

Nutrition and post covid infection: A critical review

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Abstract

In December 2019, a novel coronavirus emerged in Wuhan, China, leading to a global pandemic declaration by the WHO in March 2020. The disease exhibits a wide range of symptoms, from mild to severe, including pneumonia and multi-organ dysfunction. Some individuals experience prolonged post-COVID-19 syndrome with severe fatigue, malnourishment, and multi-organ impairments. To support medical interventions, adopting a nutrient-rich diet and a healthy lifestyle is crucial. Nutrients like vitamin A, vitamin C, vitamin D, vitamin E, zinc, selenium along with omega-3 fatty acids genuinely accelerate the immune responses that eventually helps in increasing antibody production, enhancing cell-mediated immune activity to reduce inflammation, the severity and duration of symptoms of post COVID-19 symptoms. It is very essential to maintain a healthy weight and consume a balanced diet with ample amounts of micronutrients, minerals, and probiotics or proper dietary supplements for regular nutritional requirements to potentially combat the severity of symptoms.

Keywords: Coronavirus, immune response, inflammation, micronutrients, nutrition, pandemic, post COVID-19 syndrome, SARS-CoV-2

Background & Introduction

1. Onset of covid-19 disease & the catastrophe

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that belongs to the family of Coronaviridae. Wuhan, China, was the site of the virus's initial discovery in December 2019 (Zhou *et al.*, 2020) [51], and the WHO declared the COVID-19 outbreak as a pandemic in March 2020, as it rapidly spread over the

globe, triggering a global respiratory sickness pandemic now known as COVID-19. To date, there have been about over 154 million confirmed cases and over 3.3 million deaths, with significantly disrupted people's normal lives through the implementation of restrictive measures such as lockdowns, mask usage, and limitations on personal movement (Clemente-Suárez *et al.*, 2021) [8].

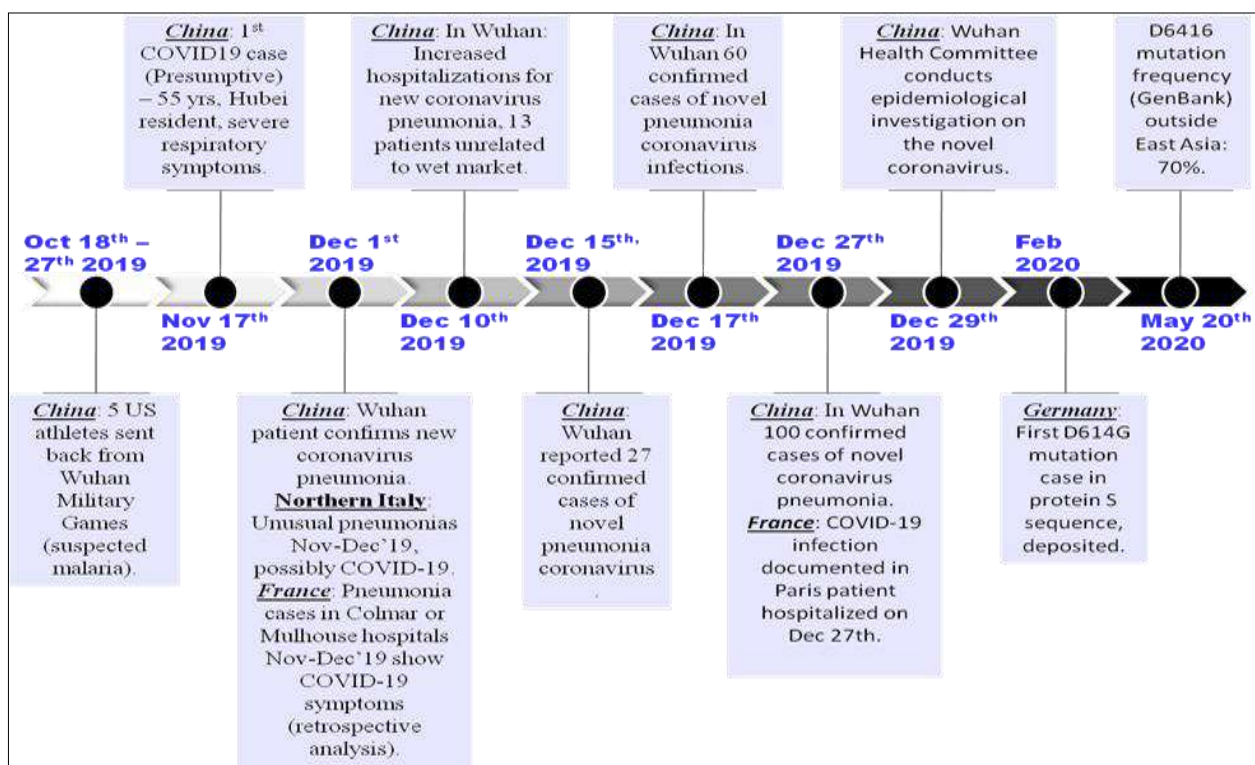


Fig 1: Diagrammatic representation of the timeline of events in COVID - 19 pandemic (Zhou *et al.*, 2020) [51]

