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Crucial Role of Vitamin D in Seasonal Viral Infections

Short communication

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Author Details

Hermann Salmhofer[1]*

[1]*Department of Internal Medicine I, Paracelsus Medical University Salzburg, Austria*

*Corresponding author

Hermann Salmhofer MD, Department of Internal Medicine I, Paracelsus Medical University Salzburg, Austria

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Short Communication

Seasonal viral infections, such as influenza, respiratory syncytial virus and corona viruses, including the novel SARS-CoV-2, occur in the cold winter months, predominantly in regions of higher latitude. Respiratory infections are the most common infections in the general population and most frequent reasons of consulting physicians and taking sick day leaves from school and work [1]. Therefore, they place a relevant burden on public health and economy in addition to individual risk. Populations in danger of severe and fatal infections include the elderly, the obese, many chronic diseases, including tumor and immunosuppressed patients, malnutrition as well as persons with genetically dark skin pigmentation (but only at higher latitudes, which will be detailed in the following).

Seasonal infections are characterised by a great variability of disease courses, from inapparent infection to severe, progressive disease, that may lead to hospital admissions, intensive care treatment and, in worst case, death. In an epidemiologic, population based view, this explains the increased death rates in winter times. With large variations, this winter surplus of approximately 0,12 % is attributed to "flu deaths" (which sums up all respiratory pathogens; [2]). Yet it has been unclear, if there is a common denominator putting risk persons at risk, and consecutively, how to modify this risk. In seasonal infections, the pathogen affects individuals in a very diverse fashion.

The great majority of people are at no risk of severe disease [3]. Therefore, assuming virulence of the pathogen as the constant, individual immunological disposition (susceptibility) seems the leading variable of disease severity [4]. In the 19th century, the dominant role of individual disposition was apparent in tuberculosis and, later on, in influenza epidemics and pandemics. This was similarly found in COVID-19 [3].

Edgar Hope Simpson had formulated conundrums of influenza epidemiology, resulting in postulation of a "seasonal stimulus" [5-7]. Since then, many factors have been analysed, such as indoor residence and crowding of people in winter, or reduced humidity of air favouring viral stability and influencing mucosal immunity [8].

Environmental toxicity, e.g. air pollution in smog regions may add to burden of mucosal integrity and immune competence. Furthermore, deficiency of micronutrients, like vitamin C and - foremost - vitamin D may add to the risk in winter times since they contribute to deterioration of the immune system. Vitamin D deficiency is a very common, world-wide problem [9,10].

In situations of seasonal infections, a pathogen directed treatment may not be available at all or soon enough. So, optimizing the individual immune system is an important factor in disease management [11]. Optimising the immune system (the "host factors") will primarily target the essential first steps of immune defense, i.e. innate immunity. This is the most effective way to mitigate disease at earliest opportunity and several measures can even be done preemptively. That seems prudent for individual risk as well as public health considerations. From both medical and ethical viewpoints, supplementation of widespread micronutrient deficiencies seems necessary, using a physiological approach to improve the immune system at near zero risk and minimum costs [12]. Even more, optimum immune response on a population base will allow for sufficient herd immunity in course of epidemic and pandemic events.

General measures in seasonal infections include the use of vitamin C, zinc and echinacea, yet mostly will not be administered in hospitals for reasons unknown [13-17]. Upholding widespread micronutrient deficiencies related to deterioration of the immune system seems to be questionable in epidemic and pandemic situations from scientific, medical and ethical viewpoints and incompatible with the physicians´ task [18,19]. The role of vitamin D in seasonality of infections and death as well in pathophysiology of immune response and treatment has been vastly investigated and is still a matter of debate [20]. Vitamin D deficiency has been associated with increased severity of infection and death [21-23]. Therefore and repeatedly, there were appeals to instant vitamin D supplementation of the populace, yet in vain [24,12].

