European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2020; 24: 4048-4052

Editorial – Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections

A. FABBRI[1], M. INFANTE[1,2], AND C. RICORDI[2]

[1]Endocrine Unit, CTO Hospital – ASL Roma 2, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy
[2]Diabetes Research Institute (DRI), University of Miami Miller School of Medicine, Miami, FL, USA

Key Words:
Vitamin D, Vitamin D deficiency, Innate immunity, Viral respiratory infections, Covid-19.

Innate immune responses represent the initial host defense against invading pathogens. Unlike the adaptive immune responses, innate immune responses are not specific to a specific pathogen and depend upon a group of phagocytic cells and proteins that recognize conserved features of microbes to quickly promote clearance of infectious agents, including viruses, bacteria, fungi and parasites. Innate immune system includes physical (i.e., epithelium) and chemical barriers (i.e., saliva, gastric acid), complement cascade, antimicrobial peptides and antigen-presenting cells[1]. Antigen-presenting cells (i.e., dendritic cells and macrophages) play a pivotal role in innate immune responses by sensing pathogen-associated molecular patterns (PAMPs) of a large variety of microbes via pattern recognition receptors (PRRs) – such as Toll-like receptors (TLRs) – and subsequently facilitate the full activation of adaptive immune responses[1].

Vitamin D deficiency represents a global pandemic afflicting more than one billion individuals across all age groups worldwide[2]. Over the last decade, several studies supported vitamin D deficiency as a potential risk factor for various diseases, including systemic infections and autoimmune diseases[3-7]. Apart from its well-known role in the regulation of bone homeostasis, vitamin D has been shown to exert several extraskeletal actions[4,8], including the regulation of innate and adaptive immune responses[9-11]. In particular, vitamin D has been recognized as an important mediator of innate immune responses[12], participating in several processes of the innate immunity. Functional VDR has been identified in almost all immune cells, including neutrophils and antigen-presenting cells (macrophages and dendritic cells)[10,13-15], as well as in human airway epithelial cells[16]. Also, *in vitro* studies have shown that vitamin D decreases the expression of pro-inflammatory cytokines and increases the production of antiviral proteins, suggesting an important role in antiviral innate immunity[4,10,16]. Of note, calcitriol (the active metabolite of vitamin D, which is also referred to as 1,25-dihydroxyvitamin D3) has been found to induce the transcription of antimicrobial peptides – such as cathelicidin and defensin β2 – in various human cell lines (keratinocytes, myeloid cells, monocytes/macrophages and neutrophils)[17-19]. Accordingly, it has been shown that TLR activation of human macrophages leads to increased expression of VDR and vitamin D-activating enzyme 1α-hydroxylase, resulting in the induction of cathelicidin[20]. In addition, calcitriol promotes differentiation of monocytes/macrophages and enhances their chemotactic and phagocytic capacity[21,22].

Besides being vitamin D targets, immune cells are also local producers of vitamin D[12]. Therefore, vitamin D can act in an autocrine fashion within a local immunological milieu. In fact, several immune cells (macrophages, dendritic cells, T- and B-lymphocytes) have been found to express the vitamin D-activating enzymes 25- and 1α-hydroxylase[23-27], allowing for local conversion of inactive vitamin D precursors into the biologically active form calcitriol[24,28] under specific immune signals (i.e., IFN-γ)[29]. Finally, several *in vitro* studies suggest that vitamin D plays an important role in local "respiratory homeostasis" either by promoting the expression of antimicrobial peptides or by directly affecting the replication of respiratory viruses[16].

Corresponding Author: Andrea Fabbri, MD, Ph.D; e-mail: andrea.fabbri@uniroma2.it

In humans, cross-sectional clinical studies showed that lower serum vitamin D levels are significantly associated with respiratory tract infections[30-32], including epidemic influenza[33]. A British cohort study revealed that the prevalence of respiratory infections displayed a strong seasonal pattern in the opposite direction to the pattern for serum 25-hydroxyvitamin D concentrations[34]. Notably, each 10 nmol/L (4 ng/mL) increase in serum 25-hydroxyvitamin D levels was associated with a 7% lower risk of infection after adjustment for lifestyle, socio-economic factors and adiposity[34]. Interestingly, in a recent Editorial published in The British Medical Journal raising debate on COVID-19 pandemic, different researchers proposed vitamin D deficiency as a putative risk factor, among others, for novel coronavirus infection[35].