SARS-CoV-2, a highly infectious RNA virus with a 30 kb genome, spreads through respiratory droplets, close contact, and surface contamination (Zhou *et al.*, 2020) [51]. It infects human respiratory cells by binding to ACE2 receptors, hijacking host machinery for replication (Zhao *et al.*, 2020) [50]. This leads to diverse symptoms, with early detection and isolation being crucial to curb transmission (Huang *et al.*, 2020) [22]. Symptoms range from fever, cough, and fatigue to severe conditions like multi-organ dysfunction and respiratory distress (Zhao *et al.*, 2020) [50]. Inflammation markers like G-CSF, MIP1A, IP10, and eosinophil counts are important for diagnosis and prognosis (Clemente-Suárez *et al.*, 2020) [5]. Disease progression can lead to pneumonia, respiratory failure, and death (Zhou *et al.*, 2020) [51].

Research has explored factors such as socioeconomic status, age, sex, and race on COVID-19 outcomes (Dastoli *et al.*, 2020) [9]. Socioeconomic disparities affect infection rates

and healthcare access, leading to worse outcomes. Advanced age is a significant risk factor for severe complications (Clemente-Suárez *et al.*, 2020) [6]. Males are more susceptible, and racial/ethnic minorities face disproportionate impacts (Fuentes-García *et al.*, 2020) [14]. Nutrition plays a crucial role in immune function, potentially reducing COVID-19 severity (Clemente-Suárez *et al.*, 2021) [8]. Here human immunity is mostly impacted by coronavirus, which makes it less effective (Tewari *et al.*, 2021) [46]. Key nutrients like vitamins A, C, D, E, zinc, selenium, and omega-3 fatty acids enhance immunity and reduce inflammation (Scarcella *et al.*, 2023) [39]. Maintaining a healthy weight, a fiber-rich diet, and regular physical activity are recommended (Lemacks *et al.*, 2023) [23]. Vitamin D deficiency is a concern, highlighting the need for targeted supplementation (Moonem and Van Zanten, 2021). This review underscores the importance of nutrition in post-COVID-19 infection based on various research studies.

