementation in chronic renal failure. Supplementing vitamin D2 delayed the development of secondary hyperparathyroidism in children in the 2nd and 3rd stages of chronic renal failure [10]. The study by Alvarez et al. suggested an impact of cholecalciferol (vitamin D3) on reduction of PTH at the early stage of chronic renal failure in adults [11]. Carmel et al. referred to a relationship between the effects of bisphosphonate therapy and the concentration of 25(OH)D. Bisphosphonates are widely

used in the treatment of patients with osteoporosis. They found a strong relationship between the long-term response of patients treated with bisphosphonates and optimal (≥ 33 ng/mL) concentrations of 25(OH)D [12]. Bertodolo et al. stated that 25(OH)D regulated the first stage of bisphosphonate therapy in a group of women with osteoporosis aged 63.7 ± 10.6 years. Optimisation of 25(OH)D concentration during bisphosphonate therapy led to a decrease in CRP levels and a decrease of elevated body temperature [13, 14].

The therapeutic effect of vitamin D supplementation has also been observed in patients suffering from depressive disorders. Combination of primary treatment and supplementation of vitamin D gave better results in the treatment of increasing depressive symptoms. The therapeutic effect of vitamin D in the treatment of mental disorders and other conditions related to the nervous system (epilepsy, multiple sclerosis) is probably due to the presence of vitamin D receptors in the cells of the nervous system as well as local prohormone hydroxylation to its active form, which is calcitriol. However, a detailed explanation of these mechanisms requires further studies [5, 15].

There are several plausible biological mechanisms relating vitamin D to coronary heart failure. The active form of vitamin D influences about 3% of the human genome [16]. After binding to VDR, calcitriol affects the proliferation and apoptosis process. This could result in inhibition of vascular smooth muscle cell proliferation, which is believed to be a cardioprotective mechanism. Another positive role of suboptimal concentration of vitamin D is the anti-inflamatory and immune modulating effect. Vitamin D affects also the renin-angiotensin-aldosterone system which is perceived by many researchers as a possible pathway linking deficiency of 25(OH)D and high blood pressure [14, 16].

According to scientific reports, a suitable vitamin D supplementation to achieve a concentration of serum 25(OH)D in adults of between 30–60 ng/mL may be a strengthening factor of therapy effectiveness in cases of infectious diseases, osteoporosis, multiple sclerosis, epilepsy, chronic renal failure and atopic dermatitis [5,17].

Relationship of vitamin D status and inflammation

Concentration of 25(OH)D significantly decreases during the acute phase of many diseases which are accompanied by multi-organ failure and extensive inflammation. A similar drastic decrease in serum 25(OH)D is observed in patients undergoing knee replacement, in patients with acute pancreatitis, congestive heart failure or myocardial infarction; all these disorders are also accompanied by an extensive inflammatory process. In many diseases, particularly during the acute phase, which is characterised by a high extent of ongoing inflammatory processes, an inverse relationship between serum 25(OH)D level and inflammatory markers levels, such as TNF and CRP, has been observed. Therefore, recently scientists have formed a hypothesis linking the decrease of serum 25(OH) D, accompanying multiple diseases, with ongoing inflammatory process [17].

Vitamin D in recent systematic reviews and meta-analyses

There are discrepancies between observational and interventional studies concerning the relationship between serum 25(OH)D and the risk of cancer development, except colorectal cancer [17]. There are many prospective studies revealing an inverse relationship between serum 25(OH)D and cardiovascular diseases, serum lipid levels, weight gain, infectious diseases, mental disorders and cognitive decline. On the other hand, there are studies that suggest slight or no effect of therapeutic use of vitamin D in a number of illnesses. The insignificant effect of vitamin D supplementation in the development and severity of many diseases may suggest a hypothesis that lowering serum concentration of 25(OH)D could be the result, but not the cause, of 'ill health' [17].

