

# An effect of single high dose of vitamin D<sub>3</sub> on the risk of nosocomial infections, hospitalization time and mortality in hospitalized elderly population. A preliminary report

*Ocena wpływu jednorazowego podania wysokiej dawki witaminy D<sub>3</sub> w populacji osób starszych na przebieg hospitalizacji ze szczególnym uwzględnieniem ryzyka zakażeń wewnątrzszpitalnych, czasu hospitalizacji i śmiertelności. Doniesienie wstępne*

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## KEYWORDS:

- vitamin D
- serum 25(OH)D
- hospital-acquired infection
- elderly population

## ABSTRACT

**Introduction:** Observational studies indicate a significant impact of serum 25(OH)D concentration on incidence of hospital-acquired infections. However, we did not find any interventional study assessing the effect of vitamin D<sub>3</sub> administration at the admission on the course of further hospitalization in internal medicine departments.

**Objective of the paper:** Investigation of the impact of one-time high-dose vitamin D<sub>3</sub> administration in elderly patients on the day of urgent admission to the hospital, on hospital-acquired infections.

**Materials and methods:** A randomized, two-arms, open pilot study in 97 adults aged 60-100. A study group was given a single dose of 60,000 IU vitamin D<sub>3</sub> and a control group was not subject to any intervention. Serum 25(OH)D and calcium were measured at the baseline and after 7 days.

**Results:** 77.32% of studied patients were vitamin deficient, and among those, in 28.87% severe vitamin D deficiency was found. After single administration of 60,000 IU of vitamin D<sub>3</sub>, only 4 patients achieved recommended serum 25(OH)D concentration. The highest increase in serum 25(OH)D was observed in patients with severe deficiency. Numbers of observed nosocomial infections such as flu, hospital-acquired pneumonia or *Klebsiella pneumoniae* MBL+ infection did not differ significantly between study and control group, however there was a trend close to significance for lower incidence of *Clostridium difficile* infection in the vitamin D<sub>3</sub> group.

**Conclusions:** Preliminary results of the presented research indicate possible protective effect of single high dose of vitamin D<sub>3</sub> against *Clostridium difficile* infection during hospitalization. Further research on larger group of patients, using higher dose of vitamin D<sub>3</sub> is necessary.

## SŁOWA KLUCZOWE:

- witamina D
- stężenie 25(OH)D w surowicy
- zakażenia wewnątrzszpitalne
- populacja osób starszych

## STRESZCZENIE

**Wstęp:** Doniesienia naukowe ostatnich lat wskazują na istotny wpływ stężenia 25(OH)D na występowanie zakażeń wewnątrzszpitalnych. Do tej pory nie przeprowadzono interwencyjnego badania z podaniem witaminy D<sub>3</sub> przy przyjęciu do szpitala i oceny wpływu takiego postępowania na przebieg hospitalizacji w oddziałach internistycznych.

**Cel pracy:** Celem pracy jest zbadanie wpływu jednorazowego podania wysokiej dawki witaminy D<sub>3</sub> w momencie przyjęcia do szpitala z pilnych wskazań internistycznych na przebieg hospitalizacji, ze szczególnym uwzględnieniem zakażeń wewnątrzszpitalnych.

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**Metodyka:** Randomizowane, otwarte, prowadzone równolegle w dwóch grupach badanie pilotażowe u 97 dorosłych w wieku 60-100 lat. Grupie badanej podano jednorazowo dawkę 60,000 IU witaminy D<sub>3</sub>, natomiast w grupie kontrolnej nie przeprowadzono dodatkowych interwencji. Oceniano stężenie 25(OH)D oraz wapnia wyjściowo oraz po 7 dniach.

**Wyniki:** U 77.32% badanych stwierdzono niedobór 25(OH)D, w tym ciężki niedobór u 28.87%. Tylko 4 pacjentów z niedoborem 25(OH)D z grupy badanej po podanie 60,000 IU witaminy D<sub>3</sub> osiągnęło stężenie optymalne. Największy wzrost stężenia 25(OH)D osiągnęli pacjenci z ciężkim niedoborem. Nie wykazano różnic między grupami w zakresie występowania szpitalnych infekcji takich jak grypa, szpitalne zapalenie płuc, *Klebsiella pneumoniae* MBL+, stwierdzono natomiast tendencje na granicy istotności statystycznej do mniejszego występowania zakażenia *Clostridium difficile* w grupie otrzymującej witaminę D<sub>3</sub>.