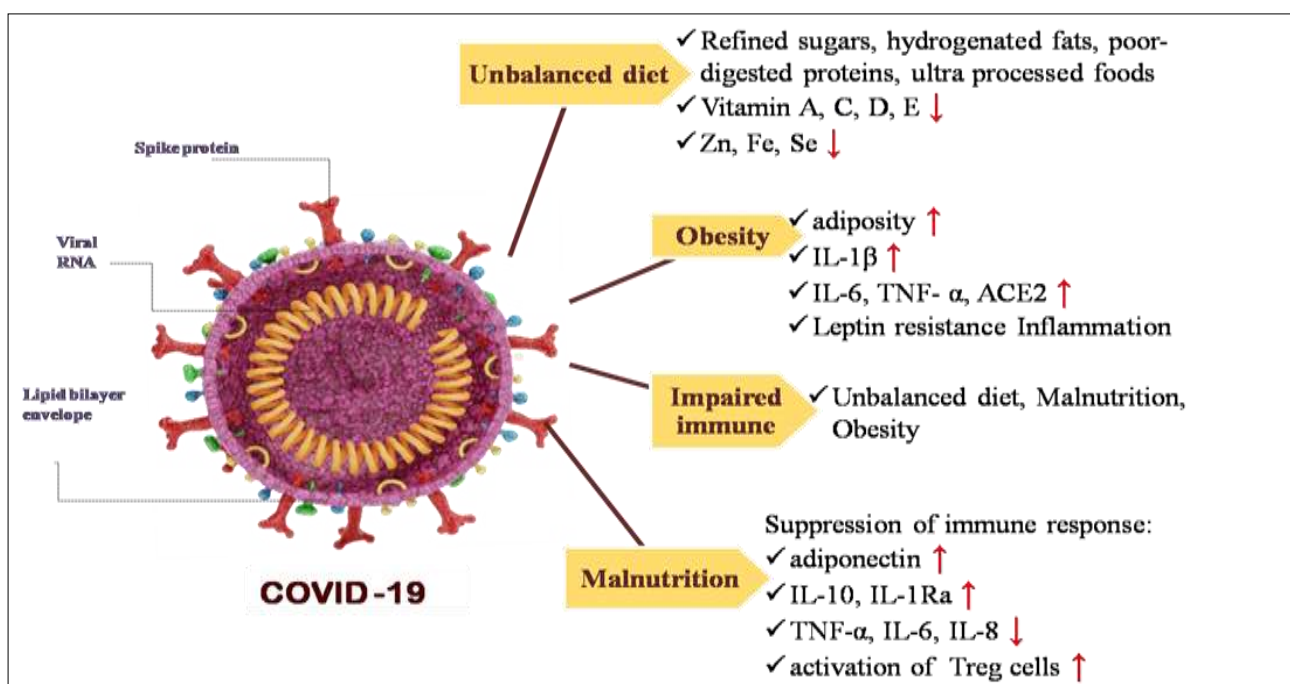


Fig 2: Diagrammatic representation of the Malnutrition, food imbalance, obesity, and reduced immune response, which increases vulnerability to severe acute COVID 19 infections (Morais *et al.*, 2021).

2. Post covid-19 in a nutshell - predicament of overall health

Over the course of more than a year since the declaration of the COVID-19 pandemic, the world continues to grapple with its profound and far-reaching impact. Beyond the immediate implications for morbidity, mortality, and healthcare services, the pandemic has unleashed an array of societal and economic consequences on a global scale (Eythorsson *et al.*, 2019). Since the declaration of the COVID-19 pandemic, extensive research has focused primarily on the acute phase of the disease, uncovering insights into its immediate impact (Maltezou *et al.*, 2021) [25]. However, it has become clear that COVID-19 can have lasting effects on health, known as post-COVID syndrome (Havervall *et al.*, 2021) [19]. This syndrome emerged in 2020 from surveys conducted by citizen scientists (Assaf *et al.*, 2020). Post-COVID syndrome includes persistent symptoms like fatigue, shortness of breath, loss of smell and taste, chest pain, muscle pain (Havervall *et al.*, 2021) [19], and

mental disorders, lasting for months and significantly affecting the quality of life (Haverall *et al.*, 2021). New clinical manifestations, including neurological abnormalities and thromboembolic complications, have been recognized, but the full extent of long-term consequences remains elusive (Sun *et al.*, 2021) [43]. Estimates suggest that 10% to 35% of non-hospitalized patients experience post-COVID symptoms, while hospitalized or severely ill patients may have rates as high as 80% (Tenforde *et al.*, 2020; Carvalho-Schneider *et al.*, 2021) [3, 44]. These enduring effects underscore the need for further research to understand the complex interplay between the virus and the human body in the context of COVID-19.

2.1 Post covid syndrome - definition with categorization

Post-COVID syndrome, or long COVID, encompasses persistent symptoms lasting over three weeks after COVID-19 diagnosis, affecting 10%-35% of individuals (up to 85% in hospitalised cases) (Maltezou *et al.*, 2021) [25]. Its

classification lacks consensus due to varied symptoms and duration. Research is ongoing to understand its characteristics and long-term effects (Venkatesan, 2021)^[49]. COVID-19 survivors may experience organ impairments, fatigue, cognitive dysfunction, and more. ACE2 receptor plays a role in multi-organ injuries seen in COVID-19. Severe COVID-19 survivors also experience multi-organ impairments post-discharge (Greenhalgh *et al.*, 2020)^[17]. Recovered patients are defined by negative Polymerized Chain Reaction (PCR) testing and absence of symptoms at discharge (Greenhalgh *et al.*, 2020)^[17].

A definition for post-COVID syndrome, also known as long COVID or long-haul COVID, is not yet agreed upon by everybody. The pioneering definition of post-COVID syndrome was introduced by Greenhalgh *et al.*, who described it as an illness associated with COVID-19 that extends for more than three weeks following the onset of symptoms. Additionally, they defined chronic COVID-19 as

the continuation of symptoms after 12 weeks from the onset of symptoms (Assaf *et al.*, 2020). However, as our understanding of this syndrome evolves, researchers continue to refine the definitions. Amenta *et al.* recently proposed a modification to the definitions for the symptoms of post covid scenario. The post covid syndrome was described as, 'for patients who remain hospitalised at three weeks after symptom onset, the post-acute period should be considered to start once the patient is discharged from inpatient acute care' (Amenta *et al.*, 2020)^[11]. These ongoing efforts to refine the definitions of post-COVID syndrome reflect the complex nature of this condition and the need to establish a standardised framework for clinical and research purposes. A clearer and universally accepted definition will facilitate accurate diagnosis, enable better characterization of the syndrome's clinical features, and aid in the development of targeted interventions and management strategies (Maltezou *et al.*, 2021)^[26].

