ÜBERSICHTSARBEIT

Vitamin D deficiency: An often underestimated risk

Emanuel Vits[a], Markus Staudt[a], Maike Berresheim[a], Ulrich Rohde[a], Thomas Eger[b], Christoph Bickel[c], Dieter Leyk[a,d]

Summary

Vitamin D does not only play an essential role in calcium and bone metabolism, but also has numerous preventive and curative effects in other organ systems. However, literature reviews show large differences regarding minimum vitamin D levels and vitamin D supplementation. In this study, a systematic literature search was conducted to determine the background for these divergent statements and to examine whether vitamin D supplementation is recommended for soldiers.

Various professional societies currently assume a vitamin D deficiency if serum vitamin D levels (calcidiol, 25-hydroxyvitamin D_3; $25(OH)D_3$) are below 20 ng/ml (= 50 nmol/l). Epidemiological studies, however, hint at higher levels for normal serum concentrations: Vitamin D serum levels of 30 ng/ml (= 75 nmol/l) are associated with lower cardiometabolic and inflammatory biomarker levels. Newer studies provide supportive evidence that the different effects of vitamin D in the organism are concentration- and tissue related. Vitamin D levels in indigenous ethnic groups living close to the equator are markedly above 40 ng/ml (> 100 nmol/ml).

Roughly 60 % of the German population has an undersupply of vitamin D. More than 80 % of men and 90 % of women do not reach the recommended daily vitamin D intake. Due to the low UV indices during the winter half year In Germany, vitamin D production in the skin (the actual main source) is insufficient. There is an increased risk of vitamin D deficiency in numerous population groups, which is further increased by staying behind window glass, in closed rooms, etc.

There are further restrictions of endogenous vitamin D production in military due to wearing of long-sleeved uniforms, protective equipment, and headgear. In a group of German Air Force personnel (> 2,000 persons) vitamin D deficiency was found in over 70 %. In view of the new findings and the special circumstances in the military sector, targeted supplementation of vitamin D in female and male soldiers is clearly recommended.

Key Words: supplementation, military; prevention; deficency; risk factors

Introduction

The interest in vitamin D has increased considerably in the last 20 years. Only in 2020, more than 5,100 scientific publications were released to PubMed (PubMed query as of March 8, 2021). There is also more media coverage of vitamin D. Reasons for the increased attention are new findings on vitamin D effects that go far beyond the known endocrine control of calcium homeostasis and bone metabolism [4, 15, 22, 31]. It is now well established that vitamin D has additional autocrine and paracrine effects in most tissues. The activated and membrane-permeable steroid hormone calcitriol (1,25-dihydroxycholecalciferol; $1,25(OH)_2D_3$) has multiple influences on, among others, gene expression [22, 58], and epigenetics [14, 15, 71].

Lowered vitamin D levels have been reported in connection with numerous diseases (see **Table 1**). According to meta-analyses, vitamin D deficiency alone is a risk factor for various diseases in several organ systems. The Umbrella Review published in 2020 [44], for example, shows

[a] Bundeswehr Institute for Preventive Medicine, Division A Health and Fitness Promotion, Andernach/Koblenz

[b] Bundeswehr Central Hospital Koblenz, Department XXIII Dentistry, Koblenz

[c] Bundeswehr Central Hospital Koblenz, Department I Internal medicine, Koblenz

[d] German Sport University Colgone, Research Group Epidmemiology of Performance, Colgone

positive effects of a vitamin D supplementation in the primary prevention of acute respiratory tract infections, as well as in dementia, cognitive decline, and depression. Among others, curative effects exist in patients with asthma and COPD [7, 44]. The outcomes of dental periodontitis and peri-implantitis therapy show more favorable treatment results [42], and there is also evidence of a positive vitamin D influence in SARS-CoV-2 infections [20, 36]. In **Table 2** diseases showing positive effects from Vitamin D treatment are listed.

Recently published RCTs showed a 13 % reduction decrease in cancer mortality through vitamin D administration [38], which would lead to savings of more than 250 million euros in Germany alone [49].

