Dietary Supplements on Inflammatory Markers and SARS-CoV-2 Infection

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A key characteristic of severe presentations of acute SARS-CoV-2 infection involves overactive host inflammatory responses, with a substantial proportion of severe outcomes such as hospitalizations and deaths from COVID-19 linked to hyper-inflammation. Inflammation and oxidative stress play pivotal roles in the progression of infectious diseases including COVID-19. Evidence suggests that high sensitivity (hs) C-reactive protein (CRP), interleukin (IL)-6, and matrix metalloproteinases (MMPs) are among the most important biomarkers of COVID-19 severity, similar to the chronic conditions involved in vascular aging. Lactate dehydrogenase (LDH) and hsCRP are also biomarkers of respiratory failure in patients with COVID-19. Furthermore, it is well established that elevated levels of other inflammatory markers are common in COVID-19 patients. These markers include IL-1β, IL-7, IL-8, IL-18, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, procalcitonin (PCT), serum ferritin, and erythrocyte sedimentation rate (ESR).

SARS-CoV-2 dietary supplements COVID-19 inflammation vitamin D probiotics quercetin

1. Vitamins and Minerals

Supplementation with vitamins such as A, B, C, D, and E is thought to play a significant role in the severity of COVID-19 infection by reducing inflammation, time to recovery, and preventing lung fibrosis [1][2]. To authors' knowledge, no RCTs have tested the effects of supplementation with vitamin A, B, or C alone, on COVID-19 severity; however, in a 7-day randomized placebo-controlled trial of 60 COVID-19 patients admitted to intensive care unit (ICU), those who received a combination of vitamins A (25,000 IU daily), D (600,000 IU; one dose), E (300 IU twice daily), C (500 mg four times daily), and a B-complex ampule (daily), demonstrated significant reductions in the duration of hospitalization, TNF-α, Il-6, erythrocyte sedimentation and hs-CRP, but not IFN-γ, as compared to a placebo [3]. In contrast, 10-days of standard treatment plus high doses of vitamin C (2 g), Melatonin (6 mg), and Zinc (50 mg), was not effective for lowering inflammatory markers or length of hospitalization in 20 patients with severe COVID-19 [4].

Accumulating data highlight the immunomodulatory role of vitamin D, and link hypovitaminosis D (25 OHD ≤ 20 ng/mL) with hyperinflammation (i.e., the so-called “cytokine storm”) and elevated risk of mortality in patients with COVID-19 [5][6][7][8]. Therefore, supplementation with vitamin D is suggested to attenuate the risk of the cytokine storm, and the severity of COVID-19 [5][9]. The impact of vitamin D on inflammatory markers and in response to

SARS-CoV-2 infection has been explored in several RCTs (see **Table 1**). The current state of evidence from RCTs indicates that higher doses of daily intake of vitamin D can reduce the levels of inflammatory markers like IL-6, hsCRP, and time to recovery in COVID-19 patients [10][11]. Ten days of supplementation with 60,000 IU/day of vitamin D in combination with standard treatment significantly reduced IL-6, hsCRP, LDH, ferritin, and Neutrophil/Lymphocyte ratio, in 87 hospitalized COVID-19 patients with vitamin D deficiency (D < 30 ng/m) as compared with the controls, who received standard treatment for 8 to 10 days [11]. Similarly, in a 2-week trial, oral intakes of two different doses of vitamin D3 (5000 IU vs. 1000 IU) resulted in significant decreases in plasma IL-6 versus baseline, with no between group differences, while hsCRP levels remained unchanged in both groups [10]. Furthermore, time required for resolving cough symptoms with D3 supplementation (5000 IU) was significantly shorter compared to the comparison group [10]. Rastogi et al. investigated the effects of high-dose vitamin D supplementation (60,000 IU) as compared with control in 40 SARS-CoV-2 RNA positive individuals. Patients with vitamin D deficiency (25(OH) D < 20 ng/mL) who were positive for SARS-CoV-2 RNA, with mild or no symptoms, significantly improved with regard to viral SARS-CoV-2 RNA clearance (62.5% vs. 20.8%) and fibrinogen levels [12]. In contrast, a single dose of vitamin D was ineffective for lowering inflammatory markers and for the treatment of patients with severe COVID-19 [13][14][15].

Evidence for the potential role of zinc supplementation for COVID-19 infection is inconclusive [16][17][18]; with only one 28-day RCT of 191 patients with COVID-19 having investigated the effects of zinc supplementation (50 mg of zinc twice daily) combined with chloroquine/hydroxychloroquine (CQ/HCQ) on inflammatory markers. The study results indicated no significant changes in hs-CRP levels or clinical recovery time [19].

