

# Do Hemodialysis Patients Need Immune Boosting with Vitamin, Mineral, and Probiotic Supplementation during COVID-19 Pandemic?

Özkan Güngör<sup>1</sup> , Sena Ulu<sup>2</sup> , Nuri Barış Hasbal<sup>3</sup> , Engin Onan<sup>4</sup> , Didem Turgut<sup>5</sup> , Mustafa Arıcı<sup>6</sup> 

<sup>1</sup>Department of Nephrology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

<sup>2</sup>Department of Internal Medicine and Nephrology, Bahcesehir University School of Medicine, Istanbul, Turkey

<sup>3</sup>Department of Nephrology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

<sup>4</sup>Department of Nephrology, Adana City Hospital, Adana, Turkey

<sup>5</sup>Department of Nephrology, Baskent University School of Medicine, Ankara, Turkey

<sup>6</sup>Department of Nephrology, Hacettepe University School of Medicine, Ankara, Turkey

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) has been accepted as a global pandemic, and poses a greater risk to the elderly and those with comorbidities. Comorbid diseases (particularly end-stage kidney disease with hemodialysis) and impaired immunity place patients in the high-risk group for COVID-19. In recent studies, it was also mentioned that exaggerated inflammation and a cytokine storm were the underlying causes related to the high mortality in COVID-19 patients. Currently, treatment modalities to balance the immune system of such vulnerable patient groups are essential, to protect them from the disease. Several vitamins (like vitamins C, D, and E), trace elements like zinc, and probiotics have been proposed as immune boosters to protect and combat infectious conditions. It is well known that these vitamins and elements are insufficient in hemodialysis patients. In this review, we aimed to evaluate the immune-boosting mechanisms of vitamins C, D, E, zinc, and probiotics, the studies related to their beneficial effects against infections, and their possible benefits for hemodialysis patients during the COVID-19 pandemic.

**Keywords:** Coronavirus 19, hemodialysis, infection, vitamin, zinc, probiotic

**Corresponding author:** Özkan Güngör ✉ ozkangungor@yahoo.com.tr

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). It was first discovered in Wuhan, China, in December 2019, and has spread worldwide, with the number of patients crossing 204.3 million and the number of deaths >4.3 million. People with underlying diseases are at a high risk for both morbidity and mortality. Hemodialysis (HD) patients have various risk factors for COVID-19 and its complications.<sup>1</sup> The functional abnormality of monocytes, neutrophils, and dendritic cells (DC), and the impaired maturation and altered functions of T lymphocytes are well-known immunological alterations in HD patients.<sup>2</sup>

Clinical data suggest that critically ill patients with COVID-19 had exaggerated immune response with high cytokine release, known as a cytokine storm.<sup>3</sup> Treatment options include steroids or cytokine inhibitors, which are used to dampen this immune response and may act broadly on the immune system at the time of viral infection, in addition to the body's own defense. At this point, supportive therapies with immune-boosting action may be helpful to modulate the immune system. Several vitamins (namely, vitamins C, D, and E), trace elements like zinc, or probiotics may enhance the immune system and are generally included in supportive therapies as supplements.<sup>4</sup> The European Society of Clinical Nutrition and Metabolism (ESPEN) 2020 guidelines recently suggested that nutritional support is required for patients



with high COVID-19 risk (e.g., patients at an advanced age, or with many comorbidities), and for patients who cannot take vitamins and minerals orally or those with dietary restrictions, who are at risk for the disease or face a poor prognosis during the disease course.<sup>5</sup>

In this review article, we summarize the need for vitamin and mineral supplementations for preventive and treatment purposes in hemodialysis patients during the COVID-19 pandemic. We aim to attract the attention of physicians and nephrologists so that they do not disregard any positive contribution of supplementation therapies in this high-risk patient population. We summarize the general properties of vitamin C, vitamin D, vitamin E, zinc, and probiotics as supplementation therapies, which would work for hemodialysis patients in infectious conditions. We conclude with some dosage recommendations under the previous data about hemodialysis patients with infections other than the COVID-19.