While the multitude of vitamin D effects are scientifically undisputed by now, there is only a partial consensus regarding vitamin D supply [71]. Thus, recommendations differ considerably with regard to vitamin D levels, actual vitamin D requirements, and the need of supplementation [53]. In literature, vitamin D serum levels are listed in ng/ml or nmol/l (1 ng/ml = 2.5 nmol/l), while the required amounts of vitamin D are given in IU and µg (40 IU = 1 µg). The recommended minimum level of calcidiol (25-hydroxyvitamin D_3; 25(OH)D_3)) varies from 10 ng/ml (= 25 nmol/l; [63]) to 30 ng/ml (= 75 nmol/l; [32]) depending on the professional society. The D-A-CH Nutrition Society (Germany: Deutsche Gesellschaft für Ernährung (DGE), Austria (ÖGE), Switzerland (SGE, SVE)) recommend minimum levels of ≥ 20 ng/ml (≥ 50 nmol/l) [48]. Much higher minimum levels (40 ng/ml–60 ng/ml (= 100 nmol/l–150 nmol/l)) are mentioned by the “VitaminD Society” [67], among others.

In this review, we present the background for the deviating reference ranges and recommendations for the normal vitamin D requirement. In addition, usefulness of vitamin D supplementation for soldiers is assessed.

Table 1: Diseases and medication frequently associated with low vitamin D levels (according to: [4, 9, 21, 54, 59, 61, 70, 71]).

Diseases
Obesity
Fat malabsorption
Diseases with granulomas (e.g.: Sarcoidosis, Tuberculosis, Histoplasmosis, …)
Hospitalised patients (ICU)
Hyperthyroidism
Hypo- /Hyperparathyroidism
Dental caries
Hepatic insufficiency
Lymphoma
Malabsorption syndromes (e.g.: cystic fibrosis, CEDs, post-bariatric surgery, radiation enteritis)
Kidney diseases
Osteomalacia
Osteoporosis
Pancreatic insufficiency
Periodontal disease
Rickets
Medication
Antibiotics (e.g.: rifampicin)
Antihistamines (e.g.: cimetidine)
Anticonvulsants (e.g.: phenobarbital, phenytoin, carbamazepine)
Antimycotics (e.g.: ketoconazole)
Antituberculotics (e.g.: rifabutin)
Bisphosphonates
Corticosteroids
Ethanol
Heparin
HIV medication (e.g.: antiretroviral medication)
Lipid-lowering agents (e.g.: cholesteramine)
Thiazides

Methodology

A systematic literature search according to the “preferred reporting items for systematic review and meta-analysis” (PRISMA recommendations) was conducted in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) in the period from 02/01/2021 to 03/23/2021. The search term “Vitamin D” was used to search for systematic reviews published in German or English in the last 10 years. In addition to an analysis of the cited literature, a hand search was carried out using the terms “Vitamin D & physiology”, “Vitamin D & recommendation”, “Vitamin D & status”, “Vitamin D & Germany”, “Vitamin D & sport”, “Vitamin D & Armed Forces”, and “Vitamin D & Bundeswehr” (time-period: last 10 years). Current articles were prioritized and other articles were screened for substantially contradictory opinions. Studies on adolescents (under 18 years), pregnant women, and seniors (over 65 years) as well as clinical reviews on specific diseases were excluded. **Figure 1** shows the PRISMA flow chart including literature selection. From a total of 1262 articles, 168 studies were evaluated in the present publication.

Results

Vitamin D effects dependent on concentration

The effects of vitamin D in the organism are concentration- and tissue-dependent [65], and primarily mediated by calcitriol (1,25$(OH)_2D_3$). However, the gold standard for determining vitamin D status are the more constant

Table 2: Diseases with confirmed positive effects of vitamin D administration.

Disease	Study Type*	Source
Asthma	RCT	44, 7
Cancer	RCT	38
COVID-19	RCT	36
Dementia	OS	44
Depression	OS	44
Primary dysmenorrhea	RCT	1
(Stress) fractures	RCT	18, 71
Complications of pregnancy	RCT	53
Migraine	RCT	28
Total mortality	RCT	53
Osteomalacia	RCT	53
Osteoporosis	RCT	53
Periodontal disease	RCT	27, 51
Peri-implantitis	OS	3
Premenstrual syndrome	RCT	2
Respiratory tract infections	RCT	44, 35
Restless legs syndrome	OS	43
Rickets	RCT	63, 54
Rheumatoid arthritis	OS	30
Tuberculosis	OS	63
Type 1 diabetes	RCT	29