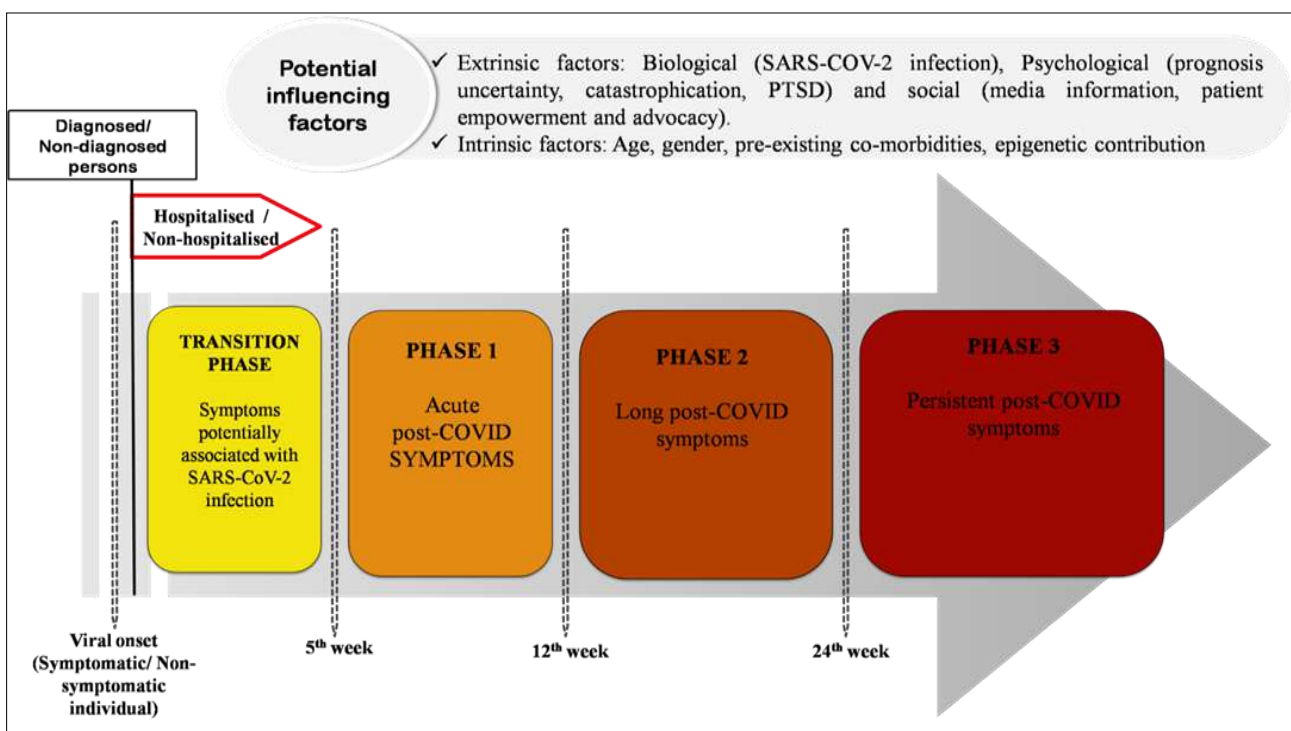


Fig 3: Diagrammatic representation of Integrative Post-COVID Symptoms model in asymptomatic, hospitalised and non-hospitalised patients with COVID-19 (Fernández-de-las-Peñas *et al.*, 2021)^[11].

The following classification for post-COVID symptoms can be seen as a dynamic and complex process, needing validation in further research. It takes into account potential biological, psychological, and social factors that may contribute to the development of post-COVID symptoms. This classification is also influenced by whether a patient required hospitalisation (Fernández-de-las-Peñas *et al.*, 2021^[11]):

- Transition Phase: symptoms that could be brought on by acute COVID-19 and linger for 4-5 weeks.
- **Phase 1:** Acute post-COVID symptoms that start between weeks 5 and 12.
- **Phase 2:** From week 12 to week 24, people suffered protracted post-COVID symptoms.
- **Phase 3:** long-lasting post-COVID symptoms that persist after 24 weeks.