### VITAMIN C

Vitamin C, known as ascorbic acid, is an essential micronutrient for humans. Epidemiological data show that hypovitaminosis C (plasma vitamin C <23 µmol/L) is common in Western populations and the deficiency of vitamin C (<10 µmol/L) is related to severe multiorgan problems.<sup>6</sup>

#### Vitamin C and the Immune System

Vitamin C contributes to the immune system by supporting epithelial barrier function, enhancing phagocytosis (via neutrophils and macrophages), sustaining T and B-lymphocyte functions, and altering inflammatory mediators.<sup>7</sup> It accumulates in leukocytes, mainly in neutrophils and monocytes, to 50-100 times higher than plasma concentrations. This accumulation is supposed to be protective against oxidative damage of the neutrophils. In earlier studies, it was demonstrated that people with severe infections have impaired leukocyte chemotaxis, and vitamin C replacement improved infection control due to this function.<sup>8</sup> Vitamin C also enhances differentiation and proliferation of B cells and T cells. Anderson et al. reported that vitamin C treatment improves lymphocyte transformation and T lymphocyte proliferation.<sup>9</sup> It was shown that a deficiency of vitamin C triggers oxidative stress (OS), and the OS parameters could be controlled with replacement therapy. The effects of vitamin C on the immune system are summarized in Table 1.

#### Vitamin C and Infection

An important finding regarding vitamin C is that its deficiency makes the respiratory tract particularly susceptible to infections. In a study related to acute viral respiratory tract infections, plasma levels of vitamin C were found to be low in the study group compared to the healthy control group.<sup>10</sup> According to the Cochrane data (2013), it was concluded that vitamin C deficiency was related to pneumonia and a greater risk of severe infection. Vitamin C replacement corrects the severity of lower respiratory symptoms in the affected patients.<sup>11</sup> In SARS disease, which was

**Table 1.** The Effects of Vitamin C on the Immune System

Immune System	Function of Vitamin C
Epithelial barriers	Enhances collagen synthesis and stabilization
	Protects against ROS-induced damage
Neutrophils-macrophages	Enhances fibroblast proliferation and migration
	Enhances chemotaxis and phagocytosis
B and T lymphocytes	Enhances microbial killing
	Enhances differentiation and proliferation
	Enhances antibody levels

the first presentation of coronavirus, the authors have argued that although vitamin C supplements may be beneficial, no studies on the subject have offered proof.<sup>12</sup> Hemila et al. showed that prophylactic vitamin C supplementation decreased the risk of pneumonia by 80% in elderly patients.<sup>13</sup> In studies related to COVID-19 patients, a significant reduction in mortality rate was obtained in the group with short-term and high-dose vitamin C replacement, compared to other treatments.<sup>14</sup>

#### Vitamin C and Dialysis Patients

Vitamin C deficiency is an expected finding in HD patients. The potassium-restricted diet and HD are mainly responsible for this deficiency. A single dialysis session may even reduce serum vitamin C levels by 30% to 40% (with 80-240 mg loss). Vitamin C supplementation after each dialysis (3 times a week, 500 mg) is sufficient to maintain vitamin C levels in these patients.<sup>15</sup> In a study related to stable HD patients, daily oral vitamin C supplementation (250 mg) significantly reduced plasma OS biomarkers.<sup>16</sup> As a contrary comment, Coombes and Fascet, reviewing 56 clinical studies, stated that vitamin C deficiency is common in dialysis patients, but vitamin C supplements are not essential to control OS.<sup>17</sup> Under the related data, we conclude that supportive therapy with vitamin C in HD patients might be kept in mind during the COVID-19 pandemic for which no treatment is evident yet.

#### Vitamin C Replacement Dose in HD Patients

It was recommended that oral vitamin C doses in the range of 100-200 mg/day or intravenous administration of 300-500 mg 3 times a week at the end of dialysis sessions are sufficient and safe dosages. As the previous studies have emphasized, 1 g/h vitamin C at the beginning of symptoms for 6 hours, followed by 3 × 1 g/day, would be appropriate in dialysis patients.<sup>18</sup>

### VITAMIN D

Vitamin D is a fat-soluble steroid hormone and is available in 2 forms, D2 and D3.<sup>19</sup> Vitamin D deficiency is associated with many diseases, such as diabetes, cancer, and cardiovascular and immune system disorders, besides musculoskeletal abnormalities.<sup>20</sup>