Table 1. Summary of Randomized controlled trials (RCTs) on the impact of dietary supplements on inflammatory markers and in response to SARS-CoV-2.

Authors/Year/Country	Duration	Participants	Study Design	TNF-α	IL-1β	IL-4	IL-6	IL-10	CRP	IFN-γ	Other Outcomes
Rastogi et al., 2020 [12] India	7-d	40 SARS-CoV-2 RNA positive individuals	RCT: 1.Daily oral cholecalciferol (60,000 IU) with therapeutic target 25(OH)D > 50 ng/mL 2. Control	-	-	-	-	-	Ø	-	↓ † Fibrinogen ↑ † Negative conversion of SARS-CoV-2 RNA (62.5% vs. 20.8%)
Murai et al., 2021 [15] Brazil	-	237 patients hospitalized for moderate to severe COVID-19	RCT: 1.A single oral dose of 200,000 IU of vit. D3 2. Placebo	-	-	-	-	-	Ø	-	Ø Same LOS (median of 7.0 vs. 7.0 days)
Lakkireddy et al., 2021 [11]	8–10-d	87 Patients hospitalized	RCT: 1. 60,000 IU/day of	-	-	-	1. ↓		1. ↓ *†	-	↓ *† LDH, ferritin, N/L

Authors/Year/Country	Duration	Participants	Study Design	TNF-α	IL-1β	IL-4	IL-6	IL-10	CRP	IFN-γ	Other Outcomes
India		for COVID-19 Vit. D < 30 ng/m	oral vitamin D +standard treatment 2. Only standard treatment				† 2. Ø		2. ↓ *		ratio
Beigmohammadi et al., 2021 [3] Iran	7-d	60 ICU-admitted COVID-19 patients	RCT: 1. Oral Vit. A (25,000 IU) daily, vit.D (600,000 IU; one dose), vit. E (300 IU twice daily), vit. C (500 mg four times daily), and one amp daily of B complex 2. Placebo	1. ↓ *† 2. ↓ *	-	-	1. ↓ *† 2. ↓ *	-	1. ↓ *† 2. ↓ *	1. ↓ * 2. ↓ *	↓ † Hospitalization rate and ESR in treatment group
Sabico et al., 2021 [10] Saudi Arabia	14-d	69 patients COVID-19 and sub-optimal vit. D status	RCT: 1.Oral vit. D3 (5000 IU) 2.Oral vit. D3 (1000 IU)	-	-	-	1. ↓ * 2. ↓ *	-	1. Ø 2. Ø	-	↓ † Time to recovery in resolving cough with D3 (5000 IU) vs. D3 (1000 IU)
Abd-Elsalam et al., 2021 [19] Egypt	4 weeks	191 patients with COVID-19	RCT: 1.CQ/HCQ + 220 mg of zinc sulfate twice daily 2. HCQ only	-	-	-	-	-	Ø	-	Ø Clinical efficacy of HCQ
Di Pierro et al., 2021 [20] Italy	2 weeks	42 COVID-19 outpatients	RCT: 1. Quercetin (500 mg/day (first week) and of 1000 mg/day (second week) 2. Standard of care	-	-	-	-	-	Ø	-	↓ † LOS, virus clearance, symptoms frequency, LDH, ferritin
Doae et al., 2021 [21] Iran	2 weeks	128 critically ill COVID-19 patients	RCT: 1. 1000 mg omega-3 daily (400 mg EPAs and 200 mg DHAs) 2. Control	-	-	-	-	-	-	-	↑ † 1-month survival rate, pH, HCO_3, and Be ↓ † Levels of BUN, Cr, and K in the treatment group