2.2 Post covid syndrome's clinical spectrum - pathogenesis, manifestation & the effects on human organ systems.

The pathogenesis of post-COVID syndrome involves several factors, including persistent viral presence, dysregulated immune response, endothelial dysfunction, and tissue damage (Trogakos *et al.*, 2021)^[48]. Even after the SARS-CoV-2 virus is cleared, viral remnants may linger in tissues, leading to chronic inflammation and immune dysregulation. This immune dysregulation can cause chronic inflammation and tissue damage, contributing to persistent symptoms. The virus can directly infect endothelial cells, disrupting blood vessel function and leading to microvascular damage and impaired blood flow to organs. These factors are associated with a wide range of post-COVID symptoms, including fatigue, cognitive impairment, and musculoskeletal issues (Nuzzo *et al.*, 2021; Maltezou *et al.*, 2021)^[26, 37].

Table 1: Post-COVID Syndrome's on various organs

Main Diagnosis of All the Systems	Features	Pathological Mechanism	Prognosis
1. Respiratory system: acute respiratory distress syndrome (ARDS) Froidure, 2021) [13].	Diffusion impairment, pulmonary fibrosis, desquamation of pneumocytes, and hyaline membrane formations are all symptoms of extensive bilateral diffuse alveolar injury.	ACE2 binding to viral protein spike S1 domain causes bilateral diffuse alveolar damage, (Froidure,2021) [13] Post Acute Respiratory Distress Syndrome fibrosis with diffuse alveolar damage.	COVID-19 survivors show pulmonary function deficit at 6 months, widespread damage that is severe; long-term thrombosis in the same place.
2. Cardiovascular system: Capillary damage; Endothelitis; hypercoagulability; Microangiopathy, Micro-thrombosis, thromboembolism; myocarditis; atrial fibrillation; supraventricular tachycardia (Østergaard, 2021) [38].	Target-to-blood pool ratio increase, capillary disruption, and reduced oxygen transport.	Endothelial dysfunction was due to macrophage activation syndrome and the cytokine storm.	The majority of COVID-19 myocarditis patients (81%) were able to survive the acute episode; however, persistent subclinical myocarditis has the potential to progress and cause myocardial dysfunction and sudden cardiac death.
3. Haematological system: Thromboembolism (Townsend <i>et al.</i> , 2021) [47].	Elevated levels of D-dimer and C-reactive protein throughout recovery; continuously elevated inflammatory biomarkers.	NA	It is necessary to look for prognostic indicators for tracking the clinical development of Long COVID-19 patients.
4. Urinary system:Acute kidney injury; renal failure (Ng <i>et al.</i> , 2021) [35].	Decrease in glomerular filtration rate (eGFR); renal infarction.	High levels of ACE2 expression are found in the kidneys.	ACE2 is expressed widely in the kidneys.
5. Digestive system: Gastrointestinal dysfunction, liver damage from hepatitis and cholestasis, and pancreatic damage (Mönkemüller <i>et al.</i> , 2020) [31].	Diffuse injury to the colon; enterocyte desquamation, edoema, small bowel dilatation, lymphocyte infiltration, and haemorrhage and necrosis of the mesenteric nodes.	Rich in ACE2 and furin expression, fecal-oral transmission, plasma cell infiltrations, and lymphocyte infiltrates into intestinal tissue lamina propria.	The majority of survivors' liver functions returned to normal two months after leaving the hospital, (Mönkemüller <i>et al.</i> 2020) [31] however the liver enzymes persisted at an elevated level for 14 days after discharge.
6. Neurological system: Mood swings, cognitive challenges, headaches, exhaustion, lightheadedness, memory loss, disorientation, and attention deficiency (Nordvig <i>et al.</i> 2021) [36].	Neuronal inflammations, microbleedings, and hypoxic damage.	Indirect T-cell and microglia damage in the brain, comparable to strokes and neuroinflammatory disorders, are caused by decreased oxygen delivery, virus infiltration into the central nervous system, and inflammatory cytokines.	Within 90 days of recovering from severe COVID-19-related respiratory failure, more than 40% of survivors without a history of mental illness had depression, and 70% of them did not seek treatment.
7. Metabolic system: Diabetic ketoacidosis, new-onset diabetes, and hyperglycemia without diabetes (Chee <i>et al.</i> , 2020) [4].	Inefficient glucose metabolism and high blood sugar levels.	Due to the exposure of the antigen from injured islet cells, invading pancreatic β -islet cells can elicit autoimmune reactions.	For diabetes mellitus, long-term medication is required.

