

Pills from the literature

Role Of Nutrient Supplements in Children with Post-COVID Condition: a Retrospective Preliminary Observation and Narrative Review

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Long-COVID, or post-COVID condition (PCC), represents a clinical syndrome following SARS-CoV-2 infection, affecting approximately one-quarter of the pediatric population and potentially persisting up to one year after the acute episode¹. It is characterized by a broad spectrum of clinical manifestations that endure despite complete viral clearance, particularly involving the cardiorespiratory, neuromuscular, and cerebral systems. The World Health Organization, through a Delphi consensus, proposed an operational definition of long-COVID as a condition occurring in individuals with confirmed previous SARS-CoV-2 infection, generally emerging 3 months after the acute infection, with symptoms lasting for at least 2 months and not attributable to alternative diagnoses². The most frequently reported symptoms include fatigue, dyspnea, headache, cognitive dysfunction, and alterations in smell and taste perception; less common, yet documented, manifestations include anorexia, sleep disturbances, chronic cough, arthralgia, thermoregulation abnormalities, cutaneous manifestations, and gastrointestinal symptoms³.

Long-COVID, rather than being a simple post-infectious condition, represents the outcome of a complex multiorgan pathological interaction involving the lungs, brain, kidneys, and heart. In children and adolescents, the underlying mechanisms are not yet fully understood; however, it is hypothesized that a synergistic interplay of inflammatory, neurological, and psychological factors contributes to the development and persistence of symptoms. Among the most relevant pathogenic processes described are persistent virus-induced inflammation, endothelial dysfunction, microthrombus formation, autoimmune phenomena, and oxidative stress⁴. These mechanisms contribute to a chronic multisystemic condition characterized by tissue damage and immune dysregulation, with elevated levels of pro-inflammatory cytokines (IL-6 and IL-1 β) and an increase in naïve B lymphocytes⁵.

Endothelial and microvascular alterations represent a key element: coagulation dysfunction and microthrombi may lead to tissue hypoxia and clinical manifestations such as dyspnea and fatigue. The coexistence of chronic inflammation and endothelial injury appears consistent with the multisystemic manifestations observed at both the pulmonary and cardiac levels⁶.

From a neurological perspective, it has been hypothesized that SARS-CoV-2 may reach the central nervous system via the bloodstream or sensory neural pathways, inducing neuroinflammation, disruption of the blood-brain barrier, and glial activation, with a consequent risk of neuronal damage and symptoms such as cognitive deficits and autonomic dysfunctions. Increased arginine levels and lipid metabolism, closely linked to a pro-inflammatory state, has also been associated with chronic headache, while concomitant dysregulation of neurotransmitter systems – including serotonin, dopamine, glutamate, and GABA – may contribute to additional neurological disturbances.

Similarly, the gastrointestinal tract, which is rich in receptors for angiotensin-converting enzyme 2 (ACE2) – the primary entry point for the virus into host cells – may represent a direct

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target of damage, with epithelial lesions, inflammatory infiltrates, and dysbiosis contributing to persistent symptoms, in connection with the close interplay between the immune system and the central nervous system.

Finally, the most common yet difficult-to-define symptom, fatigue, appears to result from a multifactorial interaction encompassing neuroinflammation, muscle damage, and psychological or social components that remain incompletely understood⁷.

Long-COVID can exert a significant impact on the physical and psychological development of children and adolescents, with potential long-term implications. In the absence of validated therapeutic protocols, interventions rely on symptomatic and supportive strategies. Several studies have also indicated that micronutrient deficiencies are associated with poorer prognosis and a higher risk of symptom persistence, particularly for vitamin D, B-group vitamins, selenium, and magnesium⁸. Vitamins and essential micronutrients play a crucial role in supporting metabolic, immunological, and antioxidant processes, making them particularly relevant in the context of long-COVID.

