

VITAMIN D AN ANTIMICROBIAL WEAPON AGAINST ACUTE RESPIRATORY TRACT INFECTIONS. A SYSTEMATIC REVIEW (2006-MARCH 2011)

RUXANDRA MOROTI^{1,2*}, ROXANA PETRE¹, IULIA NICULESCU¹,
IRINA PIGULEA¹, VIOLETA MOLAGIC¹, ADRIANA HRISTEA^{1,2},
ALINA POROJNICU³

¹*Matei Bals National Institute for Infectious Diseases, 1, Grozovici str, 021105, Bucharest*

²*Carol Davila University of Medicine and Pharmacy, 8, B-dul Eroilor Sanitari, 050511, Bucharest*

³*Department of Radiation Biology, Institute for Cancer Research Rikshospitalet – Radiumhospitalet Medical Center, Oslo, Norway*

**corresponding author: ruxandra_moroti@yahoo.com*

Abstract

Vitamin D (vitD) acts like a hormone, by binding a nuclear receptor, vitamin D receptor (VDR), stimulating the release of cathelicidin, an endogenous antibiotic and an immune-modulator. The presence of VDR in monocytic-macrophagic system and in the respiratory epithelium suggests that vitD can play a role in defending against respiratory infections. A lot of studies were published in the last years for finding the correct link between vitD and respiratory infections, in order to use it for prophylaxis and treatment. We searched on PubMed publications for piecing together the last 5 years researches on this field. Ten out of 90 articles proved to be proper for further analysis, being clinical trials regarding acute respiratory infections (including flu). We have found high variations in serum vitD levels in different races and geographic areas; we observed that despite these variations, a serum level with at least 10 nmol/L higher than the mean basic serum level concentration appears to be protective. For enhancing the serum level, the studied trials used either daily doses (800-2.000 IU), or singular higher doses (100.000 IU) eventually repeated. The conclusion from almost all trials is that roughly vitamin D may be an effective adjuvant in the anti-infective therapy.

Rezumat

Vitamina D (vitD) acționează ca un hormon, prin legarea de un receptor specific nuclear - receptorul vitaminei D (VDR), stimulând eliberarea de cathelicidină, un antibiotic endogen și un modulator imun. Prezența VDR în sistemul monocitic-macrofagic și, de asemenea, în epiteliul tractului respirator sugerează că vitD poate juca un rol în apărarea împotriva infecțiilor respiratorii. Un număr mare de studii publicate în ultimii ani încearcă să găsească legătura corectă între vitD și infecțiile respiratorii, în vederea utilizării sale în profilaxie și tratament. Am analizat publicațiile PubMed apărute în ultimii 5 ani în domeniu. Zece articole (pornind de la 90 rezultate brute) s-au dovedit a fi adecvate pentru analize ulterioare, reprezentând studii clinice privind infecții acute respiratorii, inclusiv gripa. În pofida variațiilor mari interetnice și geografice, un nivel cu cel puțin 10 nmol / L peste media din populațiile studiate pare să confere protecție. Pentru creșterea nivelului

seric, în studiile intervenționale analizate s-au folosit atât doze zilnice (800-2.000 UI), cât și doze mari (100.000 UI), spațiate. Majoritatea studiilor concluzionează că vitD este un adjuvant eficient în terapia anti-infecțioasă.

Keywords: vitamin D, acute respiratory infections, systematic review

Introduction

Recent studies have demonstrated that vitamin D has immune-modulator and antimicrobial functions. It acts like a hormone, by binding a specific nuclear receptor - vitamin D binding receptor (VDR). VDR is distributed in more than 30 different cells types, including the myeloid monocytic-macrophages system and the natural barrier epithelia (skin, respiratory, digestive and uro-genital tracts). VDR activates h-CAMP (human cathelicidin antimicrobial peptide) gene, stimulating the release of cathelicidin [15], a host defense peptide.

Host defense peptides represent ancestral components of the innate immunity of most multicellular organisms, with a wide range of biological activities, from direct killing of invading pathogens (endogenous antibiotic) to the modulation of host immune responses (immune-modulator) [10].