This hypothesis assumes that the decrease in vitamin D concentration could be a biological marker of deteriorating health in response to the development of a specific disease. Some observational studies confirm this hypothesis. An example is a Dutch cohort study, conducted on a large group of older people, among whom overall survival was gradually decreased with the decrease of 25(OH)D in the serum [17, 18].

Many cardiovascular diseases such as coronary heart disease, sudden cardiac death, peripheral arterial disease and greater carotid intima-media thickness are accompanied by low vitamin D concentration in the serum [14, 19]. A growing body of evidence indicates a moderate association between vitamin D concentration and the risk of death from coronary heart disease, cancer, lymphoma or respiratory diseases [16]. Although evidence from observational studies reveals an association between 25(OH)D and the risk of development of cardiovascular disease, cancer or a non-cancer disease, most studies with vitamin D supplementation have not demonstrated a positive effect on CVD. The lack of strong evidence may be the result of inadequate supplementation of vitamin D, and trials with higher vitamin D doses are essential for a final explanation of the effect of vitamin D on cardiovascular events [14].

In their recent systematic review and meta-analysis of observational cohort and randomised intervention studies, Chowdhury et al. indicated the inverse association of serum vitamin D concentration with risks of death from cardiovascular diseases, cancer and other causes and beneficial effect of vitamin D supplementation. Interestingly, they found that supplementation with vitamin D3 given alone reduced mortality significantly (by 11%) whereas vitamin D2 given alone had no effect on overall mortality [20].

The restoration of optimal serum 25(OH)D levels may provide an important therapeutic help during the treatment of many diseases. However, a very recent controversial report by Theodoratou et al. reveals that there is in fact no evidence which supports the argument that vitamin D-only supplementation increases bone mineral density or reduces the risk of fractures or falls in the elderly [20].

The authors indicate the possible associations of vitamin D only with some outcomes such as birth weight, dental caries in children and PTH concentrations in patients with chronic kidney disease. Finally, they state that low doses and short duration of vitamin D supplementation in the randomised controlled trials may be the reason for there not being enough evidence to draw conclusions [20]. On the other hand, Li et al. very recently published a systematic review and meta-analysis on the impact of vitamin D status on cancer patients' outcomes. This meta-analysis, involving more than 17,000 patients suffering from different forms of cancer, once again emphasised the contribution of high doses of vitamin D in remission and overall survival. The evidence from studies by Li seems to confirm that only high doses of vitamin D allow the exertion of a protective effect against cancer, particularly breast cancer, colorectal cancer, and lymphoma.

There are hypotheses confirmed by many studies which suggest that the protective effect of vitamin D on cancer is a consequence of the inhibition in the growth of tumours and modulation of the microenvironment in which tumour cells are located. Patients suffering from colorectal cancer, lymphoma or breast cancer with concentration of vitamin D in the highest quartile presented significantly better overall survival. Investigators have estimated that an increase in concentration of circulating 25(OH)D, by 4ng/mL (10 nmol/L) can reduce all-cause mortality by 4% among patients with cancer. In addition to the positive effects of vitamin D treatment of cancer, it may also alleviate adverse reactions caused by primary treatment. In the study by Li, a relationship has been observed between low levels of 25(OH)D among men with a high and a very high risk of developing prostate cancer according to the National Comprehensive Cancer Network (NCCN) criteria. Moreover, vitamin D deficiency could be a good predictor in the diagnosis of more aggressive forms of prostate cancer and supplementation may prevent prostate cancer incidence or even inhibit tumour progression [21, 22].

Current recommendations

International organisations recommend in general 800–1,000 IU/day of vitamin D to achieve optimal 25(OH)D concentration for adults, although for individuals at higher risk the doses may be up to 2,000 IU/day [14]. The Endocrine Society in the US points out that doses of 1,500-2,000 IU/day may be required for all adults to raise 25(OH)D concentration to > 30 ng/mL (optimal for adults between 30–60 ng/mL). Similarly, according to recent Polish recommendations, the optimal level of serum 25(OH)D in adults is > 30 ng/mL [23].

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