MAJOR ARTICLE

Vitamin D Supplementation for the Prevention of Acute Respiratory Tract Infection: A Randomized, Double-Blinded Trial among Young Finnish Men

Ilkka Laaksi,[1] Juha-Petri Ruohola,[4] Ville Mattila,[5] Anssi Auvinen,[2] Timo Ylikomi,[1,3] and Harri Pihlajamäki[5]

[1]Department of Cell Biology, Medical School, and [2]Department of Epidemiology, Tampere School of Public Health, University of Tampere, and [3]Department of Clinical Chemistry, Tampere University Hospital, Tampere, and [4]Finnish Defence Forces and [5]Research Department, Centre for Military Medicine, Helsinki, Finland

Vitamin D is formed in the skin from 7-dehydrocholesterol after activation induced by ultraviolet B (UVB) radiation (290–315 nm). Vitamin D is the precursor of the hormone 1,25$(OH)_2$D, which is formed in 2 hydroxylation reactions, first to 25-hydroxyvitamin D, hereafter abreviatd 25(OH)D, in the liver and then to 1.25$(OH)_2$D in the kidneys or target organs [1]. Vitamin D regulates the calcium and phosphate balance, as well as bone mineralization [2], and vitamin D deficiency leads to secondary hyperparathyroidism, which causes rickets in children and osteoporosis and osteomalacia in adults [3, 4].

Vitamin D status is determined by measuring the serum concentration of 25(OH)D, the major circulating form of the hormone [5]. The emerging consensus is that vitamin D insufficiency be defined as serum 25(OH)D levels of <80 nmol/L [6, 7]. Diet is the most important source of vitamin D in northern latitudes during the wintertime, because sunlight exposure during this time is inadequate for inducing the endogenous production of vitamin D. Vitamin D deficiency is common in all age groups in Finland from October through March [8]. As a public health policy, vitamin D fortification of liquid milk products (0.5 μg/dL) and margarines (10 μg per 100 g) has been implemented in Finland since February 2003.

Vitamin D regulates gene expression through binding with vitamin D receptors (VDR), because active vitamin D binds to the VDR, which dimerizes with the retinoic X receptor. The vitamin D/VDR complex binds to vitamin D–responsive elements inside the promoter regions of vitamin D–responsive genes. Nuclear receptor coactivator proteins enhance this transcriptional activation. VDR modulates the expression of genes that are involved in immunity [9, 10].

Toll-like receptors (TLRs) monitor the host for the presence of pathogens. TLR stimulation by pathogen lipopeptides leads to the production of antimicrobial peptides [11]. Moreover, TLR activation of human macrophages upregulates VDR expression and the vitamin D-1 hydroxylase genes, which enhances the induction of the cathelicidin. Adenosine monophosphate is upregulated by vitamin D in human monocytes in a dose-dependent manner. Liu et al [12] reported that the induction of cathelicidin messenger RNA (mRNA) was significantly lower in the presence of serum from blacks, which contains less 25(OH)D than does the serum from whites.

Respiratory infection leads to increased activation of vitamin D and increased levels of cathelicidin mRNA. Specifically, respiratory epithelial cells activate vitamin D and create a microenvironment with high levels of the active form of the vitamin. This local vitamin D activation might be an important component of host defense, because it has downstream effects, including upregulation of the cathelicidin antimicrobial peptide gene, which is an important component of innate immunity in the lungs [13].

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Reprints or correspondence: Dr Ilkka Laaksi, Medical School, Medisiinarinkatu 3, University of Tampere, Tampere, Finland 33014 (ilkka.laaksi@uta.fi).

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Clinically, antimicrobial peptides inhibit invasive pneumococcal disease, meningococcal disease, and group A streptococcal disease [14, 15]. Vitamin D deficiency seems to be a risk factor for severe respiratory infection in children <5 years of age [16].

Vitamin D production in the skin is seasonal; vitamin D deficiency is common in the winter, and $1,25(OH)_2D$ stimulates the expression of antimicrobial peptides in epithelial cells lining the respiratory tract, thus protecting the lung from infection. It has been proposed that vitamin D deficiency is a "seasonal stimulus," which explains the remarkable seasonality of epidemic influenza [17].