B-complex vitamins are indispensable for energy metabolism, DNA and protein synthesis, and the regulation of immune cells. Vitamin C, one of the main endogenous antioxidants, contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune systems. Vitamin D, with its immunomodulatory properties, has been associated with a reduced frequency of respiratory infections and may help attenuate inflammatory processes and fatigue symptoms in long-COVID. Vitamin E (alpha-tocopherol), a fat-soluble and potent antioxidant, plays a protective role against cellular oxidative stress, regulates immune function, contributes to the maintenance of endothelial and cardiac integrity, and participates in the balance of coagulation processes and the intestinal microbiota. Among minerals, magnesium is involved in the regulation of cell growth, division, and differentiation, as well as in modulating inflammatory responses and cognitive functions. Its deficiency is associated with neuropsychiatric symptoms such as insomnia, anxiety, headache, and depression, in addition to increased platelet aggregation, enhanced cellular adhesiveness, and altered microvascular endothelial function⁹. Magnesium supplementation could therefore enhance the host response to acute SARS-CoV-2 infection and support recovery during the post-acute phase¹⁰. Selenium, an essential trace element for antioxidant defense systems, plays a critical role in modulating viral pathogenicity: its deficiency not only impairs the host immune response but may also induce viral genome modifications, rendering normally benign strains highly virulent. However, evidence supporting the efficacy of zinc supplementation remains limited, despite its antioxidant and immunomodulatory properties¹¹.

Finally, zinc, a micronutrient essential for cellular homeostasis, is involved in numerous biological processes, including the regulation of the inflammatory response through cytokine modulation, particularly by reducing interleukin-6 expression. Furthermore, zinc contributes to the prevention of latent viral reactivation, highlighting its potential role in the context of persistent infections. Therefore, zinc deficiency

may be associated with an increased risk of hospitalization in children with COVID-19¹².

Available evidence suggests a significant association between nutritional deficiencies and long-term complications of COVID-19. Specifically, alterations in mitochondrial function, increased oxidative stress, and dysregulation of the immune response appear to represent key mechanisms underlying the persistence of post-infectious clinical manifestations. Micronutrient deficiencies may constitute one of the predisposing factors for the development of long-COVID, whereas adequate nutritional support could enhance the immune response during the acute phase of infection and subsequently help modulate inflammation and oxidative stress. By strengthening immune defenses and cellular protective systems, such interventions may also play a relevant role in improving symptoms and managing the chronic post-COVID phase.

In this context, the study by Morello et al. "Role of nutrient supplements in children with post-COVID condition: a retrospective preliminary observation and narrative review"¹³, aimed to evaluate the potential contribution of nutritional supplements as a supportive strategy in managing prolonged symptoms in children with long-COVID. The study conducted a retrospective analysis of supplements administered by parents to children (< 18 years) with long-COVID between February 2020 and October 2022. Inclusion criteria required the presence of persistent symptoms for at least 3 months following the initial infection, with an impact on daily activities – such as inability to attend school or engage in previously practiced sports – while excluding other potential diagnoses.

A total of 1,243 children with documented SARS-CoV-2 infection were enrolled, of whom 940 (76.2%) were classified as recovered and 294 (23.8%) as having long-COVID. All patients were evaluated at 3, 6, 12, and 18 months after the acute infection. Children with long-COVID received treatment with oral lactoferrin and/or a multielement product (MEP) possessing antioxidant, anti-inflammatory, and immunomodulatory properties. The complete MEP composition included magnesium 200 mg, quercetin 150 mg, curcumin Meriva® 100 mg, resveratrol 20 mg, vitamin E 15 mg, zinc 5 mg, folic acid 90 µg, selenium 55 µg, and cholecalciferol 20 µg per tablet. Lactoferrin, an iron-binding protein, exhibits antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant properties¹⁴.

MEP was prescribed to 161 children (13.0%) at the 3-month follow-up, 53 (4.5%) at 6 months, 9 (5.4%) at 12 months, and 3 (3.9%) at 18 months. Lactoferrin was administered to 170 children (13.8%) at 3 months, 48 (4.1%) at 6 months, 10 (6.0%) at 12 months, and 3 (3.9%) at 18 months. The combination of MEP and lactoferrin was used in 152 children (12.3%) at 3 months, 48 (4.1%) at 6 months, 9 (5.4%) at 12 months, and 3 (3.9%) at 18 months.