Randomized controlled trials evaluating the efficacy of vitamin D supplementation in reducing the risk of respiratory tract infections among children and adults have yielded controversial results[10,36-39]. However, a potential design flaw of the majority of these studies is that the study participants were almost vitamin D-replete at baseline. This could have partly affected the interpretation of the study outcomes, since participants with (severe) vitamin D deficiency at baseline may have represented the subset of subjects receiving the highest beneficial effects from vitamin D supplementation. These remarks are based on the principle of nutrition that individuals who are the most deficient in a given micronutrient – such as vitamin D – are the most likely to respond to its replacement[40]. Interestingly, a meta-analysis published by Martineau et al[41] in The British Medical Journal showed that vitamin D supplementation is safe and effective in preventing acute respiratory infections. More importantly, the authors found that the protective effects of vitamin D were stronger in subjects with a baseline serum 25-hydroxyvitamin D concentration of <25 nmol/L (corresponding to <10 ng/mL, which are serum levels indicative of severe vitamin D deficiency) compared to those with a baseline 25-hydroxyvitamin D concentration of ≥25 nmol/L (≥10 ng/mL)[41]. A subgroup analysis of the same study showed that the protective effects of vitamin D against acute respiratory infections were observed in participants receiving daily or weekly vitamin D without additional bolus doses, but not in participants receiving one or more bolus doses[41]. An explanation for the lack of efficacy of bolus dosing in preventing acute respiratory infections could depend on the fact that this therapeutic approach may lead to wide fluctuations in circulating 25-hydroxyvitamin D levels. In this regard, Vieth[42] proposed that high circulating levels of 25-hydroxyvitamin D following bolus dosing may chronically alter the activity of enzymes involved in the synthesis and degradation of the active vitamin D form calcitriol, thus leading to reduced concentrations of this metabolite in extra-renal tissues.

Another important remark regarding the study design is that randomized controlled trials evaluating the impact of vitamin D supplementation on clinical outcomes should employ a design primarily based on serum 25-hydroxyvitamin D concentrations rather than administered vitamin D doses[43,44]. In fact, serum response to a given dose of vitamin D is highly variable between individuals due to several demographic and biological factors, such as baseline vitamin D status, ethnicity, body fat percentage, use of certain medications, genetics, seasonal variations, time of sun exposure, aging and type of vitamin D supplements[45].

In conclusion, several studies support the immunomodulatory properties of vitamin D and its important role in the maintenance of immune homeostasis. However, well-designed, randomized controlled trials are needed in the future to understand the potential role of vitamin D status in sustaining the protective immune responses against respiratory pathogens and in preventing different types of respiratory tract infections (i.e., upper respiratory tract infections versus lower respiratory tract infections). Also, it will be important to clarify which is the subset of individuals that would potentially receive the highest benefits from vitamin D supplementation. According to the current evidence, we outline the importance of initiating or maintaining vitamin D supplementation (under proper medical supervision) in individuals with hypovitaminosis D, especially in those previously diagnosed with a severe vitamin D deficiency in order to attain a target serum value of 25-hydroxyvitamin D of at least >30 ng/mL. We also believe that maintenance of circulating 25-hydroxyvitamin D levels of 40-60 ng/mL would be optimal, since it has been suggested that concentrations amounting to 40 ng/mL represent the beginning point of the plateau where the synthesis of the active form calcitriol becomes substrate-independent[46,47]. Additionally, serum 25-hydroxyvitamin D levels of approximately ≥40 ng/mL could provide protection against acute viral respiratory infections, as demonstrated in a prospective cohort study published in PLoS One and conducted on 198 healthy adults[48]. To reach these concentrations in adults, a dietary and/or supplemental intake of vitamin D up to 6000 IU/day – deemed to be safe – is required[49,50]. However, elderly subjects, overweight/

obese and diabetic patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism may require even higher doses under medical supervision[50]. Finally, these remarks align well with the current recommendations for prevention and treatment of vitamin D deficiency in relation to skeletal[50] and extraskeletal health[51].

Funding

No funding is declared for this Editorial.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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