

# Evidence that maintaining optimal nutrition status for a well-functioning immune system might promote recovery for mild COVID-19 patients

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## Abstract

COVID-19 is a viral infectious disease caused by SARS-COV2. Its clinical signs and symptoms are on a broad spectrum ranging from asymptomatic to severe complications like multi-organ failure, thromboembolism, and severe pneumonia with respiratory failure. Worse outcomes and higher mortality rates have been reported in the elderly, people with co-morbidities, and malnourished individuals. Nutrition is fundamental to good health and immune function. It forms an integral component of treatment modalities for various acute and chronic diseases, especially where a causative treatment is not yet recognized. Taking into consideration the magnitude of demands this pandemic has posed on hospital resources, an orderly assessment of nutritional status and body composition may not be possible for critically ill and/or for patients with mild-moderate symptoms who are managing their illness at home. Adequate intake of various macro and micro-nutrients--energy, protein, fat, vitamins--A, B, C, D, E and minerals--iron, selenium, zinc, and copper, along with supportive health practices like hydration, meal consistency, frequency of meal consumption and physical activity, often ameliorate respiratory infections, in part by modulating the immune response. Though at present there is a lack of well-defined nutrition-based guidelines for COVID-19 patient care, this paper brings forward the existing relevant evidence base for caregivers and patients to use as a reference/guide.

## Introduction

A novel coronavirus (SARS-CoV-2), causing serious respiratory illness like pneumonia and lung failure was first reported in Wuhan city, China at the end of 2019. It rapidly spread resulting in a global pandemic. As of Dec 15, 2020, COVID-19 has rapidly spread in more than 200 countries, areas or territories causing 71 million confirmed cases and more than 1,608,648 deaths (WHO, 2020). The clinical signs and symptoms of COVID-19 are on broad spectrum, ranging from asymptomatic infection to severe complications like multiorgan failure, thromboembolism, and severe pneumonia with respiratory failure (Kofman, 2020). The most common symptoms remain dry cough, fever and fatigue, and the symptoms may appear 1-14 days after exposure to the virus. Higher prevalence of infection and death have been reported in elderly people and people with immunocompromising conditions and/or co-morbidities like hypertension, diabetes, obesity, heart

and lung problems. In the elderly, a deficient micronutrient status might contribute to a decreased immune function (Yang, 2020). However, all individuals are susceptible to this infection (WHO, 2020).

## Immune response in COVID-19

COVID-19 is not atypical of the way influenza virus or even the coronaviruses intrude in our bodies. Our immune system has a predictable response towards the surge of invading pathogens and soon the body's immune system mediates its innate response. Viral interactions with the innate immune system determine the outcome of infection to a large extent. Type 1 interferons, complement proteins, and innate immune mediators control viral replication during the initial phases of the disease (Katze et al., 2002). The innate immune response stops virus replication, stimulates virus clearance and induces tissue repair, thereby initiating a sustained adaptive immune response against the virus. However, an aggressive innate immune response can be counterproductive and result in immune pathology and ensuing tissue damage (Garcia-Sastre and Biron, 2006). Spike proteins of SARS-CoV2 are able to gain entry by unlocking the angiotensin-converting enzyme 2 (ACE2) protein on the lung cells. In most SARS-CoV2 cases, the innate immune system, upon recognizing the virus, triggers pulmonary and systemic inflammatory responses leading to lung injury (Ortega et al., 2020). Therefore, it is critical to regulate cytokine production and inflammatory response in CoV-pneumonia cases, as they cause fluid buildup in the lungs. However, targeted inhibition of specific features of the immune response without compromising the assistance of host defense remains a challenge (Li et al., 2020). This implies that mortality rates are determined by the extent to which the immune response is tolerated by the body.

In addition, the original gut bacteria in the host are known to create a defense against pathogens. However, the disease disruption breaks this barrier and supports the growth of pathogenic organisms. Administration of probiotic organisms are known to enhance the innate immunity more than the acquired immunity. These exogenous organisms act by creating a physical barrier against pathogens and generating metabolic end products like lactic acid that hinders the growth of pathogens (Thomas et al., 2010). Systematic reviews have suggested there are protective effects of probiotics particularly *lactobacilli* and *bifidobacteria*, towards respiratory tract infections (Laursen et al., 2018; Araujo et al., 2015). It is possible that these effects can have an impact on COVID-19.

