



# Vitamin D3 as a Powerful Immunoregulator - Cause or Consequence of Disbalance?



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## Opinion

For the last two decades the role of Vitamin D3 has been recognized not only as a regulatory component of a bone - kidney metabolism, but also as an important immunomodulator [1]. Low serum levels of vitamin D are detected before an exacerbation in rheumatic diseases: psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis [2,3]. Same has been shown in exacerbation of Hashimoto's thyroiditis and ulcerative colitis, multiple sclerosis, in some kinds of cancer, in cardiovascular diseases and diabetes mellitus type 2 [4-8]. Also, low levels of vitamin D3 have been confirmed many years before onset of autoimmune disease [2,9].

Recent studies have investigated new role of vitamin D in intracellular processes. Dankers et al. [10] showed possible molecular mechanisms in which vitamin D can interfere intracellular mechanisms [10]. It is known that actions of vitamin D3 are mediated by the vitamin D receptor (VDR), a ligand-activated transcription factor that functions to control gene expression [11]. VDR protein is comprised of three regions, an N-terminal dual zinc finger DNA binding domain, a C-terminal ligand-binding activity domain and an extensive region that links the two functional domains of this protein together [12].

When vitamin D3 interacts with VDR surface, VDR binds to regulatory regions of target genes and acts to nucleate the formation of large protein complexes whose activation is essential for changes in transcription [13]. These actions result in the expression of networks of target genes that control highly complex actions like growth, differentiation and activity of immune system cells, skin cells and bone metabolism as well as many other functions that are devoted to vitamin D [14]. Evans et al. [15] showed multiple binding patterns throughout heterodimerization or overlaps of vitamin D responsive elements (VDREs) in the DNA. It is considered that conformational change between retinoid X receptor (RXR) and vitamin D receptor (VDR) through their heterodimerization can activate different signaling pathways resulting in production of a large number of proteins involved in cell function [15].

All these interactions depend on vitamin D serum levels because nuclear receptors, such as VDR, can autoregulate their own activity [15], but it still remains unknown if and what receptor conformational changes are responsible for production of mRNA which is liable for protein synthesis. It's considered that maintenance of low serum levels of vitamin D and its metabolites regulates activation of immune system cells such as monocytes, dendritic cells, B- and T- Cells, macrophages, regulatory T cells and also regulates activation of NK cells and pro-inflammatory cytokines [16-22].

Even though we know many facts about protective effects of vitamin D, 2,5 million people have been confirmed for having vitamin D deficiency. Air pollution, short sun exposure, use of different types of medications and use of sun blockers, poor nutritional intake and sedentary lifestyle are causes of this condition [23]. In our studies we confirmed that lower levels of vitamin D are found in diabetes type 2 population with or without acute coronary syndrome [24,25], autoimmune thyroiditis [26], glaucoma [27] and in recurrent urinary infections in postmenopausal women.

Also, there is a study showing how vitamin D supplementation during conception and pregnancy can improve fertility and gestation in women with Hashimoto thyroiditis [28]. Despite of small number of participants we hope that it can contribute to improve our knowledge of vitamin D important role in these conditions. According to previous studies that investigated vitamin D-regulated intracellular pathways, it is still unknown if vitamin D3 deficiency is caused by its poor intake and reduction of sunlight exposure or is it cellular microenvironment that regulates these pathways causing vitamin D deficiency even though its intake is normal.

Many previously published studies have limiting factors such as small sample size, inconsistencies in the study protocols, unknown serum levels of vitamin D and unclearly defined objectives of the studies (mostly clinical outcome based studies).

We think that it's important not only to establish vitamin D serum levels in acute event, it would be useful to know its serum levels some weeks before the event occurs. Estimated level of vitamin D is only current states indicator. We still don't know which serum level is a trigger for cell state change and how long it takes for a certain serum level to cause conformational changes of receptors following changes in protein synthesis. Answers to those questions can be found in the newest intracellular researches including VDR and its molecular mechanism of action at target genes and how vitamin D3-activated VDR modulates the expression of genes at both single gene and also at the level of gene networks [11].

For the detailed assessment of modulation effects of available vitamin D3 metabolites at given serum concentration it is necessary to monitor VDR and RXR intracellular activity on a level of a certain cell function gene activator and repressor [2]. Only randomized controlled trials which will study intragenetic mutations mentioned previously can give us the answer if vitamin D is the main supervisor of intracellular metabolism or is it one of many cofactors. There is a growing number of studies like this showing unexpected results suggesting that vitamin D-regulated pathways are even more complex than we previously thought.

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