### Vitamin D and the Immune System

Vitamin D [1, 25 (OH) 2 D<sub>3</sub>] can modulate both innate and adaptive immune responses, acting as an immunomodulator.<sup>21</sup> The vitamin D receptor is expressed on many immune cells, such as macrophages, neutrophils, DCs, and T lymphocytes. These cells can synthesize the active vitamin D metabolite during inflammatory conditions, controlling local response.<sup>22</sup> Vitamin D also enhances chemotaxis, phagocytosis, and macrophage differentiation, and inhibits Th1 and Th17 differentiation (Figure 1). Vitamin D plays an important role in T cell immune responses by reducing the overstimulation of CD8<sup>+</sup> cytotoxic T cells and regulating the release of proinflammatory cytokines such as interleukin (IL) IL-17A, IL-17F.<sup>23</sup>

### Vitamin D and Infection

Vitamin D limits the production of proinflammatory cytokines like TNF- $\alpha$  and IL-12, leading to suppression of excessive inflammation.<sup>24</sup> It also regulates antimicrobial peptides like cathelicidin and  $\beta$ -defensin, which play a major role in respiratory system immune defense by controlling overactive immune response and reducing cytokine release.<sup>25,26</sup>

In a study with the elderly population, Aloia et al. showed that patients treated with vitamin D had a lower rate of influenza infection during the influenza epidemic.<sup>27</sup> In a meta-analysis of 13 randomized controlled trials related to epidemic diseases (7 related to viral infections), vitamin D supplementation reduced the symptoms and the severity of disease course. Adequate vitamin D levels were recommended for an adequate immune response.<sup>28</sup>

The COVID-19 infection is associated with increased production of proinflammatory cytokines, imbalanced regulation of CD4<sup>+</sup>T cells and CD8<sup>+</sup>T cells, and increased serum IL-6 levels. Such immunomodulatory defects in COVID-19 patients may be a target for vitamin D supplementation, to ameliorate disease

course. Greiller and Mirzavandi reported that vitamin D replacement in COVID-19 patients caused a decrease in CRP and IL-6 levels and an improvement in the patients' clinical symptoms.<sup>29,30</sup>

### Vitamin D and Dialysis Patients

Regular vitamin D replacement is recommended for all dialysis patients for bone mineral metabolism and for its potential T cell immunomodulatory effect.<sup>31</sup> In a meta-analysis evaluating 11 studies (n = 92309), vitamin D supplementation was found to be associated with a low (41%) composite infection risk (any infection, infection-required hospitalization, or infection-related death) in HD patients.<sup>32</sup> Based on the data above, we recommend that nephrologists aim to optimize vitamin D levels of HD patients during this uncontrolled COVID-19 pandemic.

### Vitamin D Replacement Dose in Hemodialysis Patients

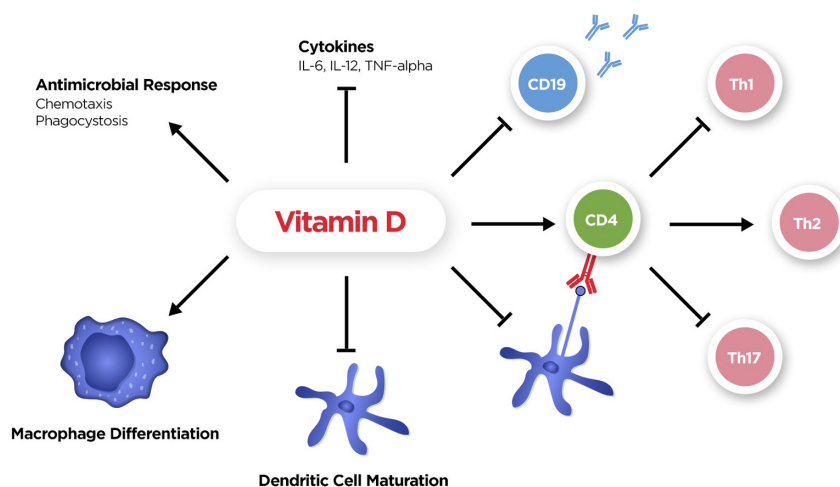
Hemodialysis patients may take 10 000 IU/day of vitamin D<sub>3</sub> supplementation for a few weeks to rapidly increase 25(OH)D concentrations and reduce the risk of infection during the COVID-19 pandemic. They may then continue to follow usage with 5000 IU as a daily dose. The target level of 25(OH)D concentrations should be raised above 40-60 ng/mL (100-150 nmol/L). It should be kept in mind that HD patients are more prone to hypercalcemia and hyperphosphatemia than the general population. Monitoring these electrolytes is crucial.