Our earlier observational study in a cohort of 754 young Finnish men demonstrated a significant negative association between serum 25(OH)D levels and the number of days absent from daily duty because of acute respiratory tract infection [18]. The present study was a blinded, placebo-controlled randomized trial, the primary outcome of which was to determine whether vitamin D supplementation decreases the number of days absent from duty because of acute respiratory tract infection.

SUBJECTS AND METHODS

Trial design. This placebo-controlled double-blinded study was comprised of 164 voluntary young Finnish men (18–28 years of age) undergoing compulsory periodic military training as conscripts in an infantry unit comprised of 400 men in the Finnish Defence Forces. The subjects represented the general conscript population of the Finnish Defence Forces. Inclusion criteria were no receipt of regular medication and having passed the entry medical examination as healthy. Exclusion criteria were the use of supplementary vitamin D, multivitamins, and cod liver oil. Of a total of 400 men entering the unit, 164 (41%) volunteered to participate in the study and met the inclusion criteria. The subjects were randomly assigned to the intervention group, which received 400 IU (10 μg; $n = 80$) vitamin D_3 (Minisun; Verman) daily, or the control group ($n = 84$), which received placebo (Pharmia; a capsule identical in size and form to the active preparation). Random allocation was performed using computer-generated random numbers. The conditions related to physical activity, nutrition, clothing, accommodation, and exposure to sunlight were homogeneous during their military service. The trial was performed from October through March in Pori Brigade, in southwestern Finland. This study was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland. Participation was voluntary, and written informed consent was obtained from all participants. The study was registered in ClinicalTrials.gov(NCT00973583).

Identification of respiratory infections. Medical records for all participants covering 6 months of military service were reviewed, and any diagnosed acute respiratory tract infection (ie, sinusitis, tonsillitis, otitis, bronchitis, pneumonia, pharyngitis, and laryngitis) was recorded. The main outcome variable was the number of days absent from duty due to acute respiratory tract infection. Secondary outcomes were self-reported symptoms of acute respiratory tract infection (cough, runny nose, sore throat, fever, or common cold symptoms) and hospitalization due to acute respiratory tract infection. The symptoms were evaluated 4 times during the study. The physicians and other personnel treating patients in garrisons were blinded to treatment allocation. All acute respiratory tract infections were treated in the garrison hospital. The shared environment and tasks, as well as the closed community of the military troops with a uniform setting, homogeneity in terms of source of infection, and large population in close daily contact makes this group susceptible to minor epidemics, which increases the probability of infection and therefore increased the statistical power of the study.

After randomization, blood samples were obtained from 73 subjects at the beginning of the study in October 2005 and again from 108 subjects in March 2006 to determine the serum 25(OH)D concentrations. The samples were coagulated at room temperature for 1 h and centrifuged at 2000 *g* for 20 min at room temperature for serum separation. Serum samples were then frozen and stored at -20°C for later analysis. Total serum 25(OH)D concentrations were measured using an OCTEIA enzyme immunoassay kit (Immunodiagnostic Systems).

Plasma parathyroid hormone (PTH) concentrations were measured by electrochemiluminescence (Elecsys PTH Kit; Roche Diagnostics) in 104 randomly chosen subjects at the end of the study. Elecsys PTH CalSet (Roche Diagnostics) was used for calibration.

Statistical analysis. We aimed to maximize the power of the study by recruiting all voluntary conscripts (ie, we did not sample the target population). Hence, formal sample size calculations were not performed prior to the study. Our primary analysis included all randomized subjects in accordance with the intention-to-treat principle. Differences between the groups in continuous variables were tested using the Mann-Whitney *U* test. χ^2 tests were used to assess categorical data. We set a 2-sided *P* value of <.05 as the alpha criterion. Hazard ratios were calculated by Cox regression analysis; the end point of the follow-up period was the first infection, with censoring at premature release from duty, or at the end of the study after a 6-month follow-up period. Cox regression analysis was adjusted for influenza vaccination and smoking at baseline. The frequency of missing variables at baseline varied from 2% to 6%, with the exception of data on smoking status, for which 20% of study subjects had missing data. Altogether, 60 subjects dropped out of the study by the end point with no specific

reason given for study withdrawal (Figure 1). Data analysis was performed with SPSS for Windows, version 15.0.1 (SPSS).

RESULTS

In October 2005, at the beginning of the study, there was no statistically significant difference in mean serum 25(OH)D concentrations (± standard deviation [SD]) between the intervention (78.7 ± 14.9nmol/L; $n = 29$) and placebo (74.4 ± 20.8 nmol/L; $n = 44$) groups ($P = .35$). Other characteristics were also comparable between the groups at baseline, although both smoking and influenza vaccination were slightly more common in the placebo group (Table 1).

