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Review

An Appraisal to Address Health Consequences of Vitamin D Deficiency With Food Fortification and Supplements: Time to Act!

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Abstract. *A symposium entitled "Vitamin D in Prevention and Therapy" was held on May 4-5, 2022, in Homburg, Germany to discuss important new advances in the field, including identification of new vitamin D signaling pathways, of new biologic effects of vitamin D-compounds (e.g., on the microbiome), and convincing proof of the relevance of vitamin D deficiency for the risk and outcome of many chronic diseases, including cancer, cardio-vascular, auto-immune, metabolic, and infectious diseases. Concerning the COVID-19-pandemic, an inverse association between 25(OH)D serum concentrations and SARS-CoV-2-infections, morbidity, and mortality was shown. In relation to cancer, several meta-analyses recently demonstrated an association of vitamin D-supplementation with significantly decreased mortality rates, which presumably would reduce health care costs. Considering the impressive body of evidence and the high safety of oral supplementation and food fortification with vitamin D, it was concluded that there is now an urgent need to act. In many countries worldwide, health care authorities need to increase efforts to address vitamin D deficiency, e.g., via food fortification and/or supplementation with vitamin D, and/or promoting moderate UV-exposure. It was estimated that in many countries, vitamin D intakes of the order of appr. 1,000 IE (25 μg)/day would be needed to bring and/or keep the vast majority of people over a serum 25(OH)D threshold of 20 ng/ml (50 nmol/l), which would be difficult to obtain alone from food fortification. New developments in personalized medicine may represent helpful tools to identify populations at risk for vitamin D deficiency and their responsiveness to vitamin D treatment.*

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International experts presented at the symposium entitled "Vitamin D in Prevention and Therapy", that was held in Homburg, Germany on May 4-5, 2022 important new advances in the field (1-23). In plenary/key note lectures and in round table discussions, recent scientific progress from epidemiologic, laboratory and clinical studies was extensively evaluated. Resulting from our present knowledge, major conclusions concerning the impact of vitamin D status on human health were drawn. It was concluded that health authorities need to increase their efforts to improve the vitamin D status in children and adults in many countries worldwide. Appropriate measures to reach this goal, which may benefit from new developments in personalized medicine, should include oral supplementation and food fortification with vitamin D_2 or vitamin D_3 and when possible moderate solar or artificial ultraviolet (UV)-B-exposure.

New Vitamin D Signaling Pathways: Ancient Friends, Revisited

There are two natural ways to supply the human body with vitamin D. Under most living conditions, the major part (appr. 70-90%) of this seco-steroid pro-hormone is produced in the skin after UV-B exposure, while only a small amount is available from nutritional sources due to the fact that very few foods naturally contain vitamin D (7, 19). These include wild caught oily fish such as salmon, cod liver oil, and mushrooms exposed to sunlight.

Because it is dramatically affected by many factors, including time of day, season, latitude, and skin pigmentation (7), the cutaneous production of vitamin D induced by solar radiation does not represent a dependable source at all times (7). Consequently, stand up devices that emit narrowband UVB radiation have been developed (*e.g.*, by Solius Inc.) for producing cutaneous vitamin D (7). The efficacy of this approach in increasing serum 25(OH)D concentrations has been confirmed in clinical studies (7). Malabsorption and obese patients show a variable and often diminished response to vitamin D supplementation (7). Individuals with fat malabsorption could benefit from using a dependable artificial UVB source (7). An alternative is to provide these patients 25-hydroxyvitamin D [25(OH)D, calcifediol]. It was shown that supplementation with $25(OH)D_3$ effectively and rapidly improves the vitamin D status in these individuals similar to healthy adults (7). Notably, the ability to rapidly improve vitamin D status with oral $25(OH)D_3$ has been efficacious in reducing morbidity and mortality in COVID-19-infected individuals (7).