Vitamin D is monitored by calcidiol, 25-hydroxycholecalciferol (25[OH]D) serum level, which reflects also the skin synthesis due to the solar radiation and the enteric vitamin D absorption. The calcidiol is hydroxylated by the kidney to the active form 1,25-dihydroxycholecalciferol (1,25[OH]D) or calcitriol. Calcitriol then binds to the VDR to exert its biologic effects. Calcitriol is rapidly metabolised by cytochrome P₄₅₀ (CYP) enzymes (CYP24A1 isoforme) [16].

A large number of studies concluded that a high 25[OH]D serum level is associated with a good general state of health [12]. The most recent researches considered a level of 75 nmol/L to be protective [12], although there are significant racial differences [14].

The last decades researches have been investigating the implication of vitamin D in the protection against acute respiratory tract infections, in order to use this hormone-like antibiotic as an adjuvant in the prophylaxis and therapy.

We performed a screening on Pubmed database of all publications related to vitamin D and respiratory infections in the last 5 years, implying human subjects.

For a coherent analysis, we examined the data provided by the studied publications in both accepted international measuring units, converting the conventional units (ng/mL) in SI units (nmol/L) using the

conversion factor (for 25[OH]D serum level, the conversion is 2.496: 1ng/mL=2.496nmol/L). Regarding the vitamin D intake, 1 microgram is equivalent with 40 IU.

From the 90 results of the screening, after excluding redundancy and non-related studies, we found 40 articles of interest. Out of 40, **10** (8 for acute respiratory infection other than flu and 2 for flu) were further analysed, representing clinical trials.

There were globally two kinds of clinical trials observing the relation between respiratory infections and vitamin D: observational studies that compared vitamin D serum levels in patients and healthy subjects or between patients regarding the infection's outcome and interventional studies that correlated the infections' incidence or outcome with the vitamin D supplementation (tables 1 and 2).

Regarding vitamin D deficiency, there are a lot of cut-offs from different studies: ≤ 30 nmol/L, ≤ 50 nmol/L; vitamin D insufficiency (VDI) being considered, ≤ 75 nmol/L.

Respiratory acute tract infections (other than flu) (table I):

The larger observational multicentric study [4] [Brehm *et al.*, 2010], implying more than 1000 asthmatic North-American children, showed that vitamin D insufficiency is highly prevalent within this population (35% of all subjects had ≤ 75 nmol/L 25[OH]D serum level) and it was associated with a higher incidence of severe asthma exacerbation over a 4-year surveillance period. The mean serum 25[OH]D concentration was the lowest in African American subjects and the highest in white subjects.

Another study from the North American continent (197 Canadian young children), who compares vitamin D serum levels of children with acute low respiratory infections (ALRI) and age-matched children without respiratory symptoms, showed that the level for the ALRI children who were admitted to the intensive care unit was significantly lower (49 ± 24 nmol/L), although no difference was observed in vitamin D levels between the entire ALRI group (81 ± 40 nmol/L) and the control group (83 ± 30 nmol/L) [9] [McNally *et al.*, 2009].

Two studies [2, 11] on young Asian children with ALRI, showed a direct link between vitamin D deficiency and the outcome of severe pneumonia (Banajeh, 2009: 79 patients) and a significantly lower mean vitamin D serum level in ALRI cases than controls (29.1 nmol/L vs. 39.1 nmol/L; $p = 0.015$) (Roth *et al.*, 2009, 50 subjects).

A Turkish study [5] (Karatekin *et al.*, 2007) on a small number of newborns with severe ALRI (25 patients) compared with healthy newborns

controls, showed that the mean serum 25[OH]D concentrations in the ALRI group was significantly lower (by half) than the control group.

Laaksi *et al* (2007) enrolled 800 North-European healthy young men in a 6 months study (winter-spring) and observed that there was a statistically significant relationship between the social absence due to respiratory tract infections and the low level of 25[OH]D (<40 nmol/L). The mean 25[OH]D serum level of this population was 80.2 ± 29.3 nmol/L [6].