* RCT = Randomized Controlled Study, OS = Observational Study/ Beobachtungsstudie

calcidiol plasma levels (25(OH)D_3), which are measurable easier [71]. Calcidiol plasma levels are, however, not necessarily correlated with calcitriol levels.
Calcidiol has a longer half-life than calcitriol (21 d– 30 d vs. 4 h–48 h) and is present in a 1000-fold higher concentration [37, 60]. More than 99 % of calcidiol in blood is bound to transport proteins, such as vitamin D-binding protein (VDP, 85 %, high affinity) or albumin (15 %, lower affinity) [8, 10]. Mainly the unbound fraction (<< 1 %) is effective [8]. Thus, the transport proteins and the widespread VDP polymorphism also influence the vitamin D effect [10]. This may lead, for example, to a sufficient amount of biologically effective, free amount of calcitriol in serum despite a seeming calcidiol deficiency. In addition, the active level is finely regulated in tissues themselves by means of 1α-hydroxylases. Furthermore, the effects can be altered via the availability of vitamin D receptor (VDR) binding sites [14, 15]. The low and spatially varying concentrations, different and insufficiently standardized analytical methods may lead to measurement based differences in calcidiol levels of over 38 % [39, 60]. This must be taken into account when interpreting vitamin D values [57]. It also provides an explanation for the divergent study results and recommendations on vitamin D.

Estimating the "normal" requirement

As previously shown, there are large differences in literature regarding normative ranges for vitamin D values. The determination of normal vitamin D requirement is crucial to the question of whether and how much vitamin D should be supplemented. The German Robert Koch Institute and other internationally renowned institutions use the classification of the US Institute of Medicine [45] to assess the vitamin D status. According to this classification, a vitamin D deficiency exists if calcidiol concentration is below 20 ng/ml (= 50 nmol/l). The current recommendations of the D-A-CH also mention 20 ng/ml (= 50 nmol/l) as a threshold value [19]. This serum level is based on the occurrence of deficiency symptoms such as rickets and other skeletal diseases.
However, more recent epidemiological studies make the case for a significantly higher normative range. Vitamin D serum concentrations above 30 ng/ml (= 75 nmol/l) reduce cardiometabolic and inflammatory biomarkers and lower morbidity for metabolic syndrome (MetS), diabetes, and cardiometabolic diseases [26]. The serum calcidiol levels of indigenous ethnic groups living close to the equator are even twice as high as the IOM recommendations. Among the traditionally living Hadzabe and Maasai in Tanzania ("model ethnic groups"), an average of 46 ng/ml (= 115 nmol/l) was measured [41]. The available epidemiological data as well as the serum levels of ethnic groups living close to the equator suggest that the vitamin D standard value ranges should be raised.

Vitamin D deficiency in the population

Due to its rather unspecific symptoms such as adynamia, susceptibility to infections, reduced muscle strength, myalgia, neurological disorders, orthostatic dysregulation, and skeletal complaints, vitamin D deficiency usually remains undetected [5]. In Germany, about 30 % of adults have a calcidiol level below 12 ng/ml (= 30 nmol/l). About 1/3 of German men and women exhibit concentrations between 12 ng/ml (= 30 nmol/l) and 20 ng/ml (= 50 nmol/l) [56]. This means that the vast majority of the German population (> 60 %) has an undersupply of vitamin D. In Europe, about 40 % of the population has a serum calcidiol level below 20 ng/ml (= 50 nmol/l) [16]. The main reasons for the undersupply are insufficient dietary vitamin D intake and reduced vitamin D production via skin. **Figure 2** shows the main factors influencing vitamin D levels.

Nutrition

Only a small part (up to roughly 20 %) of the required amount of vitamin D can be obtained from dietary intake [52]. This is due to the fact that only a few, almost exclu-

