Vitamin D in critically ill patients

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Abstract
Vitamin D deficiency is a commonly observed global phenomenon, both in the general population and in hospitalized patients, including critically ill patients. Vitamin D deficiency is associated with multiple adverse health outcomes, including increased morbidity and mortality in the general population and in critically ill patients. Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism. However, Vitamin D is also a steroid hormone that exerts multiple pleiotropic effects. Vitamin D regulates immunity, inflammation, cell proliferation, differentiation, apoptosis, and angiogenesis. There is growing evidence of a close relationship between vitamin D insufficiency and various systemic disorders, i.e., type II diabetes, certain types of cancer, obesity, and cardiovascular morbidities. The purpose of this article is to present the current knowledge on the relationship between vitamin D status and critical illness.

Key words: vitamin D, critical illness, intensive care, critically ill

There is mounting evidence of the role of vitamin D in blood serum as a factor determining the course and prognosis of numerous diseases. Knowledge of the molecular basis of vitamin D action, its extraosseous effects and its significant role in the prevention and treatment of chronic diseases, especially inflammatory diseases, is growing. This paper presents the current state of knowledge regarding vitamin D, particularly its role in critically ill patients treated in intensive care units (ICUs).

PRODUCTION AND METABOLISM OF VITAMIN D
Vitamin D belongs to the group of steroid chemical compounds with the general formula C_{28}H_{43}OH. The group contains vitamin D1 (a mixture of cholecalciferol and lumisterol occurring in cod liver oil, a compound with a similar structure as vitamin D but without the same activity), vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 occurs in plants, whereas vitamin D3 is produced in human and animal skin, mainly in the keratocytes of the proliferative epithelium, mediated by ultraviolet radiation (specifically UVB radiation). The compounds are activated in the liver by hydroxylation to 25-hydroxyderivatives and subsequently in other organs to 1,25-dihydroxyderivatives. The latter conversion occurs primarily in the kidneys and is mediated by parathormone (PTH). Calcitriol (1,25-dihydroxycholecalciferol) is an active form of vitamin D3, a substance of hormonal action regulating many organs and tissues. Although the metabolic effects of vitamin D2 and vitamin D3 are similar, they bind with different types of plasma proteins. As a result, the action of vitamin D3 is longer and 2-10-fold more effective than vitamin D2.

Vitamin D3 is one of a few vitamins that the body is able to produce endogenously; therefore, it does not fulfil the definition of a vitamin. Ultraviolet radiation is required for the production of Vitamin D3 in the body, more specifically UVB (wavelength of 280–315 nm), which enables the conversion of skin 7-dehydrocholesterol (provitamin D3) into cholecalciferol (vitamin D3). The metabolism of vitamin D3 is presented in Figure 1.

Vitamin D3 can also be derived from foods, such as milk, butter, fish and some mushrooms.

For simplification, the term “vitamin D”, referring to the group of compounds, will be used instead of “vitamin D3” in the remainder of the paper.

The production of sufficient amounts of vitamin D by the body is affected by geographic and environmental factors. These factors include the latitude, season, atmospheric conditions, sun height, translucency of the atmosphere,
cloudiness, time spent in closed spaces, and type of clothing, which may limit the amount of sunlight reaching the skin surface. Moreover, the percentage of radiation dispersed in total solar radiation is essential. Additionally, any changes in the quantity of UVB photons reaching the skin can significantly affect the dermal production of vitamin D. In winter, sunrays fall at a right angle in the early mornings and afternoons, which is unfavourable for the synthesis of vitamin D. The UVB photons are absorbed by the atmospheric ozone, and the dermal production of vitamin D is limited. According to Webb and colleagues [1], the intensity of vitamin D production in the skin during winter and at latitudes above 35°N and below 35°S is almost undetectable.

One essential factor affecting the dermal synthesis of vitamin D is age; the content of 7-dehydrocholesterol in the skin has been found to be negatively correlated with age [2]. The amount of melanin in the skin could decrease by 5 to 10 times. Limited skin surface exposure to UVB radiation and creams with sun protection factors (SPFs) reduce the skin synthesis of vitamin D. A cream with SPF 8 reduces the ability to synthesize vitamin D by 95% [3].