### VITAMIN E

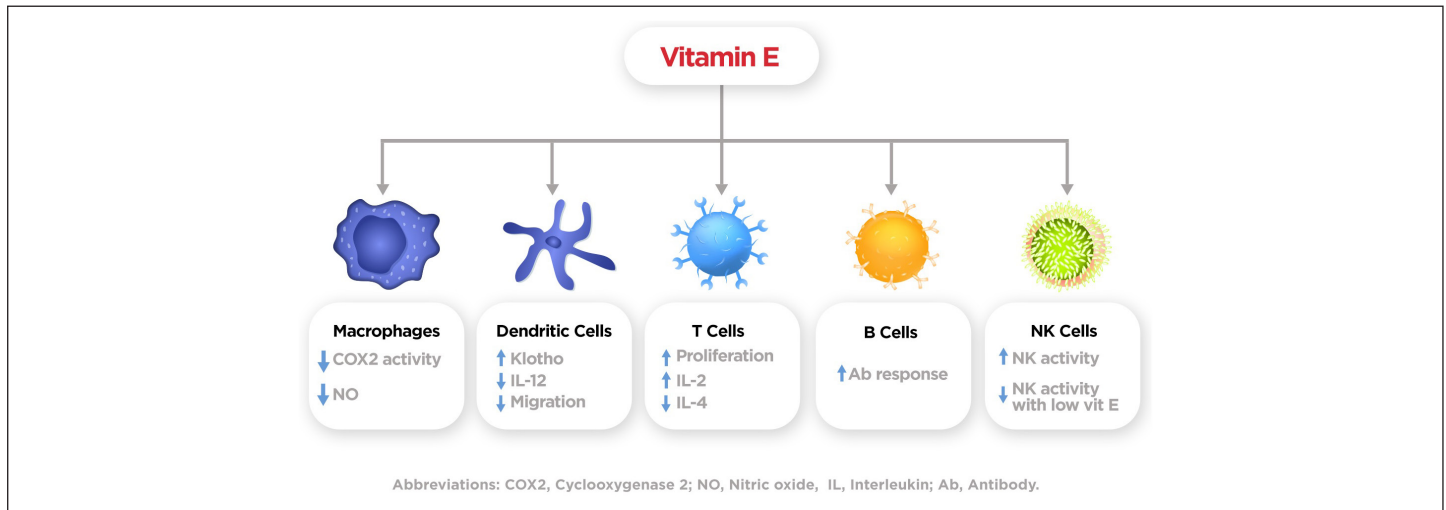
Vitamin E is a collective term for tocopherols and tocotrienols found in foods. In humans, the requirement is met by  $\alpha$ -tocopherol. Vitamin E, which is attached to the cell membrane, plays an important role in complex cell-cell interactions that trigger and regulate immune responses.<sup>33</sup>

### Vitamin E and the Immune System

Vitamin E works as an antioxidant, protecting cell membranes from oxidation and regulating the production of reactive



**Figure 1.** The effect of vitamin D on the immune system.



**Figure 2.** Immunomodulatory effects of vitamin E on the immune cells.

oxygen species (ROS). It reduces ROS production through phosphorylation of NADPH oxidase and protein kinase C (PKC).<sup>34</sup> Vitamin E supplementation increases lymphocyte proliferation, serum immunoglobulin levels, natural killer (NK) cell activity, and IL-2 production. Vitamin E also contributes to the release of different types of cytokines, increases antibody and prostaglandin secretion, and regulates NK cells and T cells (Figure 2).<sup>35</sup> It was reported that vitamin E supplementation was related to increased macrophage and NK activity and high Th1 response during the influenza virus infection.<sup>36</sup>

### Vitamin E and Infection

It was shown that  $\alpha$ -tocopherol decreased alveolar endothelial/epithelial paracellular permeability, and improved clinical symptoms, with decreased mortality in the setting of pneumonia. In another study with 2216 patients (composed of smokers and elderly individuals), the incidence of pneumonia was decreased by 69% with vitamin E supplements.<sup>37</sup> In an experimental model with influenza-infected mice, IFN- $\gamma$  production and viral titer in the lung tissue were shown to be decreased with vitamin E supplementation.<sup>36</sup>

### Vitamin E and Dialysis Patients

Patients with dialysis have mild vitamin E deficiency. High vitamin E intake may be recommended in dialysis patients because of its antioxidative and anti-inflammatory properties. Beyond oral supplementation, the use of vitamin-E-coated membranes also has beneficial antioxidant effects with similar mechanisms.<sup>38</sup> Vitamin E appears to be a rational treatment, and should be kept in mind as a prophylactic option, especially in dialysis patients with COVID-19.