3. Mitigation of the effects on health with nutrition therapy

3.1 Nutritional supports before initiation of post covid-19

The main focus in managing COVID-19 patients is respiratory and hemodynamic support. However, early nutrition intervention is essential for both critically ill and non-critically ill hospitalized patients. It helps address symptoms, metabolic issues, and nutritional problems that can lead to malnutrition, loss of lean body mass, and delayed recover (Clemente-Suárez *et al.*, 2021) [7]. During the pandemic, there's been a keen interest in how nutrition, especially vitamins and trace elements, can influence immunity. Studies of hospitalized COVID-19 patients revealed vitamin D deficiency in 76% and selenium deficiency in 42%, but no significant increase in deficiencies of B vitamins, folate, or zinc compared to healthy controls. Chronic undernutrition, as opposed to overnutrition, leads to shortages in essential micronutrients, impacting immune function and energy intake. Experts

recommend providing both calories and micronutrients, with a focus on vitamins A and D, to malnourished COVID-19 patients and those with malnutrition. (Grant *et al.*, 2020) [16].

3.2 Post covid nutritional supports

Nutrition is vital in managing post-COVID-19 syndrome and various health issues. Nutritionists are crucial in healthcare teams. Good nutrition supports overall health and boosts the immune system, especially important in COVID-19. Well-nourished individuals have better infection-fighting abilities, aid recovery, heal wounds, and restore organ function (Clemente-Suárez *et al.*, 2021) [7]. COVID-19 outcomes can be influenced by nutritional status. Malnutrition or poor nutrition may increase the risk of severe illness, longer hospital stays, and higher mortality rates (Fernández-de-las-Peñas *et al.*, 2021) [11]. Good nutritional status can lead to better outcomes in COVID-19, including quicker recovery and fewer complications. A formal nutritional assessment is essential to identify deficiencies or specific needs. Nutritionists assess factors like body weight, composition, diet, and nutrient requirements to create personalized nutrition plans. These

plans address nutrient deficiencies, ensure sufficient energy intake, and promote balanced diets. Nutritionists play a role beyond the acute phase, helping manage post-COVID-19 syndrome (long COVID) by offering dietary strategies and therapeutic diets to enhance recovery, alleviate symptoms, and boost overall well-being. (Fernández-Quintela *et al.*, 2020) ^[12]. A therapeutic diet is a modified diet prescribed to a patient with a disease condition of any kind (Tewari, 2019) ^[45].

3.2.1 Nutritional importance of Patients with Post-COVID-19 Syndromes

In COVID-19, especially in elderly individuals, acute sarcopenia and muscle loss can occur, affecting function and recovery. Steroids given to severe COVID-19 patients can further break down muscle protein. Therefore, dietary therapy is vital for treating post-COVID-19 syndrome. A recent review suggests using protein supplements alongside resistance training to enhance muscle mass and strength, especially in older individuals. For healthy older patients, a daily protein intake of 0.83 grams of high-quality protein per kilogram of body weight is recommended to increase muscle mass, strength, and physical performance. (Skalny *et al.*, 2020) ^[42]. COVID-19 patients on antibiotics experience gut microbiota changes affecting physical and mental health, including post-COVID-19 syndrome. Diet components like carbs, proteins, fats, polyphenols, and probiotics influence gut microbiota genetics. For instance, high-fat diets reduce helpful Lactobacilli, while carbs promote beneficial Bifidobacterium and suppress harmful Clostridia. Probiotics and polyphenols also benefit gut flora. A balanced diet with microbiome-friendly foods can help post-COVID-19 patients both physically and mentally. (Dhar *et al.*, 2020) ^[10].

Nutrient deficiencies can cause post-COVID-19 fatigue. Supplements like vitamin C, vitamin B, salt, magnesium, zinc, folic acid, l-carnitine, l-tryptophan, essential fatty acids, and antioxidants can help. A balanced diet with these nutrients can also ease post-COVID-19 fatigue. (Fernández-Quintela *et al.*, 2020) ^[12]. Post-COVID-19 syndrome impacts physical and mental health, causing anxiety, depression and cognitive decline. Nutrition plays a role, with studies linking fruit- and veg-rich diets to lower depression risk. Balanced diets with fruits, veggies, omega-3 fatty acids, and less trans fats and refined carbs can enhance cognitive function and well-being, aiding post-COVID-19 recovery (Shanbehzadeh *et al.*, 2021) ^[41].

3.2.2 Nutritional recommendation for post COVID-19 syndrome patients

3.2.2.1 Energy requirement

Patients experience unintentional weight loss during COVID-19 infection, as a result of increased inflammation, appetite loss linked to taste, smell changes and swallowing issues. Patients may also experience early satiety and fullness following meals and beverages. Therefore, this is most important to balance out the energy intake and expenditure. Patients can be given practical tips to increase their food intake over the estimation of their individual energy needs based on age, gender, and weight. Previous studies noted that eating smaller, more frequent meals like six meals per day, snacking every three hours, drinking before meals should be followed to avoid early satiety, and avoiding "light," "low fat," or "low calorie" foods and

drinks. To increase calorie intake, ready-to-drink, low-volume oral nutritional supplements might be taken into consideration (Holdoway *et al.*, 2020) ^[20].