Vitamin D_3 that is produced in the skin and vitamin D_2 and vitamin D_3, which are absorbed in the small intestine after being provided by the diet, are transferred to the blood where they are bound to the vitamin D binding protein (23-28). According to the classic concept, vitamin D (D representing both D_2 and D_3) has to be metabolized to 25(OH)D by cytochrome P 450 (CYP) enzymes CYP2R1 and CYP27A1 in the liver (23-28). Transferred to the blood, 25(OH)D is then transported to a broad variety of different cell types, that include the skin, kidney, and various immune cells such as activated macrophages where it is transformed by CYP27B1 into its canonical biological active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (23-28). The classical biological functions of $1,25(OH)_2D$ are mediated *via* binding to the vitamin D receptor (VDR), which exerts its effects as an agonist-activated transcription factor that binds to VDR responsive elements (VDRE) in target genes, thereby regulating their expression (23-28). Notably, recent scientific data convincingly show new emerging biological functions of non-canonical pathways of vitamin D metabolites that are induced by the action of CYP11A1, which has been characterized as a rate-limiting enzyme of steroidogenesis (23-28). The first steps of these new non-canonical pathways of vitamin D metabolites are then followed by a broad variety of modifications involving other CYP enzymes, that include CYP27B1: D_3? $20(OH)D_3$?$20,23(OH)_2D_3$? $17,20,23(OH)_3D_3$ + (OH)nD (23-28). Experimental investigations, that include functional studies, bioinformatics analyses, and molecular modeling have now convincingly shown that CYP11A1-derived vitamin D_3-hydroxyderivatives can exert agonistic effects on VDR and that the function of this receptor is increased by the addition of CYP27B1 (23-28). These vitamin D_3 derivatives can also act as inverse agonists on retinoic acid-related orphan receptors α and γ (ROR α and γ) and as agonists on the aryl hydrocarbon (AhR) and liver X receptors (LXR)-? and –β (23-28). These effects also include $1,25(OH)_2D_3$. Recent findings now indicate that the new vitamin D signaling pathways activated by these non-canonical vitamin D hydroxyderivatives (such as 20-hydroxyvitamin D) (23-28) may be relevant for the development and outcome of many diseases, including metabolic disorders, infectious diseases (including COVID-19), and cancer. Considering the fundamental differences in the metabolism of cutaneously produced as compared with orally supplemented vitamin D, it was concluded that oral supplementation with vitamin D may not compensate for all of the biologic effects of vitamin D produced in skin following exposure to UVB-radiation.

How to Evaluate a Person's Vitamin D Status and Define Vitamin D Deficiency?

In addition to the presentations reporting new biological functions of non-classical vitamin D hydroxyderivatives, several lectures presented new technical developments in their analysis (9, 14, 20). Despite the emerging new biological functions of these non-classical vitamin D

hydroxyderivatives (23-28), it was concluded that serum concentration of 25(OH)D still represents the best laboratory parameter to evaluate a person's vitamin D status. However, it was predicted that the systematic analysis of the many other biologically active vitamin D metabolites will likely be of increasing relevance in the future (23-28). Measuring their concentration in serum and other tissues may provide important additional information that will enable the determination as to the importance of newly discovered pleiotropic biological effects of various vitamin D compounds for human health and disease. Notably, it needs to be analyzed whether all of these biologically active non-classical vitamin D hydroxyderivatives are synthesized following oral uptake of vitamin D or whether some of them are exclusively produced after UV-B induced vitamin D synthesis in the skin.

