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Systematic Review of The Effect of Vitamin D Supplementation on Immune Response

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Abstract

The potential role for vitamin D and its active metabolite 1, 25-hydroxyvitamin D ($1,25(OH)_2D$) in modulating the immune response was first recognized 25 years ago. The presence of adequate levels of vitamin D is required for the proper functioning of the body's defense system such as barrier integrity, the production of antimicrobials, chemotaxis of other immune cells and regulation of inflammation in the innate and adaptive immune system.

We identified 60 studies on vitamin D and immune response. A total of 33 studies were excluded because it was not clinical trials, of the remaining 27, 21 were excluded because clinical trials were not randomized controlled trials and one was excluded because of using combined vitamin D and calcium, so the remaining five clinical trials were reviewed to evaluate the clinical evidence for the role of vitamin D in the immune system.

From the five Randomized Controlled Trials (RCTs) were reviewed in this paper, it is concluded that the results from these studies appear quite robust and consistent. Side effect profile of vitamin D preparations were minimal and rare as indicated by reports of post marketing surveilence as well as RCTs.

Abstrak

Potensi peran vitamin D dan metabolit aktifnya 1,25-hidroksivitamin D ($1,25(OH)_2D$) dalam respons imun telah dikenal sejak 25 tahun yang lalu. Vitamin D dalam kadar yang cukup dibutuhkan agar sistem pertahanan tubuh dapat berfungsi dengan baik seperti integritas sawar, produksi antimikroba, kemotaksis dari sel imun dan regulasi inflamasi dalam sistem imun nonspesifik maupun spesifik.

Penelusuran awal berhasil mengidentifikasi 60 penelitian mengenai vitamin D dan respons imun. Sebanyak 33 penelitian dieksklusi karena bukan merupakan uji klinis, dari 27 yang tersisa, 21 penelitian dieksklusi karena bukan uji klinik acak terkontrol dan satu dieksklusi karena menggabungkan vitamin D dan kalsium, sehingga tersisa lima uji klinik yang ditelaah untuk mengevaluasi bukti klinis peran vitamin D dalam respons imun.

Dari lima RCT yang diikutkan pada telaah sistematik ini, dapat disimpulkan bahwa hasil penelitian-penelitian tersebut cukup kuat dan konsisten. Profil efek samping sediaan vitamin D minimal dan jarang terjadi seperti diindikasikan baik dalam laporan *post marketing surveilence* maupun RCT.

Background

The nonclassic tissues that have vitamin D receptors are those not only participating in the classic actions of vitamin D such as bone, gut, and kidney. They are potential targets for the active metabolite of vitamin D, $1,25(OH)_2D$[1].

The presence of adequate levels of Vitamin D is required for the proper functioning of the body's defense system such as barrier integrity, the production of antimicrobials, chemotaxis of other immune cells and regulation of inflammation in the innate and adaptive immune system. In each disorder, the level of 25(OH)D that is needed for maximal

performance has not been determined but may be considerably higher than previously believed for diseases such as *M. tuberculosis* and other infections[2].

In this review, we sought to evaluate the clinical evidence for the role of vitamin D in the immune system by examining the effectiveness of vitamin D supplementation when used as a stand-alone supplementation in the treatment of diseases and to examine the quality of the published data.

Objective

To determine the beneficial effects of daily vitamin D in improving low level chronic inflammation and immune response.

Methods

Inclusion criteria:

Research that will be included in this systematic review is all double-blind randomized clinical trial with parallel or cross-over design on the effect of vitamin D on inflammation and immune response.

The types of intervention to be studied are all forms of intervention with vitamin D in any preparations, compared with placebo, given through all routes of drug administrations.

Evidence Acquisition:

We searched for articles in: MEDLINE (2000-2011), the Cochrane Database of Systematic Reviews (Cochrane Collaboration, 2000-2011), CISCOM (Centralised Information Service for Complementary Medicine), EMBASE (Excerpta Medica, 2000-2011),

The general structure of search strategy carried out are (vitamin D OR synonyms) AND (immune OR synonyms) AND (inflammation OR synonyms). Searches are limited in English but not apply the filter methodology. We used the following keywords and medical subject headings:

immunity, immune response, immune system, immunology

1,25(OH)2D, vitamin D, cholecalciferol

inflammation

To complete the primary search, we also performed a search by combining (vitamin D or synonims) and (immunity or synonims).

These resources were supplemented by the handsearching of articles' bibliographies, nonindexed medical and professional journals, and the Indonesian-language and English-language libraries and files of the authors.

Data collection and analysis

All titles and abstracts obtained from electronic searches databases and other searches was conducted by three persons (LI, NA, and PT). Potential full articles meeting inclusion criteria then were downloaded. Three reviewers (LI, NA, and PT) conducted an assessment of study eligibility according to inclusion criteria and data extraction.