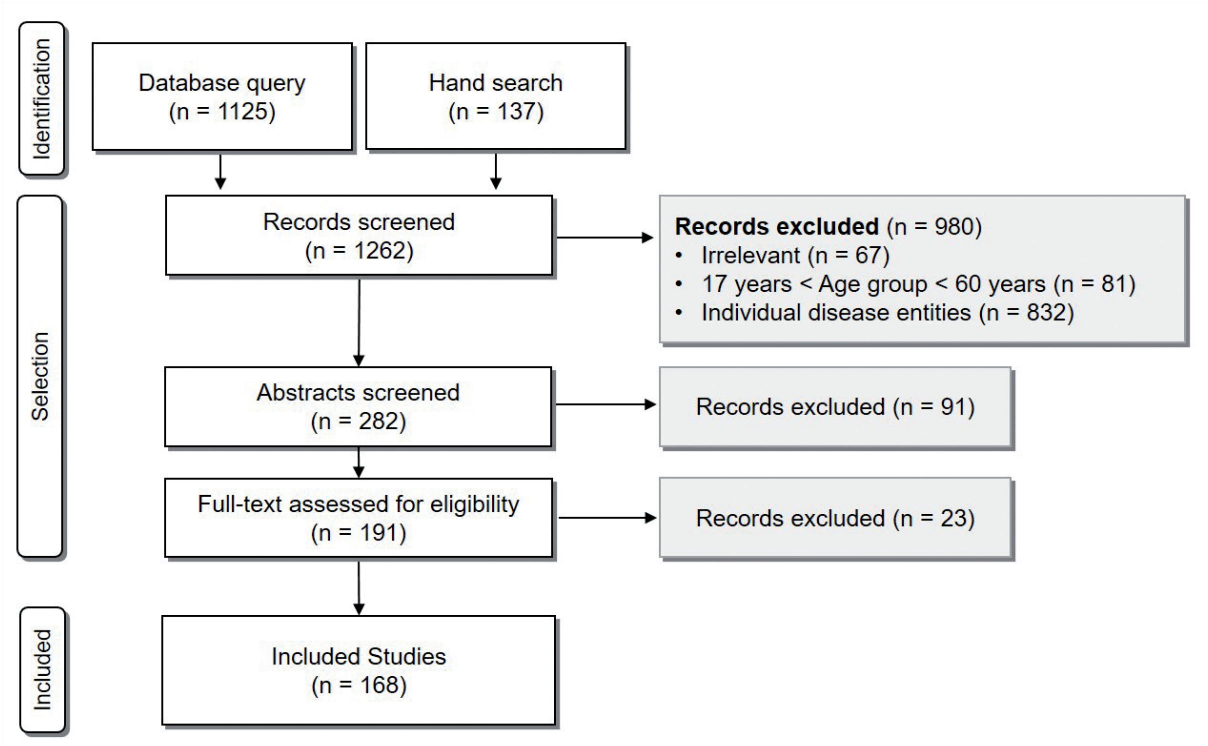

Figure 1: PRISMA flow chart of the literature search for systematic reviews; search term: "Vitamin D", search timeframe: last 10 years

sively animal-based foods contain significant amounts of vitamin D [33]. Vegetarians and vegans therefore have an increased risk of undersupply. Vitamin D is mainly found in fatty sea fish (herring: 7.8—25 µg/100 g, salmon: 16 µg/100 g), chicken eggs (2.9 µg/100 g). Trace amounts can be found in dairy products and animal liver. Fungi and lichens can produce high concentrations of vitamin D_2 (ergocalciferol) under UV irradiation, which is, however, less effective compared to vitamin D_3 [34, 40, 66]. The D-A-CH now recommends a daily vitamin D intake of 800 IU (= 20 µg) for adults [71]. According to the National Nutrition Survey II [46], over 80 % of men and over 90 % of women do not reach the daily recommended vitamin D intake. Among senior citizens, this figure rises to over 95 %.

Vitamin D production in the skin

The main source of vitamin D is endogenous synthesis, which takes place in the human skin under influence of UVB radiation from the sun which depends on a variety of factors [23] such as sun position (geographical latitude, season, time of day, altitude), environmental factors (smog/weather, shade or surface reflection of the environment), skin type, and age [23, 68]. Some of these factors that can be influenced, including exposed skin area, time of day, use of sunscreen/skin creams, duration of exposure, but also body fat percentage [69]. Sunburn should be avoided in any case because of the increased risk of skin cancer.

According to the Federal Office for Radiation Protection [11], sunbathing of uncovered face, hands, and arms (without sunscreen) for 12 minutes 2 to 3 times a week leads to a sufficient vitamin D production in the skin. These recommendations apply to a UV index of 7, which is usually reached in Germany under good weather conditions only and around midday during the months of June and July [13]. In the remaining summer months however, a much longer exposure is necessary due to lower UV indices. In the winter half-year (October to March), UVB radiation in Germany is too low for sufficient vitamin D production [12]. With regards to the vitamin D levels stated above, it is obvious that the vitamin D supplies stored in fat, muscle tissue, and liver are insufficient to compensate for the reduced UVB radiation for 6 months. The typical wave-shaped annual course of vitamin D levels for residents in Germany is shown in **Figure 3**.