Vitamin D Deficiency and Human Health: Implications for Cancer and Mortality

New findings convincingly show the importance of an optimal vitamin D status to prevent development and progression of cancer (1-4, 10, 13, 16, 18, 22, 28-34). As an example, three meta-analyses of clinical investigations concluded in recent years, that vitamin D supplementation is associated with reduced all-cause and cancer mortality rates (30, 31, 35). Scientists of Herrmann Brenner`s group at the German Cancer Research Center (DKFZ) have taken these results to analyze the situation in Germany and estimated that if all German citizens older than 50 years would use vitamin D supplements, up to 30,000 cancer deaths would possibly be prevented every year and more than 300,000 years of life would be gained (32). In addition, a substantial amount of health care costs would be saved. To compare these estimations with data in the real world, these scientists at the DKFZ investigated in a large consecutive prospective cohort study (445,601 UK Biobank population recruited between 2006 and 2010), by applying Cox proportional hazard regression, whether taking vitamin D supplements is associated with reduced mortality (all-cause, respiratory and cardio-vascular disease, and cancer mortality) in real-world settings, and validated the association of serum 25(OH)D concentrations with mortality. Overall, 4.3% of participants reported using vitamin D supplements on a regular basis, and most individuals were either vitamin D deficient (21.0%) or insufficient (34.3%). A total of 29,107 (6.5%) individuals died during the study period (median follow-up 11.8 years). Individuals with self-reported use of vitamin D supplements on a regular basis had a 6% decrease in all-cause mortality, and 24% lower respiratory disease mortality. Vitamin D deficiency and insufficiency were strongly associated with mortality (all-cause, respiratory and cardio-vascular disease, and cancer mortality). In summary, this large, population-based investigation confirmed that the efficacy of vitamin D supplements for all-cause mortality shown in randomized controlled trials (RCTs) is well in agreement with real-world data (22).

Challenge and Promise: Vitamin D and the Immune System

Several lectures convincingly demonstrated the constantly increasing role of vitamin D as a key regulator of innate and adaptive immunity, thereby contributing significantly to the fine tuning of many immunologic functions and to the outcome of a broad variety of independent diseases, including infections and autoimmune diseases (6-8, 11, 36). As an example, 25(OH)D can enter activated macrophages, where it is processed into its biologically active form $1,25(OH)_2D$, thereby increasing *via* a VDR-dependent mechanism the production of the antimicrobial peptide cathelicidin. While it was shown previously that cathelicidin is not only required for an efficient defense against mycobacterium tuberculosis and other bacterial infections, more recent findings indicate a much broader role of this peptide, contributing to the outcome of many other diseases, including metabolic disorders and cancer. It has been shown that locally released $1,25(OH)_2D$ can regulate important immunologic functions in activated B- and T-lymphocytes, where it decreases autoantibody production and modulates production of helpful and harmful cytokines, respectively.

Vitamin D Deficiency and Human Health: Implications for the SARS-CoV-2 Pandemic

At this symposium, numerous lectures convincingly reported an inverse association between 25(OH)D blood concentrations and SARS-CoV-2 infections, morbidity and mortality. There was a general consensus that the SARS-CoV-2 pandemic caused devastating consequences for the health of both children and adults. Although life years lost by the Spanish flu were much higher as compared to those lost by SARS-CoV-2, an analysis in the US, comparing latitude and solar UV radiation with Spanish flu fatalities, showed for those living in northern latitudes, a by more than 50% increased risk of mortality, as compared to individuals living in southern latitudes (data not shown). It was postulated that the peak of the flu season in winter was caused by a seasonal stimulus. Several studies have reported that individuals with 25(OH)D blood concentrations >30 ng/ml had significantly, by more than 50% reduced, SARS-CoV-2 infection rates as compared to individuals with 25(OH)D serum concentrations <20 ng/ml. With increasing 25(OH)D blood concentrations, the risk of SARS-CoV-2 infection continuously declined until the 25(OH)D serum concentration reached 55 ng/ml. Hospitalized patients with SARS-CoV-2 infections had a reduced risk for morbidity, mortality and

intensive care unit (ICU) admission, when their serum level of 25(OH)D was >30 ng/ml. Interestingly, it was shown that expression of Folate receptor 3 (FOLR3) was significantly altered in patients with severe as compared to mild SARS-CoV-2 infections, and was down-regulated in a dose-dependent manner (foldchange of FOLR3 expression=–1.0, –1.7, and –2.7 for the 600, 4,000, and 10,000 IU/day supplementation groups, respectively) in healthy adults due to vitamin D supplementation. Because FOLR3 is expressed in neutrophils as a secretory protein, it can be speculated whether decreased FOLR3 concentration results from decreased neutrophil counts induced by vitamin D supplementation, which have been recently reported in patients admitted with severe symptoms. Patients who were vitamin D sufficient had a significant decrease in the number of neutrophils compared to lymphocytes. Because it was shown that a high neutrophil count and neutrophil-lymphocyte ratio (NLR) are biomarkers for predicting severe health consequences from SARS-CoV-2, this finding may represent a mechanism through which, at least in part, a higher vitamin D status may reduce severity of SARS-CoV-2 infections.