Authors/Year/Country	Duration	Participants	Study Design	TNF-α	IL-1β	IL-4	IL-6	IL-10	CRP	IFN-γ	Other Outcomes
Darban et al., 2021 [4] Iran	10-d	20 patients with severe COVID-19	Pilot RCT: 1. Standard care + oral zinc sulfate (220 mg containing 50 mg zinc) , oral melatonin (6 mg, q6hr), and intravenous vit. C (2 g) 2. Standard care alone	-	-	-	-	-	1. ↓ * 2. ↓ *	-	Ø LOS
Sedighian et al., 2021 [22] Iran	2 weeks	30 patients with COVID-19	Single blind RCT: 1. Hydroxychloroquine + 2 g DHAs and EPAs 2. Hydroxychloroquine	-	-	-	-	-	1. ↓ †	-	† Body pain and fatigue in the treatment group Ø Olfactory
Cannata-Andía et al., 2022 [14] Spain	-	543 patients with moderate to severe COVID-19	RCT: 1. A single-oral bolus of 100,000 IU of cholecalciferol 2. Control	-	-	-	Ø	-	Ø	-	Ø Hospitalization rate and death
Shohan et al., 2022 [23] Iran	7-d	60 patients with severe COVID-19	RCT: 1. Quercetin (1000 mg daily) + antiviral drugs 2. Antiviral drugs	↓ *	↓ *	-	↓ †	-	↓ †	-	↓ † ALP, LDH Ø Mortality, duration of ICU-admission
Pimentel et al., 2022 [24] Brazil	7-d	43 adult patients with COVID-19	RCT: 1. Two 200 mL units of high-protein nutritional supplement (arginine, omega-3 fatty acids and nucleotides) over 24 h 2. Two 200 mL units of high-protein nutritional supplement alone	-	-	-	-	-	1. ↓ † 2. Ø	-	↑ Lymphocytes in the treatment group ↓ Lymphocytes in the control group
Fernandes et al., 2022 [13]	-	200 patients	RCT: 1. Single oral dose	Ø	Ø	Ø	Ø	Ø	-	Ø	-

baseline
α: tumor
nterferon
gamma; CQ/HCQ:Chloroquine/hydroxychloroquine; HCQ: Hydroxychloroquine; ALP: Alkaline phosphatase; Lactate dehydrogenase; Be: Base excess; BUN: Blood urea nitrogen; Cr: creatinine; LOS: Length of hospital stay; LDH: Lactate dehydrogenase; N/L ratio: Neutrophil/Lymphocyte ratio; ESR: Erythrocyte sedimentation rate; DHA: Docosahexaenoic acid; EPA: eicosapentaenoic acid.

2. n-3 Polyunsaturated Fatty Acids (PUFAs)

Authors/Year/Country	Duration	Participants	Study Design	TNF-α	IL-1β	IL-4	IL-6	IL-10	CRP	IFN-γ	Other Outcomes
Brazil	[26][27][28]	with moderate to severe COVID-19	of vit. D_3 (200 000 IU) 2. Placebo								
Gutiérrez-Castrellón et al., 2022 [25] Spain	[21][22][24] [21] 30-d	293 COVID-19 outpatients	RCT: 1. Probiotic (Lactiplantibacillus plantarum stains KABP022, KABP023 and KABP033 = Pediococcus acidilactici strain KABP021) 2. Placebo	-	-	- [22]	-	-	1. ↓ † hs-CRP Only on day 15	-	↓ † Complete remission (53.1% in probiotic group vs. 28.1% in placebo; $p < 0.001$)

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with n-3
ents with
OVID-19
HAs) for
ompared
function
OHA and
fatigue
a 7-day
arginine,

omega-3 fatty acids, and nucleotides (Two 200 mL units over 24 h), indicated meaningful reductions in hs-CRP when compared with the patients who were given only high-protein nutritional supplements (Two 200 mL units) [24].

3. Quercetin

Quercetin—a polyphenol with antioxidant and anti-inflammatory properties—is widely known to have favorable effects on inflammation and infection [29][30][31]. Di Pierro et al. reported that in 42 outpatients with COVID-19, two weeks of quercetin therapy (500–1000 mg daily) significantly diminished the rate (−68.2%) and length (−76.8%) of hospitalization, the need for non-invasive oxygen therapy (−93.3%), and the mortality rate (although events were very limited: none vs. 3 people) compared to the control (standard of care) [20]. Furthermore, significant reductions in LDH and ferritin levels were reported in the treatment group vs. control, while hs-CRP remained unchanged [20]. Unlike the 2-week trial by Di Pierro et al., a shorter 7-day RCT including 60 patients with severe COVID-19, treated with daily quercetin (1000 mg) along with antiviral drugs, compared with control (only antiviral drugs), did not alter mortality or ICU-admission duration significantly. Notably, significant reductions in inflammatory markers such as TNF-α, IL-1β, IL-6, hs-CRP, ALP, and LDH were shown in the treatment group as compared to the control or baseline [23].

4. Probiotics

High quality evidence from systematic reviews and meta-analyses of RCTs, indicates that probiotics may have a favorable role for responses to infections [32]. In a recent one-month RCT of 293 outpatients with COVID-19, supplementation with four-strain probiotics consisting of Lactiplantibacillus plantarum KABP033 (CECT30292), L. plantarum KABP022 (CECT7484), L. plantarum KABP023 (CECT7485), and Pediococcus acidilactici KABP021 (CECT7483), produced significant reductions in remission rates vs. placebo (53.1% in probiotic group vs. 28.1% in placebo [25].

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