3.2.2.2 Macronutrients

In post-COVID-19 syndrome, macronutrients, particularly protein, are vital for treating sarcopenia and preventing muscle loss. Previous studies suggest including high-quality proteins from both plant and animal sources. Patients should aim for 15–30 grams of protein per meal, depending on body weight, to ensure adequate intake of essential amino acids, which could have anti-inflammatory effects. Some studies propose that consuming protein throughout the day may prevent autophagy, so having a protein source with each meal and snack can be beneficial. (Fernández-Quintela *et al.*, 2020) ^[12]. Certain amino acids like arginine and glutamine may be supplemented due to their role in modulating the immune response. To reduce inflammation, previous studies recommend a daily intake of 1.5 to 3 grams of omega-3 fatty acids, specifically eicosapentaenoic acid and docosahexaenoic acid. Interestingly, research suggests that omega-3 fatty acids may hinder replication of enveloped viruses like COVID-19, potentially reducing the risk of new infections. Additionally, increasing consumption of extra-virgin olive oil can provide essential monounsaturated fatty acids, tocopherols, and polyphenols with anti-inflammatory and antioxidant properties (Majumder *et al.*, 2022) ^[24].

Recent systematic reviews found that total carbohydrate intake isn't a major concern. However, it's recommended to choose carbohydrates with a low glycemic index to avoid potential issues. High glycemic index foods have been associated with increased oxidative stress and inflammation. Additionally, increasing the consumption of viscous and fermentable fibers is advised for their prebiotic effect on butyrate-producing bacteria, which can help reduce inflammation. (Muscogiuri *et al.*, 2020) ^[34].

3.2.2.3 Micronutrients

Pandemic sparked interest in nutrition, especially vitamins and trace elements, for immune function. Pilot study found micronutrient deficiency in COVID-19 patients. Vitamin C (ascorbic acid) is a water-soluble antioxidant vital for immune function, affecting B and T-cell activity. However, excessive doses can act as pro-oxidants, reducing ROS scavenging mechanisms like GSH and NADPH (Bae *et al.*, 2020) ^[2]. High-dose intravenous vitamin C therapy improved outcomes in sepsis and septic shock. One study used IV vitamin C every six hours for 96 hours in patients with sepsis and acute respiratory distress syndrome, reducing mortality and increasing ICU-free days. Another study combined IV vitamin C, hydrocortisone, and thiamine, reducing hospital mortality and preventing sepsis-related organ failures like acute kidney injury (May *et al.*, 2021) ^[27].

Vitamin D is a fat-soluble secosteroid crucial for bone health and immune function. It's naturally found in few foods, like fatty fish, and can be obtained from sunlight. Some reports link vitamin D to COVID-19, with systematic reviews indicating that low vitamin D levels increase disease severity and mortality (Seal *et al.*, 2020) ^[40]. Vitamin D influences Helper T cell responses, reducing Th1 and promoting Th2 immune responses. Th1 produces pro-inflammatory cytokines, while Th2 produces anti-

inflammatory ones. In COVID-19, vitamin D might help prevent cytokine storms, which can harm the endothelium and alveolar membrane, potentially increasing mortality (Mercola *et al.*, 2020) [29]. Meat, fish, seafood, and fortified grains are key zinc sources. Zinc is vital for immunity, including antiviral defenses. A diet with enough vitamin C, D, and zinc can bolster both innate and adaptive immunity against COVID-19 (Skalny *et al.*, 2020) [42]. Selenium deficiency may impact COVID-19 mortality. Selenium supplementation can enhance cytotoxic effector cell activity and antibody production. Low plasma selenium is linked to

tissue damage, infection, organ failure, and ICU patient mortality. Plasma selenium levels correlate with antithrombin activity, platelet count, and protein C activity. Seafood is a rich source of selenium to address deficiencies (Lemacks *et al.*, 2023; Skalny *et al.*, 2020) [23, 42]. Iron, found in foods like meat, fish, beans, and fortified grains, is vital for immune cell activity. Severe iron deficiency increases infection risk, but high iron levels also pose risks. COVID-19 impacts iron balance, and some studies link iron levels to COVID-19 severity (May *et al.*, 2021) [27].