In Poland, the values of direct sun radiation recorded most commonly are within the range of 600–800 W m−2. In the hottest summer period, the value of sun exposure reaches 1200 W m−2; 80% of total annual solar radiation occurs during the six months of the spring-summer season (from the beginning of April to the end of September).

Deficiencies of vitamin D are common in the Polish climatic zone and in Europe. Despite the guidelines regarding vitamin D supplementation proposed by many scientific societies from various countries, the deficiency of vitamin D remains common in all age ranges and in different populations [4-6]. In 2013, a team of experts formulated and published “Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency” [7]. These guidelines contain recommendations for all age groups and for some specific populations, e.g., pregnant and lactating women, and recommendations regarding maximum safe doses for healthy individuals (Tables 1, 2) and the doses used for treatment (Table 3) and supplementation (Table 4).

**PLEIOTROPIC ACTION OF VITAMIN D**

In recent years, attention has been focused on the non-skeletal effects of vitamin D, i.e., its pleiotropic actions inducing various effects that are sometimes very distant and difficult to connect. A biologically active vitamin D, i.e., calcitriol, belongs to the superfamily of hormones and directly modulates the activity of many genes. Calcitriol binds the
vitamin D receptor (VDR) and subsequently DNA, regulating the activity of approximately 5% of the human genome (500 genes), which indicates its pleiotropic effects. Unlike in cases of other hormones from this superfamily, such as glucocorticosteroids, mineral corticosteroids, progesterone, androgens or oestrogens, the synthesis of calcitriol is directly limited by the availability of a substrate, i.e., 25(OH)D (calcidiol). Calcidiol is a metabolite produced in the liver from native vitamin D. The essence of adequate substitution of vitamin D is the provision of optimal amounts of 25(OH)D for the synthesis of the hormonally active form, 1,25(OH)2D, in all target tissues [8].

Under certain circumstances, the nuclear receptors of vitamin D can be translocated to the mitochondrial matrix of some cells, thus directly affecting the activity of the oxygen chain and energy metabolism of cells. This process occurs in platelets, megakaryocytes, macrophages and other cells. In many diseases (type 2 diabetes, metabolic syndrome, neoplastic and cardiovascular diseases), which are characterized by the persistence of chronic inflammation, the dysfunction of mitochondria and impaired energy function of cells are fundamental. Vitamin D deficiency is associated with impaired intracellular homeostasis of calcium and regulation of oxidative phosphorylation. Vitamin D, by binding VDR translocated to a mitochondrion, can modulate the inflow of calcium ions to the mitochondria or directly affect the activation of vitamin D-dependent genes [9]. The mechanism of the anti-inflammatory effects of vitamin D most likely involves weakening the activation of p38, blocking NF-κB activation and reducing concentrations of matrix metalloproteinases.

The receptors for calcitriol were found in the organs involved in maintaining mineral homeostasis, such as the intestine, bone, kidney or parathyroids, and in other tissues and organs, e.g., immune cells, pancreatic β cells, or muscular tissues. Within the immune system, vitamin D exerts multi-directional effects, stimulating the function of macrophages, T lymphocytes, activated B lymphocytes, maturation of dendritic cells, modulation of TNF expression and production of neutral antibacterial peptides, i.e., cathelicidins and β-defensins. Cathelicidins are constitutively produced by many cells involved in maintaining innate immunity, such as neutrophils, NK cells, mast cells and numerous epithelial cells [10], particularly the epithelial cells of the airway, gingiva, urinary bladder and gastrointestinal system, i.e., the cells in direct continuous contact with external pathogens. Moreover, the synthesis of cathelicidins was observed in dendritic cells, monocytes/macrophages and