## The metabolic and endocrine linkage

Recent research has suggested the existence of a link between coronavirus infection and Type 2 Diabetes Mellitus (T2DM), obesity, hypertension, and respiratory distress syndrome. In fact, the most commonly occurring co-morbidities with SARS (Severe Acute respiratory syndrome) and MERS (Middle East respiratory syndrome) are T2DM and hypertension (Bornstein et al., 2020). SARS and MERS are both respiratory infections caused by the family of coronaviruses. According to US Centers for Disease Control (CDC) coronavirus reports, there is a ten-fold higher risk of mortality in patients with T2DM and metabolic syndrome. People with diabetes and uncontrolled blood glucose levels are immune-compromised which may lead them to an increased predisposition to COVID-19 infection (Casqueiro et al., 2012). The Angiotensin Converting Enzymes (ACE) 1 and 2 together regulate the angiotensin system of our body. When ACE1 activity

is increased and ACE2 inhibited, angiotensin\_II sets off inflammatory responses along with secretion of aldosterone. Consequently, there is an increase in blood pressure and lowering of potassium levels in blood serum. SARS coronavirus on binding with ACE2 also reduces insulin release from the pancreas (Yang et al., 2010). Researchers have suggested that severe patients of COVID-19 might create an imbalance in the stimulation of these pathways, becoming more severe in an already weakened immune state (Bornstein et al., 2020). Obesity is also known to weaken the adaptive immune responses to influenza virus (Green et al., 2017). Furthermore, fat accumulation reduces cardioprotective and immune regulation efficiency. This intercedes the progression to critical illness and organ failure in severe COVID-19 patients (Sattar et al., 2020; Finucane and Davenport, 2020; Zhao, 2020). Like in any other infection, an undernourished COVID-19 patient would exert extra nutritional demands on the body to combat the severe acute inflammatory status and the development of malnutrition would result (Domingo et al., 2020). While hyperglycemia and T2DM may be independent predictors of mortality and morbidity in patients with SARS1 (SARS) and MERS-CoV (Yang et al., 2006), where obesity is an independent risk factor for COVID-19 needs further research (Zhao, 2020; Sattar et al., 2020).

## Management of COVID-19

Outpatient management is appropriate in patients with mild illness (majority of the patient population) and does not warrant hospitalization or medical intervention as is deemed necessary for patients with severe and critical manifestations (WHO, 2020). Adherence to appropriate infection control, isolation precautions for the duration of illness and recovery, adequate access to food, and assistance with activities of daily living are essential for successful home management (CDC, 2020). The treatment differs with the severity of illness, as each phase may require a specific treatment regime. Marik et al. (2020) have postulated a combined treatment strategy consisting of methylprednisolone, ascorbic acid, thiamine, and full anticoagulation with heparin, called as the MATH+ protocol for patients who are in the pulmonary phase of COVID-19. Notably, diet and nutrition form an integral part of the management regime for infections, ailments or acute and chronic diseases even where an etiologic treatment has not yet been substantiated like COVID-19 (Laviano et al., 2020; Shakoor et al., 2020).

## Role of Nutrition in management of COVID-19

Malnutrition in both forms--undernutrition and overweight, has an impact on immune response to infections. This could be a result of neuroendocrine alterations and adipose tissue generated chronic inflammation. Concurrently, this interface exerts an adverse effect on food intake through mechanisms that include hormonal changes and cytokines (Krawinkel, 2012). The availability of nutrients in the host's body determines and stimulates specific and non-specific defense mechanisms and immune responses towards the pathogen (Pereira, 2003; Weis, 2017; Assmann, 2018). An acute infectious state induces hyper catabolism in the body, subsequently causing further loss and depletion of body nutrient stores along with increased energy demands. Protein breakdown with a higher resting energy expenditure is characteristic of aggressive infections. As a consequence, there is a higher nutrient requirement for speeding up active and passive host resistance. The extent of this is defined by the type of micro-organism, severity of the disease, and the presence of other complications (Pereira, 2003).

Associations exist between nutrient deficiencies and metabolic imbalances leading to increased risk of specific infections. The way this manifest is a vicious cycle, and thus whether the deficiencies and alterations are predisposing factor to infectious diseases or vice versa is unimportant. In any case, the nutritional state of the host plays an important role in susceptibility to infections and in recovery (Calder et al., 2020). A sub-optimal micronutrient status may support the onset of COVID-19 and augment its severity (Im et al., 2020). Patients with co-morbidities are more prone to malnutrition, leading to aggravated symptoms and complications from COVID-19 (Arentz et al., 2020). Management of malnutrition in such cases should be on the basis of infection severity along with malnutrition management guidelines in co-morbidities given by the Academy of Nutrition and Dietetics (2020).