Population groups with increased vitamin D requirements

It is obvious that people with dark skin, vegetarians, and vegans are at an increased risk of vitamin D deficiency. Elderly (especially immobile) people, infants, young children, and pregnant women are also among the risk groups. Overweight, obesity [50], dental periodontitis, numerous diseases as well as certain medical drugs can have a negative impact on vitamin D levels. **Table 1** provides an overview of the corresponding drugs and diseases.

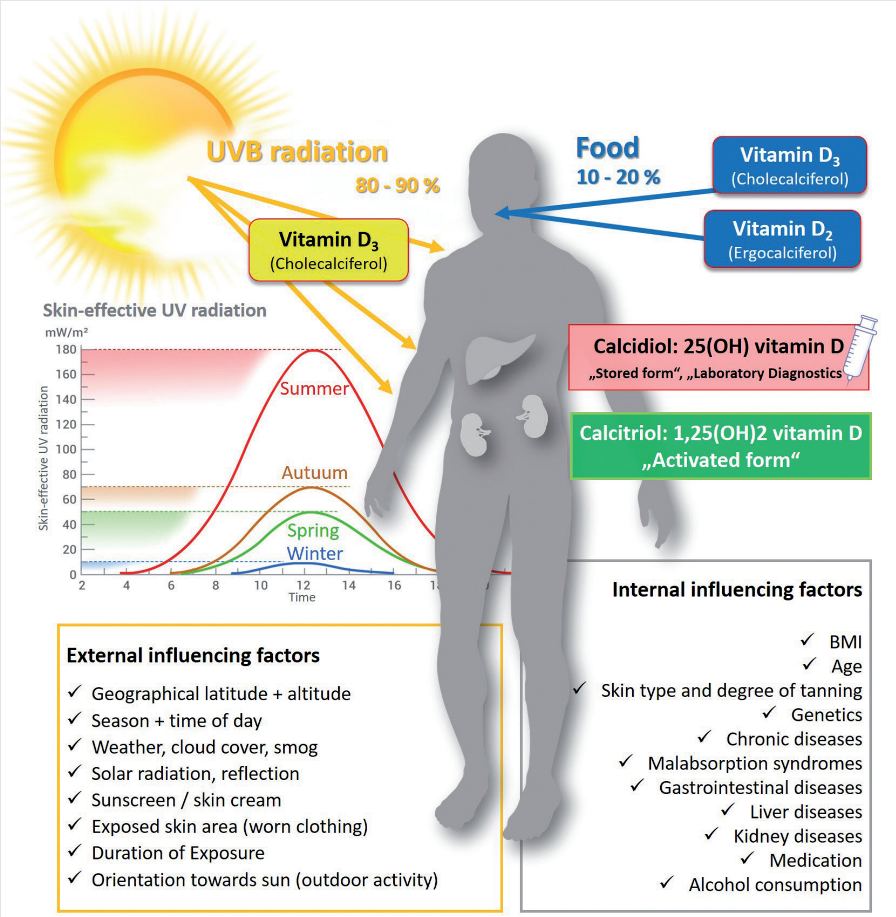

Figure 2: Physiologically active forms of vitamin D and factors influencing vitamin D levels

Living environments

The problem of an adequate vitamin D supply is further exacerbated by modern lifestyles and changes in lifestyles. When staying in closed rooms, behind glass, and in vehicles, UVB exposure is de facto almost nil – even in sunshine. However, merely spending time outdoors does not guarantee sufficient vitamin D production, as UVB radiation in the morning and evening hours is only a fraction of the radiation during midday. People who do not work outdoors and shift workers are therefore particularly often affected by a deficiency [17]. In addition, when spending time outdoors, considerable areas of skin are usually covered by lotions, sunscreen, and clothing and thus insufficiently involved in vitamin D production. For example, a sunscreen with an UV protection factor of 8 reduces vitamin D synthesis by 93 % [71].

Female and male soldiers

In the military, the wearing of uniforms, protective equipment, and headgear as well as indoor activities, and staying in air, land and water vehicles lead to a significant restriction of endogenous vitamin D production. Therefore, a widespread and often unrecognised vitamin D deficiency in soldiers may be assumed. So far, current figures on vitamin D supply in the Bundeswehr are only available from a small and non-representative collective of 2176 pilots and aircrew. Of these, 71.6 % showed vitamin D deficiencies [55].