### Vitamin E Replacement Dose in Hemodialysis Patients

It may be recommended to take any of the forms available in the market (alpha-tocopheryl acetate or succinate) once a day, with the dose of 10-15 mg for men and 8-10 mg for women, with no need for dose adjustment in dialysis patients.

### ZINC

Although zinc has been known as one of the basic elements for the development of plants and animals for a long time, it was accepted as an essential element for humans only in the 1960s. An adult human body contains an average of 2-3 g of zinc, and 60% of it is in the muscle. For adults, 8-15 mg of a daily dose of zinc intake is recommended. Zinc deficiency is observed in approximately one-third of the world population.<sup>39</sup>

### Zinc and the Immune System

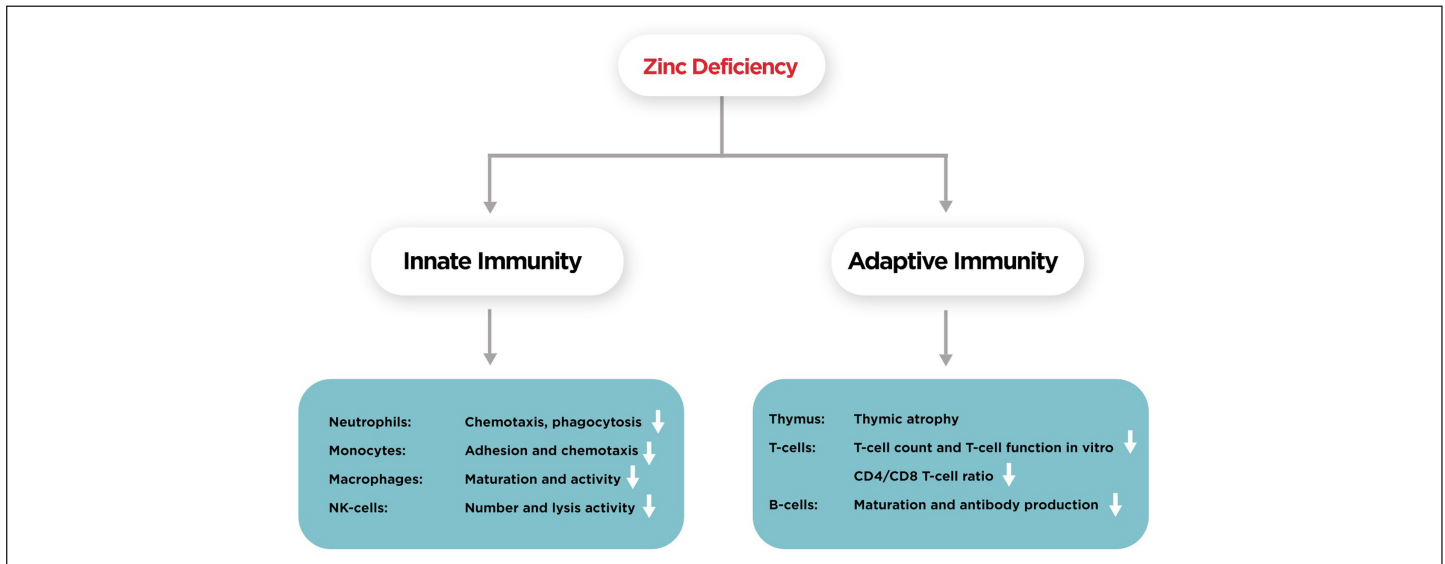
Zinc is a trace element affecting the stabilization of the immune system in a narrow therapeutic serum range. In vivo studies have shown that the activity of NK cells, phagocytic functions of neutrophils and macrophages, and control of oxidative damage were affected by low zinc serum levels.<sup>40</sup> Serum zinc level is also important for the regulation of T cell activation, proliferation, and apoptosis. Significant antioxidant effects of zinc are also proven. The effect of zinc on the immune system is summarized in Figure 3.