**Wnioski:** Wstępne wyniki prezentowanego badania wskazują na możliwy protekcyjny wpływ jednorazowego podania wysokiej dawki witaminy D<sub>3</sub> na występowanie zakażenia *Clostridium difficile* w trakcie hospitalizacji. Konieczne jest przeprowadzenie dalszych badań na liczniejszej grupie chorych z użyciem większej dawki witaminy D<sub>3</sub>.

## Introduction

Understanding the pathways of action and metabolism of vitamin D led to the discovery of 1,25(OH)<sub>2</sub>D (calcitriol) as a steroid hormone. Calcitriol and vitamin D receptor (VDR) form a universal transcriptional complex controlling about 3% of human genome (1). Among the non-classical effects of vitamin D the immunomodulation seems to be especially important.

The expression of vitamin D receptors (VDR) was discovered in all immune system cells: monocytes, macrophages, lymphocytes T and B, antigen-presenting cells (2). Vitamin D affects innate immunity by stimulation of macrophages to produce antimicrobial peptides – cathelicidins and defensins, acting bactericidal, antifungal and antiviral (3). The first reports on the beneficial effects of vitamin D on the immune system concerned tuberculosis treatment. It is currently known that this effect also applies to other bacterial and viral infections.

The increasing incidence of hospital-acquired infections (5-10% of hospitalized patients), especially *Clostridium difficile*, *Klebsiella pneumoniae* MBL/NDM and multi-resistant strains of other bacterias is a major problem in all hospitals, also common in countries with the highest standards of medical care (4). Nosocomial infections results in prolonged hospitalization time, necessity of isolation infected patients, usage of multiple antibiotics and increased mortality, as well as significant increase in direct medical costs. In the light of the above, the growing interest in the impact of the supply of vitamin D<sub>3</sub> on the incidence of hospital infections is becoming understandable.

A retrospective cohort study of Quarishi et al. showed a 3-fold higher risk of *Clostridium difficile* infection in patients with serum 25(OH)D <10 ng/ml compared to patients with level >30 ng/ml (5). A similar relationship was demonstrated in a study of patients with inflammatory bowel disease: a group with *Clostridium difficile* infection had significantly lower levels of serum 25(OH)D (6). Moreover, the results of trials indicate that the serum 25(OH)D may be an important factor in predicting the severity of infection and may influence the risk of its recurrence (7, 8). Some of the reports indicate a significant effect of 25(OH)D concentration on hospital-acquired blood infections. A retrospective analysis of 2,135 patients with positive blood cultures showed 2.3-fold increase in risk of this type of infection in patients with serum 25(OH)D <10 ng/ml (9). According to recent studies, the proper supply of vitamin D<sub>3</sub> plays a key role in preventing influenza virus infection. In a multicentre randomized study of children infected with influenza virus,

patients who received a high dose of vitamin D<sub>3</sub> had statistically significantly shorter duration of fever and cough (10). However, there are no reports regarding the effect of the vitamin D<sub>3</sub> supply on the risk of *Klebsiella pneumoniae* MBL/NDM infection.

Hospital interventional studies using a high dose of vitamin D<sub>3</sub> have been carried out only in critically ill patients in intensive care units (11, 12). A study of Quraishi et al. showed that a single administration of 400,000 IU vitamin D<sub>3</sub> is an effective intervention to quickly improve serum 25(OH)D. The increase in serum 25(OH)D positively correlated with the serum cathelicidin – a peptide with bactericidal and antiviral properties. Amrein et al. showed that administration of a single dose of 540,000 IU vitamin D<sub>3</sub> did not affect the length of hospitalization and 6-month mortality, while significantly lower hospital mortality was observed in people with severe 25(OH)D deficiency (<12 ng/ml), compared with placebo group. No hypercalcemia events were observed in either study. Nevertheless, the safety of giving a single high dose of vitamin D<sub>3</sub> is being questioned. In the study of Sanders et al. annual administration of a single dose of 500,000 IU in the elderly women significantly increased risk of falls and fractures (13). This relationship has not been demonstrated in studies with a lower dose of vitamin D<sub>3</sub>, such as a New Zealand trial with 5108 adults aged 50-84 (100,000 IU/month), for a median of 3.3 years and British study of 2686 seniors (100,000 IU/4 months for 5 years) (14, 15, 16). Only in study of HA. Bischoff-Ferrari et al. with 200 participants, a vitamin D<sub>3</sub> bolus of 60,000 IU /month for 1 year increased risk of falls compared with the group receiving 24,000 IU (17).