The same group of authors, in 2010 published an interventional trial [7] on over 150 North-European healthy young men (Finnish Army) volunteers, almost 50% receiving vitamin D3 supplement 400 UI/day, 6 months (winter-spring) and 50% receiving placebo. After 6 months, the interventional group registered a decrease in serum levels with a mean of 5 nmol/L versus 25 nmol/L for the placebo group. The social absence due to respiratory tract infections did not differ between groups. The proportion of men remaining healthy throughout the 6-month study period was greater in the intervention group (41 [51.3%] of 80) than in the placebo group (30 [35.7%] of 80; $p=0.045$).

Another interventional trial, published by Manaseki-Holland *et al* (2010) [8] enrolled over 400 Asian children (1-36 months) with pneumonia from an outpatient clinic and monitored them over 90 days period. Along with the standard therapy for pneumonia, half of these children received 100.000 IU vitamin D3 as single oral dose and the other half received placebo. There was no significant difference in the mean number of recovery days between the intervention and placebo, but the risk of repeating a new episode of pneumonia within 90 days of supplementation was lower in the intervention group.

Table I

Vitamin D and acute respiratory tract infections (other than flu)

Ref	Subjects/ Treatment regimen /Serum concentration	Results	Conclusion
[8] 2010	453 Asian children (1-36 months) with non-severe or severe pneumonia (outpatient clinic): 224 receiving vitamin D3 (vitD3) 100.000 IU a single oral dose along with antibiotics and 229 receiving placebo along with antibiotics	There was no significant difference in the mean number of days to recovery between the vitD3 ($4.74 \text{ days} \pm 2.22$) and placebo ($4.98 \text{ days} \pm 2.89$; $p = 0.17$). The risk of a repeated episode of pneumonia within 90 days of supplementation was lower in the intervention (92/204; 45%) than the placebo group [122/211; (58%; relative risk 0.78; 95% CI 0.64, 0.94; $p = 0.01$). Children in the vitD3 group survived longer without experiencing a repeated episode (72 days vs. 59 days; HR 0.71; 95% CI 0.53-0.95; $p = 0.02$).	A single high-dose oral vitD3 supplementation to young children along with antibiotic treatment for pneumonia could reduce the occurrence of repeat episodes of pneumonia.

Ref	Subjects/ Treatment regimen /Serum concentration	Results	Conclusion
[6] 2010	164 North European healthy young men (Finnish Army) volunteers: 80 receiving vitD3 supplement 400 UI/day and 83 receiving placebo, 6 months (October 2005-March 2006) Registration of 25[OH]D serum levels at baseline and after 6 months	At baseline there was no difference in mean serum 25[OH]D concentrations between the intervention (78.7 ± 14.9 nmol/L) and placebo (74.4 ± 20.8 nmol/L) groups. After 6 months, the interventional group registered a decrease in the serum level with a mean of 5 nmol/L vs 25 nmol/L for the placebo group [71.6 ± 22.9 nmol/L vs 51.3 ± 15.5 nmol/L ($p < 0.001$)] The absence on duty due to respiratory tract infections did not differ between groups. The proportion of men remaining healthy throughout the 6-month study period was greater in the intervention group (41 [51.3%] of 80) than in the placebo group (30 [35.7%] of 80; $p = 0.045$).	The present placebo-controlled double-blinded study involving 164 young Finnish men provided some evidence for a preventive effect of vitD supplementation against respiratory tract infections
[4] 2010	1024 North American children with mild-to-moderate persistent asthma had serum 25[OH]D measured. The incidence of any hospitalization or emergency department visit over the 4 years of the trial were established. VitD insufficiency was defined ≤ 12 nmol/L.	35% of all subjects were vitD insufficient. Mean vitD levels were the lowest in African American subjects and highest in white subjects. After adjusting for age, sex, body mass index, income, and treatment group, insufficient vitD status was associated with a higher incidence of any hospitalization or emergency department visit (odds ratio, 1.5; 95% CI, 1.1-1.9; $p = 0.01$)	VitD insufficiency is common in North American children with asthma and is associated with higher incidence of severe exacerbation.
[9] 2009	197 Canadian children: 105 ALRI patients (bronchiolitis and pneumonia) and 92 age-matched subjects without respiratory symptoms recruited from the same hospital, in the same winter period and the 25[OH]D levels were measured and compared.	The mean vitD level for the entire ALRI group was not significantly different from the control group (81 ± 40 vs. 83 ± 30 nmol/L, respectively). The mean vitD level for the ALRI subjects admitted to the intensive care unit (49 ± 24 nmol/L) was significantly lower than that observed for both control (83 ± 30 nmol/L) and ALRI subjects admitted to the general pediatrics ward (87 ± 39 nmol/L).	Although no difference was observed in vitD levels between the entire ALRI group and the control group, significantly more children admitted to the intensive care unit with ALRI were vitD deficient.