### Zinc and Infections

Many studies have shown the benefits of zinc supplementation on infectious diseases such as diarrhea, acute lower respiratory tract infections, and measles. Yakoob et al. concluded that prophylactic zinc supplementation reduced pneumonia development by 19%, and pneumonia-related mortality by 15%.<sup>41</sup> The Zinc Investigators' Collaborative Group carried out an analysis of 4 randomized controlled studies on zinc supplementation during pneumonia. In the group treated with zinc, there was a 41% reduction in the incidence of pneumonia.<sup>42</sup> Wang et al. found that zinc, given in addition to treatment, is effective in reducing the mortality in patients with severe pneumonia.<sup>43</sup>

### Zinc and Dialysis Patients

It is a fact that 40-78% of individuals with chronic kidney disease (CKD) have low serum zinc levels. In HD patients, decreased CD3 and CD4 T lymphocyte levels were found along with zinc



**Figure 3.** The effect of zinc on the immune system.

deficiency. Skarupskiene et al. revealed that HD patients with zinc deficiency had more infectious complications.<sup>44</sup> In an observational prospective study in which patients were followed over 2 years, each 1 mg/dL decrease in serum zinc level was associated with a 2% increase in infection-related hospitalization and a 2.8% mortality of infection in HD patients.<sup>45</sup> It is rational to speculate that zinc replacement would be beneficial during the COVID-19 pandemic in HD patients, who are significantly prone to severe courses of infection.

#### Zinc Replacement Dose in Hemodialysis Patients

As prophylactic zinc supplementation, a 15-30 mg/day dosage was considered as sufficient for adults. For dialysis patients, doses of 25-35 mg/day were generally used. We suggest a 30 mg/day zinc supplementation for these patients.

#### PROBIOTICS

Microbiota, the microbial community in the large intestine, is considered a symbiotic “additional organ.” Probiotics are living supplements that work by improving microbial balance.

#### Probiotics and the Immune System

Probiotics play a key role in the development of proinflammatory cytokines and chemokines. They are involved in many immune system modifications, such as increasing mucosal antibody production, phagocytosis and the activity of NK cells, and inducing T cell apoptosis. Probiotics increase the production of intestinal anti-inflammatory cytokines such as IL-10 and TGF- $\beta$ , and reduce the production of proinflammatory cytokines such as TNF- $\alpha$ , FN- $\gamma$ , and IL-8. They also inhibit the nuclear factor kappa-B (NFkB) pathway.<sup>46</sup> Probiotics control CD4/CD8 regulator T cell activation. Some probiotic agents have toll-like receptor (TLR)-specific immune-stimulating effects and regulate epithelial barrier function by affecting TLR-2.<sup>47</sup>

#### Probiotics and Infection

It was recently shown that probiotics play a significant role in patients’ immune systems, disease-related mortality, and morbidity.<sup>48</sup> In an experimental study with influenza-infected mice, oral supplementation of probiotics decreased virus titers and inflammatory markers in the lower respiratory tract. Improved clinical symptoms and decreased mortality were also established. A significant increase in NK cell activities in lung cell and spleen, and over-expression of NK cell activators such as IFN- $\gamma$ , IL-2, IL-12, and IL-18 were also documented.<sup>49</sup> Several studies have shown that probiotic use can protect against viral infections like influenza and decrease viral replication.<sup>50,51</sup>

#### Probiotics and Dialysis Patients

Patients with CKD have dysbiosis (disruption of microbiota balance). Uremic rats have been shown to have fewer probiotic strains.<sup>52</sup> Impaired kidney functions, in turn, worsen the condition of dysbiosis and alter the integrity of the intestinal barrier, causing impaired colonic epithelial tightness and increased intestinal permeability. It all ends with bacterial translocation, which is responsible for endotoxemia and inflammation.<sup>52,53</sup>

#### Probiotic Use in Hemodialysis Patients

It may be recommended to take any of the probiotic forms available in the market, once a day, with no need for dose adjustment in dialysis patients.

In conclusion, HD patients are under significant risk for the COVID-19 infection and its alarming outcomes, because of their accompanying clinical problems, higher ages, and already defective immune systems. Diet restrictions and the inability to exercise properly entrap this patient group in their weak condition. As always, our priority is to provide adequate and



effective dialysis even during the pandemic. In this review, we summarized the benefits of vitamin C, vitamin D, vitamin E, zinc, and probiotics as immune-boosting supplements. We tried to explain the increased requirement of related agents in HD patients, with their savior effects during viral infections. Although insufficient data exist, recent evidences indicate that supplementation with multiple micronutrients and probiotics can modulate immune function for overcoming COVID-19 and its severe course. As the COVID-19 pandemic appears prolonged, nephrologists should be alerted to strengthen the dialysis patients with immune-boosting supplements that are known to be harmless but supportive.

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