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Editorial

Can Raising Vitamin D Status Slow Down Covid-19 Waves?

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Several mitigation and suppression policies such as social distancing, city lockdowns, remote working, testing, providing personal protective equipment and health care resource availability have been implemented by the governments in response to Covid-19 pandemic. Until now (October 23, 2020), over 1.14 million global deaths, including 31,650 in Iran, have been officially attributed to this newly emerged viral disease (1). Multiple variations are reported in clinical symptoms of Covid-19, ranging from a mild common cold to severe symptoms such as acute respiratory distress syndrome (ARDS) and septic shock. Several factors may influence the severity of Covid-19such ascoinfections and comorbidities, as well as genetic and host factors, including race, age and obesity (2). Currently, there is no effective drugs available to cure the disease (3) but three Covid-19 vaccines are now candidates to receive WHO authorization (4). Vitamin D deficiency (VDD) is a serious health problem globally, including the Middle East, with a noticeable attributable disease burden (5, 6). Several studies from Iran have documented high occurrence of VDD and its association with certain health parameters in various population subgroups (7-11). Liver, heart and kidney dysfunctions, granuloma-forming disorders, gastrointestinal diseases, reduced exposures to ultraviolet B (UVB) radiation, hyper and hypoparathyroidisms, pregnancy, respiratory diseases, genetic variations of genes and many other factors may lead to vitamin D deficiency (12, 13).

Vitamin D deficiency is associated with several chronic diseases, such as viral acute respiratory infections (ARI), metabolic bone disorders, autoimmune disorders, anemia, diabetes, cardiovascular disease, metabolic syndrome, increased rate of infection and cancers (11, 14, 15). Status of vitamin D is one of the factors influencing the risks of Covid-19 mortality(16). This vitamin, as a pluripotent steroid hormone, is responsible for the regulation of calcium and phosphate levels in circulation as well as modulation of innate and adaptive immunities (17). As a fundamental feature in their normal development, antigen-presenting cells synthetize the active form of vitamin D by CYP27B1 enzyme. Therefore, vitamin D deficiency leads to modulation of immune responses (18). The 1,α,25-dihydroxyergocalciferol (ercalcitriol), as the physiological activated form of vitamin D, can strengthen immunity via regulation of cathelicidin antimicrobial peptide (CAMP) and defensin β-4 (DEFB4) genes in normal and transformed cells to combat pathogenic infections (19).

The viral respiratory tract infections such as common cold and influenza are the major seasonal outbreaks and evidences suggest that vitamin D may be useful in prevention and treatment of these viral diseases through different pathways (20). Vitamin D supresses inflammation by limiting excessive production of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ), interleukin 6 (IL-6) and IL-12. These mediators can crucially contribute in the clinical outcomes of acutely ill ventilated Covid-19 patients (21). Moreover, vitamin D can have an important roles in immune defence of respiratory system by enhancing recruitment of phagocytes and upregulating antimicrobial peptides such as cathelicidin and β-defensin. Vitamin D may also interfere with viral replication (22). The vitamin D receptor (VDR) is involved in antiviral activity of vitamin D (23). Vitamin D deficiency is prevalent in patients with ARDS. In a Korean study, 95.4% of ARDS patients had vitamin D deficiency (24). Studies have shown that VDD is associated with increased mortality in pneumonia. As reported from nearly 21,000 patients, circulating 25-hydroxycalciferol(25(OH)D) below 20 ng/mL increases the risk of community acquired pneumonia up to 64% (25).

An investigation on 25(OH)D concentrations in the PCR-positive and negative Covid-19 Swiss subjects revealed lower 25(OH)D concentrations in PCR-negative, as compared to PCR-positive , subjects (11.1 vs. 24.6 ng/mL) (26). Overall deaths during the influenza pandemic have shown that doses of UVB and vitamin D are inversely associated with case fatality rates (27). As previously reported, vitamin D can suppress dipeptidyl peptidase IV (DPP IV) adenosine deaminase binding protein (ADAbp), which is a putative adhesion molecule for S1 domain of Covid-19 spike (S) glycoprotein (28). Thus, VDD increases expression of DPP-IV CD26 receptor (29). Though Iran is

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a sunny country in its most areas, VDD is prevalent in almost all provinces with higher rate in women probably due to their full body coverage (8, 9, 30). During recent city lockdowns for Covid-19, outdoor activities inevitably decreased, which might adversely affect vitamin D status of the citizens. However, unpublished reports have shown increased uses of nutritional supplements, including vitamin D. Additionally, scientific bodies released guideline for vitamin D supplementation during Covid-19 pandemic (31). Fortification studies motivated industries to produce D-fortified products including dairies, juices and edible oils (32, 33). Nevertheless, we have a dim idea of the vitamin D status of the population and its subgroups in Iran following these events. On the other hand, the reported mortality rates due to Covid-19 in Iran is noticeable with being male, having underlying diseases, older age, higher body mass index, lymphopenia, hypomagnesemia and raised C-reactive protein (CRP) and/or creatinine levels on admission as the main risk factors (34, 35).

Recent evidence suggests that VDD may also contribute to Covid-19 mortality (36). Even D fortification of foodstuffs such as bread and milk has been proposed as a strategy to fight Covid-19 (37). However, mass fortification programs, despite having many advantages including broad population coverage, needs several infrastructures and preliminary studies which are inevitably time taking. Supplementation, on the other hand, is rather fast acting though may not be sustainable. Therefore, to resist Covid-19, it is recommended to Iranian health care workers, vulnerable groups and those with suboptimal concentrations of circulating 25(OH)D to be supplemented with 20–50 µg/day of vitamin D (21). The circulating 25(OH)D should be in optimal level of 75–125 nmol/L (38). There must be little fear of vitamin D intoxication in this strategy as this is rather rare due to very high capacity of human body to store this vitamin and also very unusual high doses needed to induce intoxication (39). Supplement labels must be quite clear and comprehensive to prevent adverse effects of vitamin D overdosing, including hypercalcemia. In addition to social distancing, new policies on shifting public attention to strengthening immunity should be made by health stakeholders. Timely dissemination of clear information on links between vitamin D status and severity of Covid-19 can play important roles in precise evaluation of the effectiveness of vitamin D supplementation.

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