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**Table 2. Maximum daily doses of vitamin D recommended by the European Food Safety Authority. According to [7]**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Daily Dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns and infants</td>
<td>1000 IU d⁻¹</td>
</tr>
<tr>
<td>Children aged 1–10 years</td>
<td>2000 IU d⁻¹</td>
</tr>
<tr>
<td>Children and teenagers aged 11–18 years</td>
<td>4000 IU d⁻¹</td>
</tr>
<tr>
<td>Adults and elderly people with normal body weight</td>
<td>4000 IU d⁻¹</td>
</tr>
<tr>
<td>Obese adults and obese elderly people</td>
<td>10,000 IU d⁻¹</td>
</tr>
<tr>
<td>Pregnant and lactating women</td>
<td>4000 IU d⁻¹</td>
</tr>
</tbody>
</table>

**Table 3. Recommended therapeutic doses of vitamin D. According to [7]**

**Vitamin D deficiency: 25(OH)D < 20 ng mL⁻¹ or <50 nmol L⁻¹**

Recommended therapeutic doses (1–3 months):
- Newborns: 1000 IU d⁻¹
- Infants aged 1–12 months: 1000–3000 IU d⁻¹
- Children and teenagers aged 1–19 years: 3000–5000 IU d⁻¹
- Adults: 7000–10,000 IU d⁻¹ according to body weight or 50,000 IU week⁻¹

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**Table 4. Doses of vitamin D recommended for healthy adult populations. According to [7]**

Adults > 18 years of age and the elderly
- 800–2000 IU d⁻¹ according to body weight from September to April
- 800–2000 IU d⁻¹ according to body weight throughout the year, when effective dermal synthesis of vitamin D is not provided during summer months

Elderly individuals (65+) 800–2000 IU d⁻¹ according to body weight throughout the year due to reduced capacity for dermal synthesis of vitamin D
lymphocytes. In keratinocytes and monocytes, the expression of the cathelicin-encoding gene is regulated by the biologically active vitamin D metabolite (calcitriol), which is a ligand of nuclear VDR. The synthesis of cathelicidins is stimulated by bacterial infections and potent proinflammatory cytokines (TNF-α, IL-1, IL-6, and interferon-γ). Cathelicidins recruit leucocytes, induce chemotaxis of immunocompetent cells to the infection sites, cause degradation of walls of immunologically foreign cells and biofilm, and bind lipopolysaccharide residues. Moreover, cathelicidins are involved in the inhibition of lipopolysaccharide-dependent activation of the endothelium and vasodilatation. Before antibiotics, vitamin D was used to treat tuberculosis, and its metabolites are found to be active against Mycobacterium in vitro [11]. There is also evidence that low pre-hospitalization levels of vitamin D are correlated with the incidence of Clostridium difficile and bloodstream infections during hospitalization [12, 13]. In the extra-hospital population, low levels of vitamin D are positively correlated with the incidence and severity of respiratory infections [14]. In some viral infectious diseases, (e.g., influenza), low concentrations of vitamin D can be a risk factor of infection or its more severe course [15].

β-defensin 4 stimulates innate immunity by direct antibacterial activity in phagosomes and phagolysosomes. The activation of Toll-like receptors 2/1 on monocytes results in vitamin D-dependent activity directed against intracellular pathogens [16].

Furthermore, the antineoplastic effects of vitamin D have been recently implicated and are associated with the biological activity of neoplasms and the ability to inhibit cell proliferation and to regulate cell differentiation. The antineoplastic action of 1,25(OH)2-cholecalciferol is most likely mediated by VDR affecting the gene expression [17]. Bound to its natural ligand, i.e., VDR, active vitamin D enhances apoptosis of neoplastic cells and, as a transcription factor, regulates the activity of more than 60 genes responsible for cell differentiation, antiproliferative effects and inhibition of angiogenesis. Numerous epidemiological studies have demonstrated that the most common forms of cancer, such as breast, colon, rectal, uterine, ovarian cancers and lymphatic leukaemia, are negatively correlated with the serum levels of vitamin D. Vitamin D is also involved in the development of metabolic syndrome, type I diabetes, arterial hypertension, rheumatoid arthritis, and multiple sclerosis. A concentration of 25(OH)D3 within the range of 80 nmol L−1 or higher has preventive effects. According to a meta-analysis published in 2011, the risk of colon cancer decreases by 15% with an increase in plasma concentration of vitamin D by 10 ng mL−1 on average [18]. The substitution of vitamin D is recommended in early breast cancer cases [19].