In March 2006, after daily supplementation with 400 IU vitamin D or placebo for 6 months, the mean serum 25(OH)D concentrations (±SD) were 71.6 ± 22.9 nmol/L ($n = 58$) in the intervention group and 51.3 ± 15.5 nmol/L ($n = 50$) in the placebo group ($P < .001$).

The main outcome variable, which was the number of days absent from duty due to respiratory tract infection, did not differ between groups. Mean number of days absent (±SD) was 2.2 ± 3.2 days in the intervention group and 3.0 ± 4.0 days in the placebo group ($P = .096$). There was an effect during the first 6 weeks of the study, with a mean (±SD) of 0.7 ± 2.1 days of absence in the intervention group and 1.4 ± 2.6 days absent in the placebo group ($P = .060$). After the first 6 weeks, there tended to be no difference between groups (Table 2). Nevertheless, 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; $P = .045$). In a Cox regression analysis with adjustments for smoking and influenza vaccination, the adjusted hazard ratio (HR) for absence from duty due to respiratory tract infection was lower in the intervention group (HR, 0.71; 95% confidence interval [CI], 0.43–1.15). The number needed to treat, calculated from the proportion of men without any days absent from duty, was 6.4 (95% CI, 3–257). Self-reported cough (65% in the intervention group vs 57% in the placebo group; $P = .30$), runny nose (74% vs 75%; $P = .86$), sore throat (48% vs 45%; $P = .77$), fever (31% vs 38%; $P = .36$), and common cold symptoms (56% vs 52%; $P = .40$) did not differ between the groups. The mean number of hospital days (±SD) was 0.31 ± 1.21 per subject in the intervention group and 0.90 ± 2.22 in the placebo group ($P = .06$). Mean plasma PTH concentrations (±SD) did not significantly differ between the 58 individuals in the intervention group (4.3 ± 1.3 ng/L) and the 50 individuals in the placebo group (4.4 ± 1.4 ng/L) ($P = .55$).

Two subjects in the intervention group reported nausea, stomachache, and diarrhea. One subject in the placebo group dropped out of the study because of a facial rash acquired during the study.

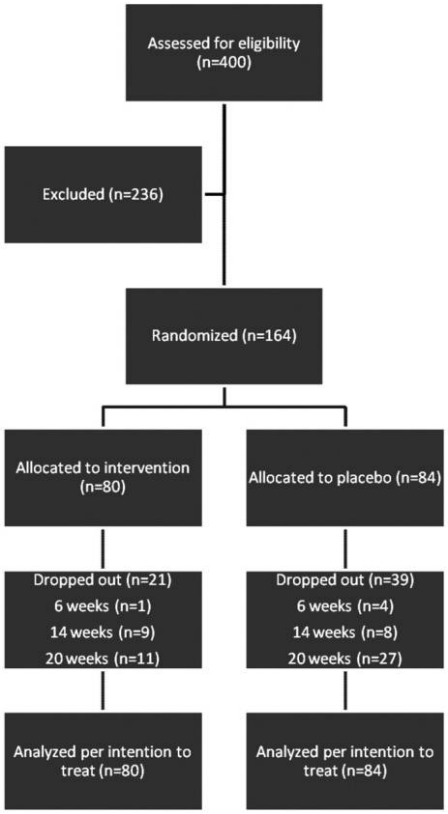

Figure 1. Patient flow chart for this study.

DISCUSSION

The present placebo-controlled double-blinded study involving 164 young Finnish men provides some evidence for a preventive effect of vitamin D supplementation against respiratory tract infection. The Cox regression analysis indicated that the hazard ratio for absence from duty due to respiratory tract infection was lower in the vitamin D supplementation group than it was in the control group. The number of days absent was slightly lower and the proportion of subjects without any days absent was slightly higher in the vitamin D supplementation group, compared with the control group. The number needed to treat, calculated from the proportion of men without any days absent from duty, was as low as 6.4, but there was a very wide 95% CI of 3–257. Furthermore, subjects who received 400 IU vitamin D daily had fewer days of absence due to respiratory infection during the first 6 weeks of follow-up than did other subjects.