Ref	Subjects/ Treatment regimen /Serum concentration	Results	Conclusion
[2] 2009	79 Asian young children with vitD status established, among 152 Asian children aged 2-59 months with WHO-defined very severe pneumonia (VSP), were treated and followed for up to 30 days and the association of rickets with treatment outcome and the correlation between VDD and both the circulating neutrophils (PMNs) and oxygen saturation (SpO ₂) were studied. A concentration of ≤ 30 nmol/L defines VDD.	Treatment failure occurred in 24 cases (15.8%) and 21 (87.5%) were rachitic. Of the 79 subset, 29 had VDD of which 23 (79.3%) had rickets. Treatment failure was significantly higher in the rachitic compared to non-rachitic patients [20.6% (21/102) vs. 6% (3/50); OR(odds ratio) 1.38 (95% CI 1.13-1.69), $p = 0.031$]. In multivariate regression, VDD was strongly associated with reduced PMNs% [Mean (SD) 37 (17) vs. 47 (17); Adjusted OR 0.71 (95% CI 0.53-0.95), $p = 0.02$], and reduced blood oxygen saturation (SpO ₂) [Mean (SD) 85.9 (7.9) vs. 89.8 (7.1); OR 0.96 (95% CI 0.93-0.99), $p = 0.021$]	In VSP, rickets was significantly associated with treatment outcome and VDD significantly predicted both reduced circulating polymorphonuclear leukocytes (PMNs), and hypoxemia (Blood oxygen saturation - SpO ₂ <88%).
[11] 2009	50 Asian children aged 1-18 months: 25 hospitalized cases with acute low respiratory infection (ALRI) were individually matched with 25 controls and the mean serum 25[OH]D was compared	Mean 25[OH]D was significantly lower among ALRI cases than controls (29.1 nmol/L vs. 39.1 nmol/L; $p = 0.015$). The unadjusted odds of ALRI was halved for each 10 nmol/L increase in 25[OH]D (OR 0.53, 95% CI 0.30-0.96). Adjustment for confounders increased the magnitude of the association.	A deficiency in VitD status was associated with early childhood ALRI
[5] 2007	40 Turkish newborns: 25 newborns with ALRI admitted to the intensive care unit were compared with 15 healthy newborns controls, regarding the 25[OH]D serum concentrations for assessing vitD status in the two groups	In 87.5% of all newborns serum 25(OH)D concentrations were lower than 20 ng/mL (50 nmol/L). The mean serum 25[OH]D concentrations in the ALRI group newborns were lower than those of the control group (9.12 $\pm$ 8.88 ng/mL and 16.33 $\pm$ 13.42 ng/mL respectively) ($p=0.011$)	The newborns with subclinical vitamin D deficiency may have an increased risk of ALRI incidence.