The kinetics of activity of the calcitriol-synthesizing 1-α hydroxylase enzyme suggest that the optimal serum concentration of 25(OH)D should be 40 ng mL−1 (100 nmol L−1). The rate of 1,25(OH)2D synthesis reaches half of its maximum value at a 25(OH)D concentration of 40 ng mL−1 (100 nmol L−1). The effects of calcitriol on the enterocytes, increasing the absorption of calcium from the gastrointestinal tract, are most effective at a concentration of 25(OH)D exceeding 30 ng mL−1. Beneficial clinical effects, e.g., enhanced immunity and reduced risk of cardiovascular, autoimmune and neoplastic diseases, are observed at a serum concentration of 25(OH)D of 30–50 ng mL−1, which provides proper conditions for adequate synthesis of 1,25(OH)2 vitamin D in all body compartments.

SIGNIFICANCE OF VITAMIN D IN ICU PATIENTS

Vitamin D deficiency is common in the general population and in ICU patients. The deficiency is associated with impaired calcium-phosphate metabolism and with bone metabolism and leads to secondary hyperparathyroidism, which results in mobilization of calcium from the skeleton to maintain its serum concentration within normal limits. ICU patients, especially those undergoing long-term treatment, are at risk of numerous causes of vitamin D deficiency, such as earlier deficiency, immobilization, lack of adequate exposure to sunlight, malnutrition, increased conversion of 25(OH) vitamin D to 1,25(OH)2 vitamin D, inflammation, and liver or kidney failure. Pleiotropic effects of vitamin D on the immune system, epithelia, glucose metabolism, and calcium homeostasis are essential in critically ill patients. ICU patients, particularly those undergoing long-term treatment, often suffer from osteoporosis, immunological dysfunction, changes in body composition (loss of muscle mass, increase in the adipose tissue) or neurohumoral disorders, which significantly hinders their rehabilitation and recovery.

Hypocalcaemia is common in ICU patients, despite strict hormonal monitoring to maintain the serum calcium concentrations within narrow physiological ranges. In addition to rarer causes of hypocalcaemia, such as massive transfusions, post-thyroidec tomy parathyroid failure, acute pancreatitis, alkalosis or some drugs, vitamin D deficiency is its likely, frequent and underestimated cause. Hypocalcaemia positively correlates with the incidence of complications in ICU patients, APACHE II score and mortality [20]. Supplementation of calcium appears to be a beneficial therapeutic option in ICUs. However, a Cochrane systematic review has not justified this practice [21]. Considering the above findings, the substitution of vitamin D could be one therapeutic option. Unfortunately, vitamin D deficiency is rarely recognized, is even less frequently treated in ICUs and is an underestimated issue.

The minimum desirable concentration of vitamin D in ICU patients is likely to be within the range of 20 to 30 ng dL−1 [22]. According to estimates, the incidence of vitamin D defi-
ciency in the population of critically ill patients ranges from 17% to 79% [23–25].

Due to the ubiquity of VDR, widespread expression of 1α-hydroxylase and its effects on apoptosis and cellular differentiation, vitamin D could significantly affect atherosclerosis, cardiovascular diseases, circulatory and respiratory failure, sepsis and other disorders typical in critically ill patients [26]. Therefore, the hypothesis that vitamin D deficiency is a potentially modifiable risk factor in critically ill patients appears logical.

In contrast to the extra-hospital population, in which the lowest concentrations of vitamin D are associated with increased overall mortality [27], the data regarding a correlation between the concentration of 25(OH)D and prognosis are inconsistent. The cause and effect analysis is undoubtedly hindered by widespread deficiency of vitamin D in many populations, including a considerably differentiated population of critically ill patients, and by the fact that patients with multiple organ failure and sepsis have lower concentrations of vitamin D-binding protein (DBP), which could cause hypovitaminosis D in this group of patients. Polymorphisms of DBP and of the enzymes responsible for the activation and degradation of vitamin D and its metabolites are also affected by serum concentrations of 25(OH)D [28].