The study of S. De Niet et al. comparing daily supplementation of 2000 IU with a dose of 50,000 IU per month, showed that a high one-time dose results in more effective and faster normalization of 25(OH)D with a significant increase observed from the second day after drug administration (18).

## Material and methods

The randomized, two-arms, open pilot study which was conducted in internal departments of Bielański Hospital in Warsaw.

Study population was made out of 97 caucasian, male and female patients, aged from 60 to 100 years old, admitted to internal departments on an emergency basis in Bielański Hospital from January to June 2019. The exclusion criteria were: hypercalcemia, nephrolithiasis, serum

creatinine level >1.5 mg/dL (women) or 2.0 mg/dL (men), due to differences in muscle mass and documented vitamin D metabolism disorders such as sarcoidosis, parathyroid disease or genetic defects. Subjects were not allowed to take any other medications or supplements containing vitamin D<sub>3</sub>. Patients were randomized in two groups: study group – 45 subjects, receiving 60,000 IU of vitamin D<sub>3</sub> (two tablets for oral use containing 30,000 IU of vitamin D<sub>3</sub>), and control group – 52 subjects. All participants provided written informed consent. The study was approved by Ethics Committee in Centre of Postgraduate Medical Education (Warsaw, Poland).

### Laboratory tests

Blood samples for determination of 25(OH)D, calcium and creatinine was collected at admission and after 7 days. Serum 25(OH)D was determined by the CLIA chemiluminescence method, using the LIAISON DiaSorin analyser as "Total 25(OH)D", a combined determination of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>.

Serum total and ionized calcium and serum creatinine were measured by routine automated method (Roche autoanalyser). All the analyses were performed at the laboratories of Bielański Hospital in Warsaw.

### Statistical analysis

Statistical analysis was performed with the use of following software: Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States) and STATISTICA 13.3. (TIBCO Software Inc., Palo Alto, California, United States). Descriptive data was presented as numbers, percentages, and means with standard deviations and medians. P-value (p) <0.05 was considered statistically significant.

None of the analyzed numerical parameters showed a normal distribution, which was checked with the use of Shapiro-Wilk test (for all p <0.05). On this basis, only non-parametrical test were applied. Mann-Whitney U test was used to compare two independent samples. The strength of association between two events was determined using the Chi-squared test. Wilcoxon signed-rank was used for the detection of differences between dependent variables. Additionally, correlations between 25(OH)D level and its increase after a single high dose in the study group were expressed using the Spearman's coefficient.

### Results

Patients from the study (n = 45) and control group (n = 52) did not differ significantly at the baseline (Table 1).

**Table 1. Baseline characteristics of study participants.**

Variable	Vitamin D <sub>3</sub> (n = 45)	Control group (n = 52)	p-value
<b>Age</b>			
Mean (±standard deviation [SD])	75.44 (±8.94)	74.83 (±9.88)	0.745
Range	61-100	60-99	
<b>Sex</b>			
Female	44.44% (n = 20)	46.15% (n = 24)	0.866
Male	55.55% (n = 25)	53.85% (n = 28)	
<b>Ionized calcium [mmol/l]</b>			
Mean (±SD)	1.14 (±0.05)	1.14 (±0.08)	0.933
Range	1.04-1.21	0.93-1.30	
<b>25 hydroxyvitamin D on admission [ng/ml]</b>			
≥30	22.22% (n = 10)	23.08% (n = 12)	0.811
≥20 and <30	11.11% (n = 5)	17.31% (n = 9)	
≥10 and <20	42.22% (n = 19)	26.92% (n = 14)	
<10	24.44% (n = 11)	32.69% (n = 17)	
<b>Creatinine [mg/dl]</b>			
Mean (±SD)	0.89 (±0.31)	0.87 (±0.39)	0.421
Range	0.37-2.00	0.17-1.99	
<b>Antibiotic therapy prior to admission</b>	68.89% (n = 31)	63.46% (n = 33)	0.321
<b>Admitting diagnosis</b>			
Heart failure	22.22% (n = 10)	25% (n = 13)	–
Arrhythmias	6.66% (n = 3)	11.54% (n = 6)	
Pneumonia	33.33% (n = 15)	30.77% (n = 16)	
Exacerbation COPD	15.55% (n = 7)	11.54% (n = 6)	
Urinary tract infection	8.88% (n = 4)	11.54% (n = 6)	
Anaemia	6.66% (n = 3)	13.46% (n = 7)	
Diabetes	15.55% (n = 7)	15.38% (n = 8)	
Hyponatremia	4.44% (n = 2)	7.69% (n = 4)	
Malignant disease	11.11% (n = 5)	11.54% (n = 6)	
Other infections	4.44% (n = 2)	7.69% (n = 4)	