Ref	Subjects/ Treatment regimen /Serum concentration	Results	Conclusion
[7] 2007	800 North European healthy young men (Finnish Army), enrolled in July 2002 and were followed up 6 months. [25(OH)D] concentrations were measured in July and the number of days of absence from duty due to respiratory infection were counted in the follow up period.	The mean serum 25[OH]D concentrations were 80.2 ± 29.3 nmol/L (n = 756). Subjects with serum 25[OH]D concentrations < 40 nmol/L (n = 24) had significantly (p = 0.004) more days of absence from duty due to respiratory infection (median: 4; quartile 1-quartile 3: 2-6) than did the control subjects (2; 0-4; n = 628; incidence rate ratio 1.63; 95% CI: 1.15, 2.24)	Clinical trials of vitD supplementation are needed to investigate whether it enhances the immunity to microbial infections.

Flu and vitamin D (table II):

There are two interventional trials published and analysed. The most recent one (Urashima & al 2010) [13] on over 300 schoolchildren (placebo controlled), showed that vitamin D3 supplementation during winter (1200 IU daily) may reduce the incidence of influenza A.

The second one, by Aloia & Li-Ng (2007) [1] on over 200 postmenopausal women (placebo controlled) showed that vitamin D3 supplementation, particularly at higher doses (2000 IU daily), may protect against the 'typical' winter cold and influenza.

Table II
Vitamin D and flu

Ref	Subjects/Treatment regimen/Objectives	Results	Conclusion
[13] 2010	334 Japanese schoolchildren: 167 receiving vitD3 (1200 IU/day) during the winter period were compared with 167 receiving placebo, regarding the incidence of influenza A during the studied period	Influenza A occurred in 18 of 167 (10.8%) children in the vitD3 group compared with 31 of 167 (18.6%) children in the placebo group [relative risk (RR), 0.58; 95% CI: 0.34, 0.99; p = 0.04]. In children with a previous diagnosis of asthma, asthma attacks occurred in 2 children receiving vitD3 compared with 12 children receiving placebo (RR: 0.17; 95% CI: 0.04, 0.73; p = 0.006).	VitD3 supplementation during winter may reduce the incidence of influenza A, especially in specific subgroups of schoolchildren.

Ref	Subjects/Treatment regimen/Objectives	Results	Conclusion
[1] 2007	208 African-American post-menopausal women, 104 receiving vitD3 (800 IU/day 2 years and 2000 IU/day the next year) and 104 receiving placebo were observed during a 3 years study. The upper respiratory infection symptoms (colds or influenza) were reported every 6 months.	Over 3 years, a total of 34 patients reported cold and influenza symptoms, 8 in the vitD3 group vs. 26 in the placebo group ($p<0.002$). Regarding the seasonality of the symptoms, the placebo group had cold/influenza symptoms mostly in winter. The vitD group had symptoms throughout the year using on 20 µg/day, whereas only one subject had a cold/influenza using on 50 µg/day. None of the 34 patients with reported cold and influenza symptoms had significant comorbidities.	VitD supplementation particularly at higher doses, may protect against the 'typical' winter cold and influenza.

Conclusions

Regarding the 25[OH]D serum levels, there are variations between studied populations in the analysed publications: for asthmatic North-American children: the African-Americans have the lowest 25[OH]D levels and the Caucasians have the highest levels. Healthy North-American children and healthy North-European young men have 25[OH]D mean serum levels of 80 nmol/L. In contrast, the values reported for healthy Asian young children are much lower: 39 nmol/L (South Asia) and 41nmol/L (16.3 ng/mL) for the Turkish newborns.

A mean increase of 10 nmol/L in vitamin D serum concentration (relatively to the mean levels of the patients from a distinct geographic area) appears to confer protection against acute respiratory infections occurrences.

Without supplementation, during the cold seasons (winter and next spring period), there is a decrease of around 25 nmol/L in the mean serum 25[OH]D level in North-European populations.

Administration of either one single high dose of oral vitamin D3 (100.000 IU) or daily oral doses (400-2000 IU) over cold seasons in temperate zones may reduce the incidence of influenza and may protect against acute respiratory tract infections.

Vitamin D seems to be at least an effective adjuvant agent in the anti-infective therapy in acute and chronic respiratory tract infections.

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