The studies available reveal a correlation between low levels of 25(OH)D and short- and long-term mortality rates in ICU patients (on day 30, 90 and 365), increased risks of sepsis [29, 30], cardiac failure, critical illness myopathy, hyperglycaemia and impaired microcirculation [31]. The findings, reported by Amrein and colleagues [32], have revealed that the vast majority (87%) of ICU patients had low or very low concentrations of vitamin D, which was positively correlated with mortality. The study carried out by Venkatram and colleagues [33] demonstrated a correlation between the concentration of 25(OH)D in patients in a multi-specialized ICU and hospital mortality. Extremely low levels of vitamin D were found in 77% of patients. Azim and colleagues [34] did not observe a correlation between the concentration of vitamin D and mortality. According to a study published in 2015 of 10 Dutch general intensive care units involving approximately 1,400 patients, vitamin D deficiency on admission was observed in less than 38% of cases. Vitamin D deficiency on admission was associated with higher incidences of sepsis, higher APACHE II scores and longer hospitalization, yet was not clearly correlated with mortality [35]. In the study conducted by van der Berghe et al. [36], intravenous supplementation of vitamin D in patients hospitalized in ICUs for a long time did not lead to increased serum concentrations of vitamin D or resulted in its increase, which did not affect the patient’s condition. According to one study, the vitamin D supplementation had beneficial effects on critically ill patients [37].

The strongest known correlation between vitamin D metabolites and the immune system results from the effects of vitamin D on the production of cathelicidins. In animal models, the deficiency of cathelicidins has been associated with a higher susceptibility to bacterial infections, whereas overexpression has been connected with antibacterial protection [38, 39]. In humans, the only known cathelicidin with antibacterial potential is the human cathelicidin antimicrobial protein hCAP18. Both 25(OH) vitamin D and 1,25(OH)₂ vitamin D induce the production of hCAP18 in vitro in immune cells (neutrophils, monocytes, macrophages) and in many other cells, e.g., epithelial cells and keratinocytes [40, 41]. Having assumed significant immunomodulatory and antibacterial effects of vitamin D, Leaf and colleagues [42] administered calcitriol to sepsis and septic shock patients at a dose of 2 µg i.v. vs. placebo. These authors did not find statistically significant changes in the concentrations of cathelicidins and markers of inflammation (IL-10, IL-6, TNF-α, IL-1β, IL-2). Nevertheless, lower concentrations of 25(OH) vitamin D on day 1 of ICU treatment correlated with low levels of hCAP18 and a higher risk of death on day 90. The study in question involved a small group of patients; according to the authors, further multi-centre randomized studies are required [43].

Increased mortality in population of critically ill patients with vitamin D deficiency could be associated with disorders of calcium and glucose metabolism and with immunological dysfunction of the endothelium [44]. Endothelial dysfunction is likely to be the cause of multiple organ dysfunction syndrome; moreover, vitamin D deficiency, by enhancing metabolic and immunological disorders, could contribute to a worse prognosis in critically ill patients, particularly patients with sepsis. These disorders include immunosuppression, impaired chemotaxis, phagocytosis and increased production of antibacterial cathelicidins.

Tarcin and colleagues [45], comparing selected parameters in a group of patients with asymptomatic vitamin D deficiency with data from individuals with normal levels of vitamin D, demonstrated that vitamin D deficiency is associated with increased peroxidation of lipids and endothelial dysfunction. The supplementation of vitamin D beneficially affected the studied parameters of endothelial function.

In several interventional studies carried out in ICU patients, various doses of vitamin D (200 IU to 540,000 IU) with a saturating dose or otherwise, different forms (cholecalciferol, calcitriol), different administration routes (enteral, parenteral), and different treatment durations were applied. The scientific societies do not specifically refer in their recommendations to the ICU patient population [46, 47]. An initial dose ranging from 50,000 to 60,000 IU, depending on the baseline patient’s condition and body weight, should be considered [48]. However, due to possible severe complica-
tions after very high doses of vitamin D, e.g., hypercalcaemia, hypercalciuria, extraosseous calcifications and kidney calcifications, such doses cannot be routinely recommended for critically ill patients without further studies [49].