In contrast to the civilian sector, vitamin D may be even more important in military, police, and fire services. Due to high additional loads caused by protective clothing, equipment, and armament, duty related activities may lead to acute or persisting situations with significantly increased risks of stress fractures, among other things, especially if a vitamin D deficiency exists [18]. This is even more relevant for female soldiers [47].

Conclusion and recommendation

A high vitamin D level provides numerous health benefits. More and more professional organisations recommend vitamin D supplementation, ranging from 800 IU (= 20 µg) to 10,000 IU (= 250 µg). In some countries (USA, Canada, India and Finland), foods such as milk, yoghurt, and orange juice are already enriched with vitamin D [52].

Although there is no representative data on vitamin D levels in Bundeswehr soldiers, a widespread vitamin D deficiency among male and female soldiers is highly likely, especially throughout the winter half-year. Therefore, targeted supplementation with vitamin D seems to be appropriate. Studies with soldiers from other nations show that daily doses of 2000 IU/d (= 50 µg/d) vitamin D in combination with calcium lead to an improvement in

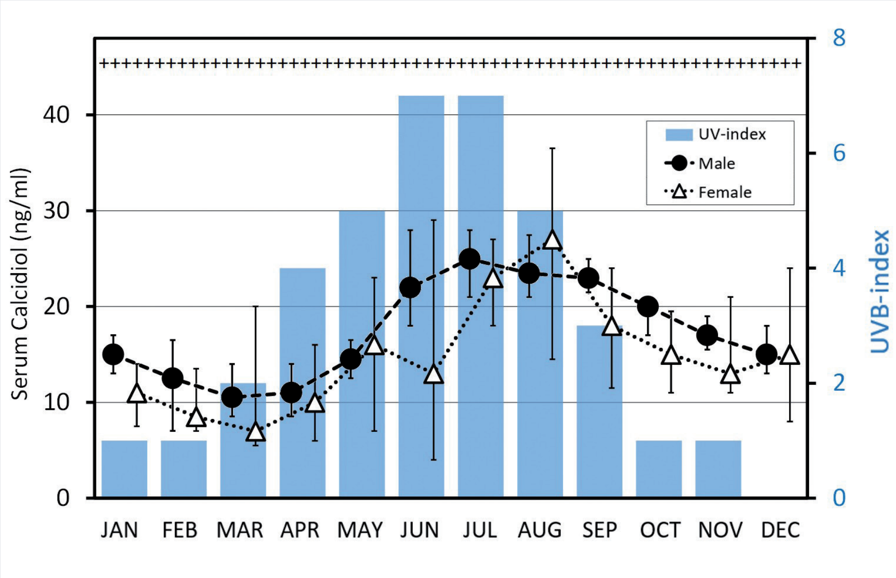

Figure 3: Typical seasonal course of vitamin D serum levels [24] and UVB indices (bar chart) [12] in Germany. The physiological levels of vitamin D in indigenous ethnic groups living close to the equator never drop below 40ng/ml (> 100 nmol/l) [41] and are marked with +++.

bone health and a decrease in fracture rates [64]. The recently published systematic review "Nonexercise interventions for prevention of musculoskeletal injuries in armed forces" also confirms a preventive effect of vitamin D, calcium and protein supplementation [6].

A common argument against vitamin D supplementation is the risk of overdosing. However, hypervitaminosis with vitamin D is very rare. An elevated risk exists primarily in the presence of an idiopathic infantile hypercalcemia [62], which can, however, be easily diagnosed in suspected cases by determining the 24,25 : 25 vitamin D metabolite ratio in the blood [4]. Hypervitaminoses in healthy individuals normally occur only in case of massive overdosing, such as in daily amounts exceeding 50,000 IU (= 1,250 µg/d), usually over months or years [25]. There, toxic serum concentrations measured ranged from 150 ng/ml to 1,220 ng/ml (= 375 nmol/l–3,050 nmol/l) [25]. In case of suspicion, hypervitaminosis can be easily detected and prevented by determination of vitamin D levels.

In view of the current state of studies and the specific demands of the military sector, a targeted supplementation of vitamin D for soldiers is clearly recommended.

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For the authors
Major (MC) Dr. Emanuel Vits
Bundeswehr Institute for Preventive Medizin
Division A – Health and Fitness Promotion
Andernacher Str. 100; D-56070 Koblenz
E-Mail: emanuelvits@bundeswehr.org