Autocrine, Paracrine and Endocrine Effects of Vitamin D Hydroxyderivatives Contribute to the Function of the Hormone Factory Skin as a Neuro-immuno-Endocrine Organ

Several lectures reported that the "hormone factory skin" represents a fully functional peripheral neuro-immuno-endocrine organ, which regulates *via* auto-, para-, and endocrine effects both local and systemic homeostasis (25-28). To fulfill this goal, the skin uses the same mediators and signal transduction pathways as those functioning in the central nervous (CNS), endocrine and immune systems, including corticotropin releasing hormone (CRH), urocortins, propiomelanocortin (POMC)-peptides, cytokines, enkephalins, biogenic amines, melatonin, steroids, secosteroids, lumisterols, and others. In many cases, the cutaneous synthesis of these molecules and their consecutive release to the circulation depends on or can be induced by solar radiation (*e.g.*, UVB). Many of these cutaneous messengers modulate both local and systemic homeostasis through a highly organized network that consists of a broad variety of interacting pathways. Effects exerted on these pathways include the activation of the central hypothalamic-pituitary adrenal axis (HPA) that in turn stimulates corticosteroids release to inhibit immune activity and counteract stress with feedback termination. Thus, released from the skin, CRH and urocortin may modulate pituitary gland activity, and cytokines (including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)α) may stimulate both the hypothalamus and pituitary gland, all in order to impact on the adrenal cortex. Additionally, UVB-induced stimulation of local nerves can induce rapid responses transmitted by ascending nerves to the CNS, which translates them into descending signaling resulting in the suppression of systemic and local immune activities. These findings have been reported 30-60 min after UVB exposure. A specific feature of the "hormone factory skin" is the UVB-induced production of secosteroids/sterols that, after metabolic activation by CYP enzymes, would exert immunomodulatory effects at the local and systemic levels. These pathways/systems that are modulated by UVB, separately or in concert, not only contribute to defending the skin integrity but may also reset the body homeostasis and systemic immune activities to the environmentally most desirable mode.

Challenge and Promise Regarding Vitamin D Deficiency and Human Health: Implications for Autoimmune Diseases

Several lectures at this symposium presented convincing scientific evidence that vitamin D represents a potent and essential modulator of the immune system whose effects include a reduction in the risk for autoimmune disorders (6-8). It was shown that vitamin D signaling contributes as a key regulator to the fine tuning of many different immunologic functions. As an example, 25(OH)D can enter activated macrophages, where it is transformed into its active form $1,25(OH)_2D$, thereby increasing *via* a VDR-dependent mechanism the production of the antimicrobial peptide cathelicidin. As mentioned before, it has been shown that locally released $1,25(OH)_2D$ can regulate important immunologic functions in activated B- and T-lymphocytes, where it decreases autoantibody production and modulates production of helpful and harmful cytokines, respectively.

Time to Act: Rationale and Suggestions for Addressing Vitamin D Deficiency Through Increasing Vitamin D Intake and/or Solar UV-Exposure

Food fortification with vitamin D should increase 25(OH)D serum similarly to vitamin D supplementation and lead to similar reductions in cancer mortality. There are voluntary and mandatory policies for vitamin D food fortification, but distinguishing them is not always easy. Whereas some European countries (*e.g.*, Finland) have already implemented widespread fortification of some foods with vitamin D, in other countries (*e.g.*, Germany, where addition of vitamin D to food is restricted to margarine, based on a law from 1942) only few or no foods are fortified (37, 38). The production of vitamin D-biofortified animal and fungi/yeast-based foods has shown variable effects on the levels of vitamin D over non-biofortified equivalent foods.