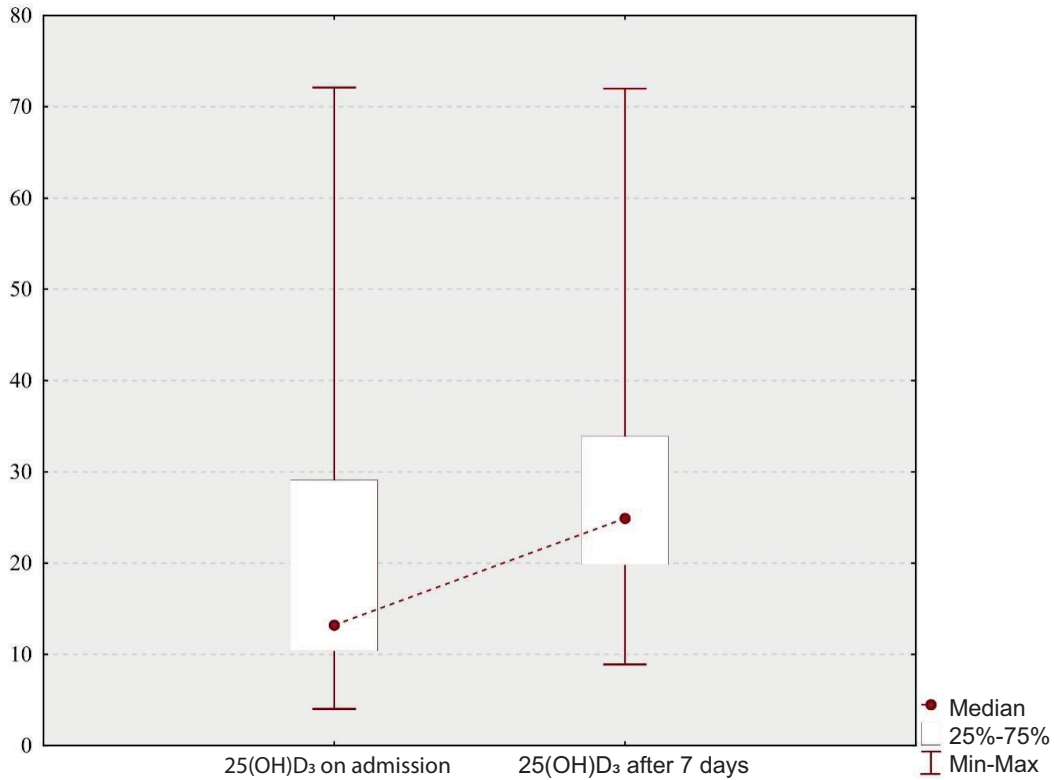


Figure 1. Increase in serum 25(OH)D after single high dose in the study group.

Initial serum 25(OH)D concentrations were similar in both groups [in study group: mean 19.85 ( $\pm$ 15.21), in control group: 18.70 ( $\pm$ 12.64);  $p = 0.811$ ]. Vitamin D<sub>3</sub> deficiency [serum 25(OH)D <30 ng/mL] was found in 77.32% ( $n = 75$ ) of subjects in the whole study group: 35 out of 45 patients from study group (77.78%) and 40 out of 52 patients from control group (76.92%); ( $p = 0.920$ ).

A statistically significant increase in serum 25(OH)D was observed after 7 days from baseline in the study group ( $p < 0.01$ ) (Figure 1.).

The observed increase in serum 25(OH)D in study group was inversely correlated with baseline 25(OH)D levels ( $r = -0.32$ ;  $p < 0.05$ ) (Table 2).