This study has some limitations. The primary end point (number of days absent from duty) did not differ significantly between groups, and an effect emerged only in the secondary

Table 1. Patient Characteristics at Baseline

Characteristic	All subjects (n = 164)	Vitamin D supplementation group (n = 80)	Placebo group (n = 84)
Height, mean cm (±SD)	179.5 ± 5.9	180.4 ± 5.8	178.8 ± 5.9
Weight, mean kg (±SD)	75.3 ± 8.8	75.5 ± 9.0	75.2 ± 8.5
Body mass index calculated as kg/m^2	23.4 (2.7)	23.3 (2.6)	23.6 (2.8)
Daily smoking, no. (%) of patients	35 (21.3)	15 (24.0)	20 (29.9)
Influenza vaccination, no. (%) of patients	122 (74.8)	57 (71.3)	65 (77.4)

outcome measures. A formal a priori power calculation could not be performed because of the lack of a defined clinically meaningful difference in infection rates. In addition, the power of the study was limited by the number of subjects who withdrew from the study.

The original sample size was sufficient to show a difference between the mean number of days (±SD) absent (1.9 ± 2.9 vs 3.0 ± 4.0), assuming that no subjects withdrew from the study. The observed effect was 72% of that size, which was similar to the drop-out rate in the intervention group. Thus, with perfect study compliance, we might have been able to demonstrate an effect with a study group of the original size. Nonetheless, the difference in the mean number of days absent between the trial arms would have been statistically significant had a 1-sided P value been used in accordance with the direction of the study hypothesis.

In a recent 6-month double-blinded vitamin D intervention study involving Finnish men 21–49 years of age, a winter-time elevation of serum PTH concentration was inhibited by vitamin D supplementation (800 IU/day). In our study, vitamin D supplementation with 400 IU/day had no statistically significant effect on plasma PTH concentrations. [19]

Serum 25(OH)D concentrations were insufficient in the conscripts at baseline in October 2005 (mean value, 76 nmol/L). In March 2006, after 6 months of vitamin D supplementation, the study group still had an insufficient vitamin D status (mean

Table 2. Study Events

Variable	All subjects (n = 164)	Vitamin D supplementation group (n = 80)	Placebo group (n = 84)	P
Days absent from duty, mean days (±SD)				
Overall	2.6 ± 3.6	2.2 ± 3.2	3.0 ± 4.0	.096
1–6 Weeks	1.1 ± 2.4	0.7 ± 2.1	1.4 ± 2.6	.060
7–14 Weeks	0.7 ± 1.8	0.7 ± 1.4	0.8 ± 2.1	.903
15–20 Weeks	0.5 ± 1.0	0.4 ± 1.0	0.5 ± 1.1	.120
21–24 Weeks	0.4 ± 1.5	0.4 ± 1.8	0.3 ± 1.1	.311
No days absent from duty[a]				
Overall	71 (43.3)	41 (51.3)	30 (35.7)	.045
1–6 Weeks	121 (73.8)	64 (80.0)	57 (67.9)	.077
7–14 Weeks	121 (76.1)	61 (77.2)	60 (75.0)	.845
15–20 Weeks	106 (75.7)	58 (82.9)	50 (69.4)	.077
21–24 Weeks	84 (80.7)	47 (79.7)	37 (82.2)	.284
Self-reported symptoms				
Cough	100 (61.0)	52 (65.0)	48 (57.1)	.303
Runny nose	122 (74.4)	59 (73.8)	63 (75.0)	.855
Sore throat	76 (46.3)	38 (47.5)	38 (45.2)	.772
Fever	57 (34.8)	25 (31.3)	32 (38.1)	.357
Common cold symptoms	89 (54.3)	45 (56.3)	44 (52.4)	.619
Hospitalization due to respiratory tract infection	9 (5.5)	3 (3.8)	6 (7.1)	.396
Length of hospital stay, mean days (±SD)	0.2 ± 1.1	0.2 ± 0.8	0.3 ± 1.3	.338

NOTE. Data are no. (%) of subjects, unless otherwise indicated. SD, standard deviation.