As explained above, meta-analyses of RCTs demonstrated that, in many populations, vitamin D supplementation reduces cancer mortality by 13%. A study presented at this

symposium estimated the reduction in cancer mortality presumably already achieved by current fortification policies in 2017 and the potential for further reductions if all countries had effective fortification. Information regarding current vitamin D food fortification policies in 34 European countries was obtained following review of the literature and contacting health authorities.

To estimate the number of cancer deaths that they had been probably prevented and the number of deaths and years of life lost that would have been avoided, country-specific cancer death statistics, life expectancy information, and data from studies on supplementation and serum 25(OH)D increases and cancer mortality were used. It was estimated that current vitamin D food fortification may prevent approximately 11,000 cancer deaths per year in the European Union and 27,000 in European countries. Therefore, if all countries implement policies for adequate vitamin D fortification of foods, approximately 129,000 cancer deaths [113,000 in the European Union (EU)] could be prevented, corresponding to almost 1.2 million prevented years of life lost (1.0 million in the EU) or approximately 9% of cancer deaths (10% in the EU). The Authors concluded that the burden of cancer deaths in Europe might be reduced by systematic fortification of foods. Considering its high prevalence world-wide and the resulting severe consequences for human health, the experts recommended that vitamin D deficiency urgently needs to be addressed in many countries by governments and health care authorities.

Food fortification, oral supplementation with vitamin D and/or moderate UV-exposure should be implemented and/or increased in combination to improve the vitamin D status of the population.

Several lectures depicted the increasing importance of personalized medicine for the management of vitamin D deficiency (9). Besides new data demonstrating the importance of known risk factors (including lack of solar or artificial UV-B exposure, age, and body mass index (BMI); cancer/melanoma patients), new molecular and technical approaches such as identifying individuals with a partial or complete CYP24A1 (24-hydroxylase) deficiency were presented as promising new tools to detect and how to treat vitamin D-deficient individuals.

Time to Act, But What Are the Strategies/ Concrete Steps that Must Now Be Taken?

The guidelines of the World Health Organization (WHO) define the goal of food fortification as follows: ".... to provide most (97.5%) individuals in the population groups at greatest risk of deficiency with an adequate intake of specific micronutrients, without causing a risk of excessive intakes in this or other groups" (39). Thoughtful strategies for the implementation of vitamin D food fortification in countries where the dietary requirements in vitamin D are not met by a significant part of the general population have been published previously (37-39). Several systematic reviews and meta-analyses of randomized controlled trials (RCTs) with vitamin D fortified foods demonstrate the efficacy of food fortification in elevating a person's vitamin D status (37-39). It has been reported that, if the goal is to bring and/or maintain the majority of people over a serum 25(OH)D threshold of 20 ng/ml (50 nmol/l), it would require vitamin D intakes of the order of appr. 25 μg/day, which would be challenging to achieve *via* food fortification alone. While an approach that gets vitamin D intakes in the population to appr. 10 μg/day offers maximal advantage in terms of preventing serum 25(OH)D dropping below 25 nmol/l in 97.5% of individuals, this represents a sizeable increase in intakes for many populations. Considering the safety and cost-effectiveness of these measures, both oral supplementation and food fortification with vitamin D should be implemented for addressing vitamin D deficiency. Moreover, the importance of moderate UV exposure for obtaining and/or keeping a healthy vitamin D status needs to be highlighted. In this context, it must be emphasized that oral supplementation with vitamin D does not compensate for the broad variety of all biologic effects that are mediated by the many different UV-induced photoproducts that are synthesized in the human skin.

Conflicts of Interest

Saarland University (with JR and TV as investigators), received a research grant from the Jörg Wolff foundation (Stuttgart, Germany).

Authors' Contributions

Conception of the manuscript: JR, WM, WG, AS, MH, TV and SP. Writing the manuscript: JR, WM, MH, TV and SP. Revising the manuscript: JR, WM, FDG, RV, WG, AS, MH, TV and SP.

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