In the corona pandemic, a cut-off vitamin D level of 30 ng/ml separating mild and severe infections was found in many investigations world-wide (e.g. [25-35]). A meta-analysis of 448 million people (Europe) revealed an inverse linear association of vitamin D levels and death, resulting in a theoretically zero death rate at 50 ng/ml [36]. In the USA and the United Kingdom, the death toll among persons with genetically dark skin pigmentation was fourfold higher than in caucasians, which was independent of social status [37-40]. In contrast, COVID-19 deaths in African countries were extremely low. This was called the "African paradoxon". The simple biological explanation, that this group was at increased risk due to extreme vitamin D depletion

at higher latitudes, but not in Africa, was never taken up by health care policies – and so, many lives, that could have been saved, were lost. Political correctness seems to have prohibited this discussion in favour of ideological dogmas, adding to disruption of society.

Generally, comparing 88 countries of various latitudes, a significant correlation was found between a country´s latitude and COVID-19 mortality, further supporting the role of sunlight and vitamin D status [41]. Moreover, small prospective randomised trials [42, 43, 9] resulted in improved survival of the vitamin D group. Upon the results of the Spanish trials, the province of Andalusia supplemented the elderly and home-care patients with calcifediol (25-hydroxy-vitamin D3, which has excellent bio-availability and restores blood levels within several hours), which led to a drop of deaths from 50 to 2 per day within two weeks in the corona pandemic. In Brazil, a prospective, randomized trial [44] using native cholecalciferol gave negative results. Yet this well performed study showed that vitamin D (25-hydroxyvitamin D3) blood levels reached target seven days after the vitamin D (cholecalciferol) bolus, a time point, when disease had already progressed to the late pulmonary stage. This clearly was too late for the immunological benefits of vitamin D repletion. The "evidence based" approach demands randomized controlled trials to evaluate the effects of vitamin D (which, on the other hand, is not a new drug, but a physiological hormone). Many studies on health effects of vitamin D have remained negative so far, yet these have many flaws in study design, e.g. concerning basal and post-interventional vitamin D levels, sun exposure, dosage, bio-availability, skin pigmentation, latitude, etc, which will, in cumulation, result in a huge bias (see also [45]). The new guidelines of the Endocrine Society on calcium and vitamin D supplementation [46] could not give new evidence, mostly due to the persistent lack of randomized, controlled trials.

Unfortunately, the group could not specify a target level of vitamin D and therefore did not recommend measurement of vitamin D at all. In consequence, no new supplementation recommendations were given, although the tenfold dose (4.000 I.U.) of Institute of Medicine recommendations (400 I.U.) was regarded safe, according to these same experts. Undoubtedly, the original dose of 400 I.U. per day does hardly affect blood levels, let alone replete a deficiency. Of note, many other investigations have shown earlier, that a dose of 4.000 I.U. per day is necessary in adults, including breast-feeding mothers, and dosage may be further dependent on body weight [47-49].

Since the discussion has been futile so far, I want to give some additional facts on pathophysiology as well as treatment of seasonal virus infection: the "physiological" approach would be to define target levels of vitamin D and replete the deficient patients, since in vitamin D deficiency, early innate immune response is impaired. The initial anti-viral response, leading to rapid production of interferons and cathelicidin, is insufficient, allowing for viral spread and disease progression to lower airways [50-52]. Furthermore, in vitamin D deficiency, the TNF-alpha-induced NFkB-pathway will be activated, leading to massive secretion of pro-inflammatory cytokines ("cytokine storm"), which is regarded as crucial step towards progressive disease [50-53]. Concurrently, the corona pandemic has given us ample data, that a vitamin D level below 30 ng/ml may put patients at risk of severe disease and death.

Repeatedly, appeals were published to supplement vitamin D in the pandemic to save lives [24], yet to no effect. Up to 90 % of COVID deaths may be attributed to vitamin D deficiency [12]. Of note, efficacy of any vaccination is essentially dependent on the predisposition of the individual immune system, quite similar to infections (see correlation of measles vaccination titres and vitamin D levels in the NHANES collective [54], and insufficient efficacy of influenza vaccinations in the elderly despite antibody generation [55]).

So, what rationale is there, NOT TO ACT according to improving immunity and health of individual people without costs or risk, and, simultaneously, improve public health resources by mitigating the effects of an epidemic. From my point of view, physicians need to do the best to their patients and, if scientists disagree, perform a pro/contra-evaluation of risk and benefit. As outlined here, I believe, that vitamin D is essential for human health and may be beneficial in seasonal infections.

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