[a] Proportions are calculated from subjects at the time of the study.

value, 72 nmol/L), and the subjects in the placebo group had a vitamin D deficiency (mean value, 51 nmol/L; $P < .001$). Furthermore, serum 25(OH)D levels were >80 nmol/L in only 8% of the placebo group, compared with 29% of those in the intervention group. On the basis of the average consumption of milk and margarine in the Finnish Defence Forces, we estimate that these young men typically receive 7 μg (280 IU) of vitamin D daily from vitamin D–fortified products. The results of the study indicated that additional supplementation with 400 IU/day of vitamin D is not sufficient to maintain an adequate level of vitamin D throughout the winter [8].

All Finnish men must complete 6, 9, or 12 months of compulsory military service from 18 through 29 years of age. Military service is voluntary for women. Each year, an average of 26,500 male conscripts and 500 enlisted females undergo military training. Our study population of 164 conscripts is homogeneous with respect to age and conditions, including physical activity, nutrition, clothing, living areas, and exposure to sunlight in the military environment. Because the conscripts live in close quarters, respiratory infections are common in garrisons, which thereby offers an optimal setting for this kind of study. The homogeneity of our study setting and population is exceptional and is a strength of the study. The completeness of the outcome data (respiratory infections identified) regarding absence from duty is also a strength.

In a study involving 25 newborns with acute lower respiratory infection and 15 healthy newborns as controls, mean serum 25(OH)D concentrations were lower in the acute lower respiratory infection group ($P = .011$), which suggests that vitamin D deficiency might be a risk factor for developing acute lower respiratory infection [20]. Another study involving 56 young children hospitalized with acute lower respiratory infection and 64 children without a history of acute lower respiratory infection reported an association of VDR polymorphism with a 7-fold higher risk for acute lower respiratory infection [21]. On the other hand, in another study involving patients ranging in age from 1 to 25 months who were admitted to the hospital with uncomplicated acute lower respiratory infection and healthy similarly aged patients without a history of hospitalization for acute lower respiratory infection as a control group, serum 25(OH)D concentrations were equivalent between groups, and there was no case-control difference in the prevalence of vitamin D deficiency [22].

Interestingly, a recent study of the Third National Health and Nutrition Examination Survey that included 18,883 participants ⩾12 years of age reported that lower 25(OH)D levels were independently associated with recent upper respiratory tract infections. The median serum 25(OH)D level was 73 nmol/L, and 19% of participants reported a recent upper respiratory tract infection. Upper respiratory tract infection was reported by 24% of the participants with 25(OH)D levels <25 nmol/L, 20% with levels of 25–75 nmol/L, and 17% with levels of ⩾75 nmol/L ($P < .001$). The relative risk for upper respiratory tract infection was 1.4 times higher among participants with serum 25(OH)D levels <25 nmol/L (odds ratio, 1.36; 95% CI, 1.01–1.84) and 1.2 times higher among those with serum 25(OH)D levels of 25–75 nmol/L (odds ratio, 1.24; 95% CI, 1.07–1.43). Furthermore, the association seemed to be stronger among individuals with asthma and chronic obstructive pulmonary disease (odds ratio, 5.67 and 2.26, respectively) [23].

A recent study of vitamin D supplementation showed no benefit in decreasing the incidence or severity of symptomatic upper respiratory tract infection during the winter season. In that study, 162 adults were randomized to receive 50 μg (2000 IU) of vitamin D_3 daily or placebo for 12 weeks. The subjects filled out a biweekly questionnaire to record the incidence or severity of upper respiratory tract infection. There was no difference in either the incidence of upper respiratory tract infection ($P = .57$) or the duration or severity of upper respiratory tract infection symptoms ($P = .86$) between the vitamin D group and the placebo group. In addition, in that study, the mean 25(OH)D level ($\pm$SD) at baseline was similar between the vitamin D group and the placebo group (64.3 $\pm$ 25.4 and 63.0 $\pm$ 25.8 nmol/L, respectively). It is noteworthy that, at 12 weeks, 25(OH)D levels had significantly increased to 88.5 $\pm$ 23.2 nmol/L in the vitamin D group, but there was no decrease in vitamin D levels in the placebo group [24].

Finally, both our earlier findings that a low vitamin D status at initial entry into military service and subsequent respiratory infections are significantly related [18] and the results of the present study provide some evidence for the vitamin D supplementation for the prevention of respiratory infections. In accordance with the recommendation for vitamin D use by the Finnish Ministry of Social Affairs and Health, 400 IU of vitamin D daily was used in the study. Randomized controlled trials with higher doses and larger populations are warranted to explore the preventive effect of vitamin D supplementation on acute respiratory tract infection.

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