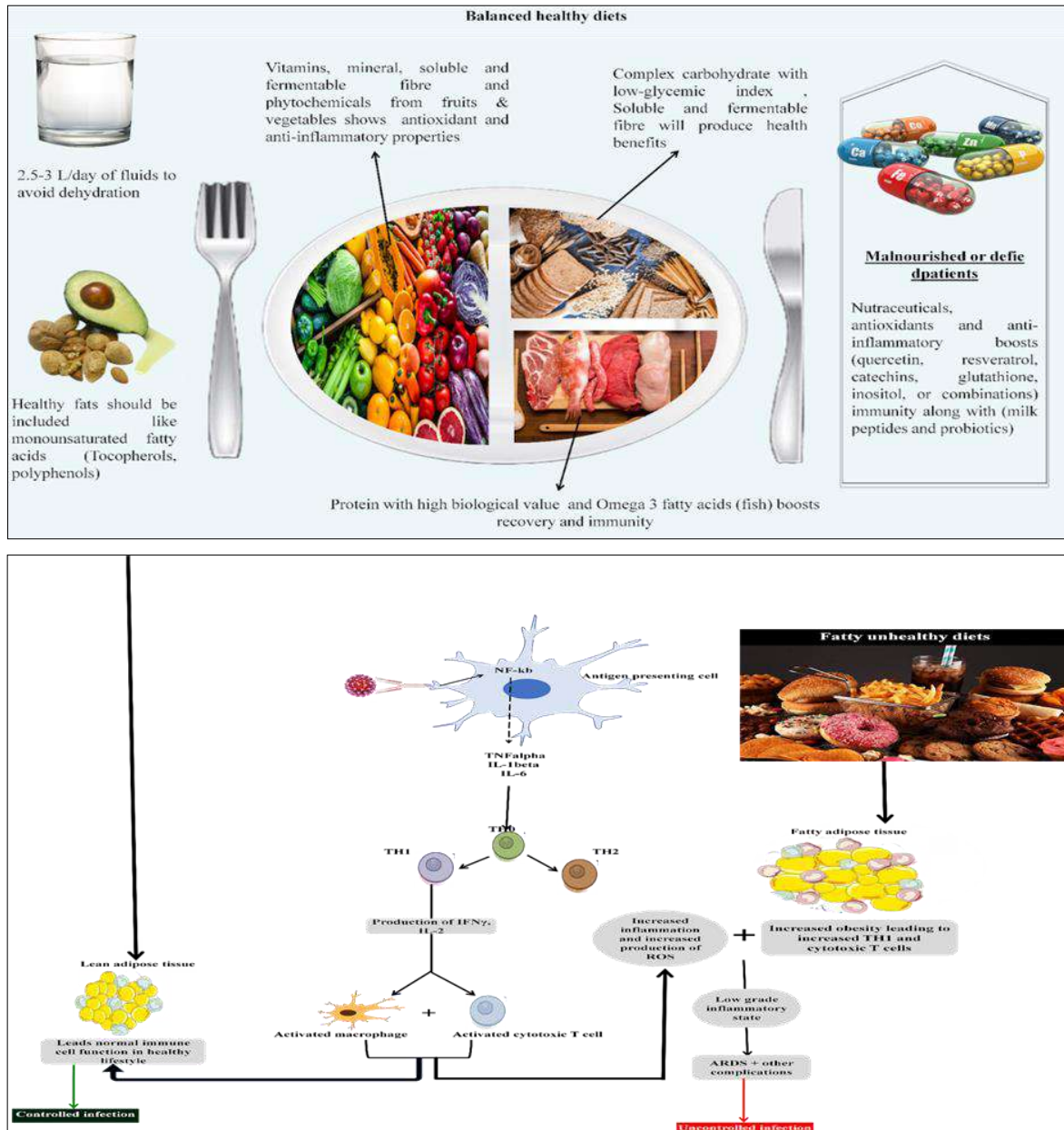


Fig 4: Diagrammatic representation of the relationship between infection control and diets through the response by the immune system. [The proposed malnutrition and prolonged infection due increased inflammation. Where healthy and balanced diet with green leafy vegetables, fruits, complex carbohydrates etc is responsible for speedy recovery and better infection control.

Conclusion

In conclusion, nutritional support is pivotal in post-COVID-19 syndrome recovery, impacting immune function and healing. Customized assessments are crucial to identify deficits and enhance overall health. Recommending anti-inflammatory, nutrient-rich foods is essential. Adequate

hydration, protein, omega-3, vitamin D, and antioxidants aid in recovery. Probiotics promote immune function. Minimize processed food intake to prevent immunological issues. Gradual exercise and vitamin monitoring support healing. Scientifically-backed diets accelerate post-COVID recovery by boosting natural healing and resilience.

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