The most promising outcomes of the treatment of vitamin D deficiency in critically ill patients have been reported by Amrein et al. [50]. Their one-centre double-blind, placebo-controlled randomized clinical trial VITdAL involved almost 500 individuals. Although a negative outcome was found at the primary final point (length of hospitalization), beneficial effects have been demonstrated (higher chances of survival, NNT 6) in patients with very low levels of 25(OH)D (≤ 12 ng mL⁻¹) who received 540,000 IU of cholecalciferol, followed by 90,000 IU a month over the next 5 months. The group with such a high vitamin D deficiency included 200 individuals, i.e., 42% of the study population. The doses of vitamin D used in the study were undoubtedly pharmacological but not physiological [50].

Both the initial dose and further doses, as well as the administration routes, raise doubts. The majority of ICU patients have contraindications for intramuscular injections, and intravenous preparations containing high doses of vitamin D are not available. With the enteral forms, uncertainty of intestinal absorption, impaired peristalsis and circulatory efficiency within the intestine should be considered. Moreover, the coexistence of sepsis and multiple organ failure should be considered.

The intravenous vitamin preparations commonly used for substitution contain small doses of vitamin D, which correspond to the daily doses for healthy people recommended earlier. The doses of some vitamins (C, D, B1) are insufficient to meet the requirements of critically ill patients. Cernevit®Baxter, a multivitamin preparation, contains 220 IU of vitamin D3, whereas Vitalipid N Adult® FreseniusKabi contains 200 IU of vitamin D2, which is inconsistent with the recommendations for the healthy population. In enteral diets, the content of vitamin D is standard and may not cover the requirements at low serum doses of vitamin D, particularly in ICU patients with impaired absorption and tolerance of enteral nutrition.

The recommendations for vitamin D substitution in healthy individuals with vitamin D deficiency should probably assume its supply at a dose between 1000 and 10,000 IU a day. Such doses should enable the target concentration to be reached within 2-3 months. Some groups require special attention, i.e., monitoring of serum vitamin D levels and tailoring a substitute dose based on the findings. These groups include patients with renal dysfunction, malabsorption syndrome, those receiving anticonvulsants and obese individuals.

A different strategy is required to optimize the serum concentrations of vitamin D in critically ill patients. The standard methods of substitution do not provide effective treatment of hypovitaminosis/avitaminosis D in this group of patients. A high saturating dose ranging from 50,000 IU to 600,000 IU should be considered, depending on the baseline concentration of vitamin D and the body weight. Further large-scale studies are necessary to confirm the efficacy of such therapies and the absence of adverse effects.

Oral and enteral supply could be effective in ICU patients due to malabsorption caused by gastrointestinal oedema and inflammation. The unpredictable process of absorption, changes in hydroxylation (impaired renal function), transport of vitamin D and degradation of its metabolites (impaired hepatic function) hinder treatment via the gastrointestinal tract. Moreover, increased vitamin D requirements at the tissue level are of importance, which leads to enhanced conversion of 25(OH)D into 1,25(OH)₂D. An intravenous form of vitamin D3 would be ideal; unfortunately, this form is not available.

There are no explicit data from multi-centre randomized studies demonstrating a correlation between vitamin D deficiency, prognosis and mortality in ICU patients. The available guidelines lack specific recommendations for the critically ill patient population. The same is true about the updated Canadian Clinical Practice Guidelines [published as the “Summary of Recommendations” on www.criticalcarenutrition.com on May 25th, 2015]. Nevertheless, there are numerous potential beneficial effects of vitamin D, which is likely to be used in future in the therapy of critically ill patients. Notably, the standard diets and multi-vitamin preparations available on the market contain insufficient amounts of vitamin D to meet the increased demand and to correct vitamin D hypovitaminosis.

Because of financial limitations and an underestimation of the problem, concentrations of vitamins, including vitamin D, are not determined or are rarely determined, predominantly in cases of suspected anaemia or osteoporosis. Considering the available data indicating the extraosseous, pleiotropic effects of vitamin D, special attention should be paid to its deficiency in ICU patients.

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References:


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