In study group, only 4 out of 35 (11.43%) patients with baseline deficiency reached recommended serum 25(OH)D (>30 ng/mL) on seventh day after oral administration of 60,000 IU of vitamin D<sub>3</sub>.

In the whole group, 11 out of 97 (11.34%) patients underwent hospital infections, however there were no significant differences between the study and control groups ( $p = 0.479$ ). However, Clostridium difficile infections were less common in the vitamin D<sub>3</sub> group than in control group [0.22% ( $n = 1$  out of 45) vs 11.54% ( $n = 6$  out of 52)],

difference on the verge of statistical significance ( $p = 0.08$ ). The number of other nosocomial infections (influenza, hospital-acquired pneumonia, MBL-positive Klebsiella pneumoniae infection) did not significantly differ between groups.

Time of hospitalization was similar in both groups (in treatment group median 8 days; in control group median 9 days;  $p = 0.291$ ). There were 7 in-hospital deaths, 2 in the vitamin D<sub>3</sub> group and 5 in the control group.

## Discussion

Increasing problem of nosocomial infections, associated with the enormous medical costs is one of the most pressing challenges of modern medicine. Consequently it is exceedingly important to study all factors which can have impact on reducing the risk of prevalence of these type of infections. The latest research articles indicate that one of those factors may be maintaining proper levels of 25(OH)D. That is why we deemed it promising to conduct intervention study by administrating one high dose of vitamin D<sub>3</sub> after admission to Internal Medicine ward with evaluation of course of hospitalization in terms of nosocomial infections. The pilot

Table 2. Mean increase in 25(OH)D<sub>3</sub> level in patients from study group after administration of 60,000 IU in different subgroups separated basing on the initial result.

Baseline 25(OH)D [ng/ml]	Percent and number of patients	Mean increase ( $\pm$ SD)
<10	24.44% ( $n = 11$ )	10.57 ( $\pm$ 4.86)
$\geq 10$ and <20	42.22% ( $n = 19$ )	9.57 ( $\pm$ 4.51)
$\geq 20$ and <30	11.11% ( $n = 5$ )	7.08 ( $\pm$ 4.95)
$\geq 30$	22.22% ( $n = 10$ )	6.23 ( $\pm$ 6.50)



study included 97 patients. In 79% of those patients serum 25(OH)D was below 30 ng/ml, and among those in 28% was below 10 ng/ml. This result confirms past data on the prevalence of vitamin D<sub>3</sub> deficiency in Poland (19). Single oral dose of 60,000 IU of vitamin D<sub>3</sub> resulted after seven days in significant increase in serum 25(OH)D. An increase in serum 25(OH)D concentration was significantly higher in the group of subjects with the lowest concentrations at the baseline compared with group with normal basal serum 25(OH)D. Consequently it proves that liver 25-hydroxylase works more efficient in lower level of substrate. Only 4 participants of the researched group achieved optimal serum 25(OH)D concentration (>30 ng/mL) after single administration of 60,000 IU of vitamin D<sub>3</sub>. According to recent studies such concentration is needed to achieve full pleiotropic effect of vitamin D<sub>3</sub>. In terms of nosocomial infections, the prevalence of *Clostridium difficile* was less common in experimental group, however this difference did not reach statistical significance. There was also no differences in other nosocomial infections between the two comparing groups. Furthermore, there was no difference in the length of hospitalization or in mortality depending on the vitamin D<sub>3</sub> supply. Primary, the weakness of this study is small group of patients, which makes it impossible to fully analyze the complex etiology of nosocomial infections in a multifactorial way; the other one is the lack of a placebo group. However, initial results are promising and encourage further research on bigger group of patients. Because of very high deficiencies of vitamin D<sub>3</sub> in population of elderly (over 30% <10 ng/ml) and only slight improvement of serum 25(OH)D after a single dose of 60,000 IU of vitamin D<sub>3</sub>, we plan to continue the study with a higher disposable dose of vitamin D<sub>3</sub> and to include an earlier vitamin D supplementation as a criterion for exclusion from the study for improved safety of the patient.

## Conclusion

The results of this pilot study indicate the possibility of a protective effect of a single high dose of vitamin D<sub>3</sub> on the risk of *Clostridium difficile* infection during hospitalization.

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