Quality Scoring

The quality of controlled clinical trials was examined based on the method of Jadad, a method for assessing the quality of controlled clinical trials

Basic Jadad Score is assessed based on the answer to the following 5 questions.

The maximum score is 5.

Question	Yes	No
1. Was the study described as random?	1	0
2. Was the randomization scheme described and appropriate?	1	0
3. Was the study described as double-blind?	1	0
4. Was the method of double blinding appropriate? (Were both the patient and the assessor appropriately blinded?)	1	0
5. Was there a description of dropouts and withdrawals?	1	0

Quality Assessment Based on Jadad Score

Range of Score	Quality
0–2	Low
3–5	High

Result

In our initial screening, we identified 60 studies on vitamin D and immune response. A total of 33 studies were excluded because it was not clinical trials, of the remaining 27, 21 were excluded because clinical trials were not randomized controlled trials and one was excluded because of using combined vitamin D and calcium, so the remaining five clinical trials were evaluated. Summary of the search process can be seen in Figure 1 while the characteristics of the included studies in this systematic review are summarized inTable 1.

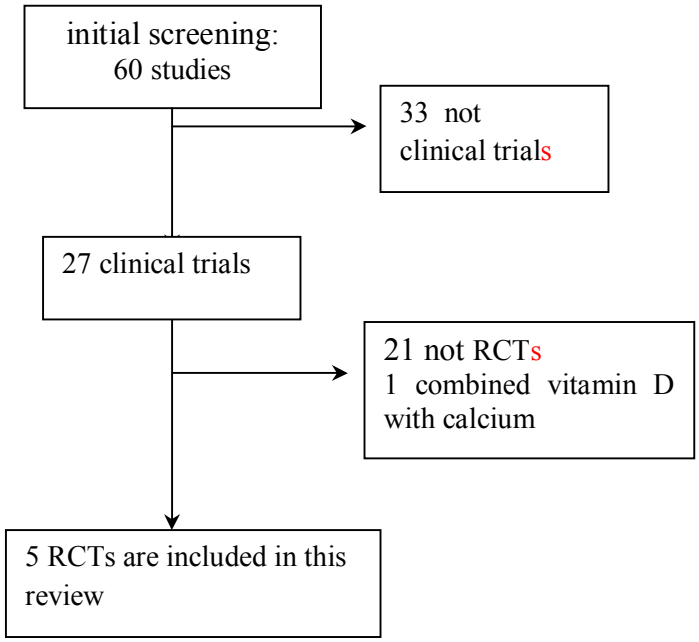

Figure 1. Summary of the search process

Table 1. Human studies with vitamin D supplementation relating to the Immune Function

Referensi	**Dose**	**Subjects n**	**Duration of treatment**	**Outcome**	**result**	**discussion**	**Jadad Score**	**Adverse efeect**
Schleithoff, *et al*., 2006[3].	50 _g vitamin D3/d plus 500 mg Ca/d [D(+) group] or placebo plus 500mgCa/d [D(–) group]	Ninety-three patients with CHF	9 mo	survival rate and different biochemical variables	Significant treatment effects were observed on logarithmic-transformed serum concentrations of 25-hydroxyvitamin D, parathyroid hormone, tumor necrosis factorα, and IL 10	Vitamin D3 reduces the inflammatory milieu in CHF patients and might serve as a new antiinflammatory agent for the future treatment of the disease	2 (low)	NA

Wejse *et al*., 2009[4].	Use of 100 000 IU	365 adult patients with TB starting antituberculosis treatment; 281 completed	at 1, 5 and 8 months.	clinical outcome and mortality.	Vitamin D does not improve clinical outcome among patients withTB and no overall effect on mortality	Dose may not be high enough to result in a difference	5 (high)	No serious adverse effects were reported; mild hypercalcemia was rare and present in both arms.
Nursyam, E. W. *et al* [5].	10 000 IU vitamin D	sixty seven tuberculo	six weeks	clinical improvement,	77.1% sputum conversion rate in	Highly significant	2 (low)	NA

	daily	sis patient		nutritional status, sputum conversion, and radiological improvement	antibiotic only group (placebo) compared with 100% in vitamin D group	results. However, small sample size		
Bishoff-Ferrari, H. *et al* [6].	800 or 2000 IU daily cholecalciferol	173 patients with acute hip fracture	12 months	Primary outcome was rate of falls; secondary outcome was rate of	39% reduction in hospital readmission in the group using 2000 IU daily cholecalciferol, but did not reduce falls	90% reduction in infection rate	5 (high)	NA

				hospital readmissions				
Urashima, M. *et al* [7].	1200 IU vitamin D	334 schoolchildren	4 months	incidence of seasonal influenza A	RR of 0.58 compared with control group p=0.04 Asthma attacks significantly reduced in treatment group p=0.006 (secondary outcome)	Significant reduction of influenza A but not B	5 (high)	NA

Discussion

The potential role for vitamin D and its active metabolite 1,25(OH)2D in modulating the immune response was first recognized 25 yr ago with three crucial discoveries: 1) the presence of vitamin D receptors (VDRs) in activated human inflammatory cells, 2) the ability of 1,25(OH)2D to inhibit T cell proliferation, and 3) the ability of disease activated macrophages to produce 1,25(OH)2D (*i.e.* express CYP27B1). Vitamin D and CYP27B1 play important roles in both innate and adaptive immunity, which impact a number of clinical conditions [1].