The primary aim of the study was to evaluate symptom evolution in children with long-COVID at 6 months after the initial infection, treated with lactoferrin, MEP, or their combination. Patients were considered recovered when they no longer presented persistent symptoms and had resumed pre-COVID daily activities.

Correlation analysis showed that the use of MEP alone (OR 5.7, 95% CI

3.8-8.5) or in combination with lactoferrin (OR 5.06, 95% CI 3.3-7.6), initiated 3 months after infection and continued for the subsequent three months, was associated with a significantly reduced risk of developing long-COVID at 6 months. Both MEP monotherapy and the combination with lactoferrin demonstrated a greater protective effect compared to lactoferrin alone (OR 7.6, 95% CI 5.1-11.4). Conversely, initiation of supplementation at 6 months or later after infection did not show a significant association with long-COVID resolution, suggesting that the timing of administration may influence the effectiveness in reducing symptom persistence.

In conclusion, this study provides a promising contribution to the management of children with long COVID and highlights the potential role of targeted nutritional supplementation in supporting post-infectious recovery, particularly when incorporated into a multidisciplinary clinical care framework.

Current evidence underscores the importance of specific micronutrients in both prevention and recovery from infections, including SARS-CoV-2. Vitamins D and E, magnesium, zinc, and selenium have been associated with reduced disease severity and modulation of immune responses. Pediatric studies on vitamin D indicate a potential attenuation of COVID-19 clinical progression¹⁵ with moderate COVID-19, who required hospitalization and supplemental oxygen. They were randomized into two groups: the VD group, which received doses of 1,000 (children < 1 year, while adult studies combining vitamin D, magnesium, and vitamin B12 suggest beneficial effects on clinical outcomes¹⁶. Zinc and selenium are linked to improved immune competence, though pediatric clinical data remain limited. Although vitamin E has a well-established immunological rationale, direct evidence regarding SARS-CoV-2 is scarce and primarily observational.

Regarding curcumin and quercetin, small clinical studies in adults with COVID-19 have reported improvements in inflammatory and clinical parameters¹⁷; however, no pediatric evidence or data on post-COVID in children are available. Therefore, their supplementation cannot be recommended outside of controlled clinical trials.

Current clinical implications suggest that pediatric supplementation should be individualized, based on nutritional status assessment, adherence to recommended doses, and careful safety monitoring. Vitamin D remains the micronutrient with the strongest evidence base, whereas other micronutrients present a biologically plausible rationale but lack sufficient data to support strong recommendations. The study by Morello et al. presents several strengths: the recruitment of a large cohort of 1243 children, the availability of a prolonged follow-up of up to 18 months, and the focus on a topic that has been scarcely explored in the pediatric population, making it one of the first systematic studies addressing the role of nutritional supplements in pediatric long-COVID. These aspects enhance the clinical relevance of the study and support its biological plausibility.

However, several methodological limitations should also be considered: the retrospective nature of the study precludes the establishment of causal relationships; the absence of randomization

and a control group limits the robustness of the conclusions; administration of supplements by parents may introduce adherence and reporting bias; moreover, the lack of baseline assessment of micronutrient levels does not allow determination of whether the observed benefits stemmed from correction of pre-existing deficiencies.

Therefore, the implementation of randomized, controlled, multicenter clinical trials in pediatric populations will be necessary, with standardized dosing and clinically relevant endpoints, to confirm the efficacy and safety of these interventions, as well as to more precisely identify which supplements may be truly indicated and in which patient subgroups.

Despite these limitations, the work by Morello et al. represents a significant contribution, laying the groundwork for further research on innovative and non-invasive therapeutic strategies. The hypothesis of a potential benefit from targeted nutritional interventions is consistent with the proposed pathophysiology and warrants further investigation through future controlled clinical studies, with the goal of exploring new recovery opportunities for children with long COVID.

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Conflicts of interest statement

The author declares no conflict of interest.

Author's contributions

F.L.C. drafted the manuscript, reviewed the literature, and takes full responsibility for the information reported herein, remaining available for any discussions or revisions that may be required.

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