For example, a low vitamin D status is involved in various infectious diseases such as tuberculosis, and 1,25(OH)2D3 has long been considered to potentiate the killing of mycobacteria by monocytes. The underlying mechanism of these observations has recently been found by the observation that the monocyte, when activated by mycobacterial lipopeptides, expresses CYP27B1, producing 1,25(OH)2D from circulating 25OHD and in turn inducing cathelicidin, an antimicrobial peptide that increases killing of the mycobacterium. Inadequate 25OHD levels fail to support this process. As a second example, it has been discovered that vitamin D deficiency and/or living at higher latitudes (with less sunlight) are linked with a number of autoimmune diseases including type 1 diabetes mellitus, multiple sclerosis, and Crohn's disease. In a large Finnish study, giving infants 2000 IU vitamin D for their first year of life decreased the incidence of type 1 diabetes mellitus by 80%. Other studies have related vitamin D deficiency to high risk of multiple sclerosis, asthma, and other immunologic diseases[1].

Epidemiological data showed that Upper Respiratory Infection (URI) incidence has been inversely associated with 25(OH)D3 levels. In a randomized, double-blind trial of vitamin D supplementation, vitamin D was shown to have no effect on the clinical course of URIs [8].

In 2006 Cannell *et al*[9]. proposed that children who received vitamin D supplements had a low incidence of respiratory infections and linked this observation to vitamin D regulation of the antimicrobial peptides cathelicidin and defensin b2. Vitamin D has been shown to enhance the expression of antibacterial peptides; however, the effect of vitamin D on these antibacterial peptides *in vitro* or *in vivo* against influenza has not been tested[10].

From a public health point of view, the improved outcomes in treatment of and prevention of devastating diseases as summarized in Table 1 may result in considerable cost savings to health care.

Conclusions and Limitation

The nonclassic actions of vitaminD are cell specific and provide a number of potential new clinical applications for 1,25(OH)2D3 and its analogs. However, the use of vitamin D metabolites and analogs for these applications remains limited by the classic actions of vitamin D leading to hypercalcemia and hypercalcuria.

In this systematic review we conducted a search of the double-blind randomized clinical trial on the effect of vitamin D in improving low-level chronic inflammation and immune response. It was found that five clinical trials met inclusion criteria, they were clinical trials on the effects of vitamin D on postoperative complications, incidence of influenza A, and different biochemical and clinical variables of tuberculosis and CHF. Almost all of the studies were conducted with good methodology.

The effectiveness of vitamin D is shown with a reduction of the incidence of influenza A, the inflammatory milieu in CHF Patients, hospital readmission, and increasing sputum conversion rate. Only one study showed that vitamin D did not improve clinical outcome among patients with TB and overall effect on mortality but it may be caused by the dose was not high enough.

It is concluded that the results from these studies appear quite robust and consistent. Furthermore, there is an increasing amount of data from experimental data suggesting mechanisms for observed beneficial effects.

Side effect profile of vitamin D preparations are good enough as indicated by report of side effects that were minimal and rare. Much still needs to be learned in this area of study. It appears appropriate to call for new and innovative studies using appropriate doses of vitamin D, which may greatly reduce morbidity and mortality worldwide.

Limitation

In the five clinical trials, outcomes measured were not the same and measurement techniques were also varied. Search on this systematic review was also conducted only in English. This has the potential to cause bias because study reported in other languages can not be found.

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Nursyam *et al.*[11] was to assess the benefit of vitamin D were clinical improvement, nutritional status, sputum conversion, and radiological improvement. Primary outcome of Bischoff-Ferrari *et al*. study was rate of falls, secondary outcome was rate of hospital readmissions during the 12-month follow-up. The primary outcome of Wejse *et al*.[7] study was to assess the benefit of vitamin D on clinical improvement as assessed by TBscore. The Objectives of Martineau *et al*. study was to determine the effect of vitamin D supplementation on antimycobacterial immunity and vitamin D status while Kawaura *et al*[12]. study aimed to know the effect of long term supplementation with 1α hydroxyvitamin D3 on serum pepsinogen and gastrin levels and rate of H. pylori infection.