## Screening for malnutrition and nutritional assessment

Screening for malnutrition followed by comprehensive nutritional assessment in confirmed or suspected individuals are key steps in the nutrition care process and should be performed at hospital admission (Zhang and Liu, 2020; Jin et al., 2020). This allows individuals to get optimal nutrition care from the Registered Dietician (RD) which has been proven to prevent further malnutrition, reduce complications, and improve clinical outcomes post hospitalization (Singer et al., 2019; Gomes et al., 2018; Volkert et al., 2019). While other screening tools are available Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening (NRS-2002), Subjective Global Assessment, the Mini Nutritional Assessment, the Nutrition Risk in Critically ill (NUTRIC), and Global Leadership Initiative on Malnutrition (GLIM), the Academy of Nutrition and Dietetics advocates that irrespective of the age, medical history or setting, the Malnutrition Screening Tool (MST) should be used to screen adults for malnutrition (undernutrition) (Skipper et al., 2020). While studies that screen for malnutrition in COVID-19 suspected or confirmed patients are lacking at this time, the MST is an appropriate, rapid, easy-to-use, and validated screening tool based on decreased intake due to poor appetite and recent unintentional weight loss (Ferguson et al., 1999; Handu et al., 2020). The medical nutrition therapy (MNT) of the patients vary based on the severity of the symptoms, being different for patients in the ICU who are mechanically vented vs not vented, post intubation and post discharge. Hancu and Mihaltan (2020) suggest focusing on feeding methods, caloric and macronutrient intake along with the gut microbiome for MNT in COVID-19. Since a majority of the patients exhibit mild to moderate symptoms and manage their illness at home (Huang et al., 2020), it is crucial for dietitians to provide outpatient or remote MNT in order to achieve or maintain optimal nutrition status (Handu et al., 2020).

Our paper particularly focuses on nutrition management for suspected or confirmed COVID-19 patients who are managing their illness at home on the premise that optimal nutritional status plays a role in patient recovery and immunity. Based on the existing literature, we aim to provide guidance/references for macro and micro-nutrient intake, hydration, meal frequency and consistency, flavorings and physical activity for patients and caregivers to use as a guide.

## Intake of macronutrients

Carbohydrate, protein and fats are the macronutrients responsible for yielding energy in their own distinctive ways. Cariero et al. (2016) state that these macronutrients together maintain the energy balance, though their needs in the body separately could be based on specific health conditions.

Caccialanza et al. (2020) and Barazonni et al. (2020) emphasize the use of macronutrients in overcoming illness-associated anorexia during COVID-19, as energy requirements are likely to be elevated in an inflammatory state. Anorexia-associated underconsumption and weight loss are common occurrences in this condition (Caccialanza et al., 2020). Increase in energy intake and consumption of high calorie-high protein foods are crucial though obtaining them may be a challenge with self-isolation and social distancing (Naja and Hamadeh, 2020). In order to compute energy requirements, experts recommend the use of prediction equations based on body weight. Caccialanza et al. (2020) suggested the use of Harris Benedict equation for determining the energy needs, both in people with normal BMI (23kg/m<sup>2</sup> is the ideal body weight) and BMI >30 kg/m<sup>2</sup> (obese patients). Further, ESPEN researchers recommend a calorie consumption of 27 kcal/kg body weight/day (for polymorbid patients - with two or more chronic health conditions, aged >65 years), 30 kcal per kg body weight/day for severely underweight polymorbid patients (Gomes et al., 2018) and 30 kcal/kg body weight/day for elderly (Volkert et al., 2019), keeping in view the disease progression and individual tolerance (Barazonni et al., 2020). An increase of 400-500 calories is suggested in infection over the caloric requirement for maintenance of normal body weight with emphasis on carbohydrate consumption, to protect against breakdown of muscle for energy (ASPEN, 2020).

**Carbohydrates:** The metabolism of carbohydrate is altered during an infection. The liver glycogen stores are depleted and there is increased gluconeogenesis in acute infection, even if carbohydrate intake is sufficient. Therefore, an adequate intake of carbohydrates is suggested to replenish the depleted glycogen stores of the body. A caloric intake of 45-50% from carbohydrates in a day's diet is suggested for patients with mild COVID-19 illness (Handbook of COVID-19 Prevention and Treatment, 2020). The British Dietetic Association recommends consuming starchy foods and whole grains with limited consumption of high sugar foods in order to avoid undue weight gain. Research has consistently shown the beneficial effects of consuming complex carbohydrates over refined and processed foods for resisting increased risk of respiratory infections (Zhang et al., 2015; Berthon and Wood, 2015), boosting anti-inflammatory microbiome, decreasing the growth of infections arising from *Clostridium difficile*, and discouraging dysbiosis that occurs due to consumption of processed sugars (Brown et al., 2012). Non-digestible carbohydrates present in whole grains, dietary fibers like inulin, polydextrose and maize fiber should also be consumed as they have shown to improve the immunity, gut microbiota diversity and digestion (Keim and Martin, 2014; Chaari et al., 2020). Moreover, research has linked carbohydrate consumption to an anti-stress effect, useful, as illness may bring along isolation and boredom (Muscoguirri et al., 2020).

**Protein:** Likewise, protein needs can be estimated on a body weight basis, as 1g/kg body weight/day for older persons (Volkert et al., 2019) and  $\geq$  1g/kg body weight/day for polymorbid patients (Gomes et al., 2018). ASPEN (2020) recommends an intake of 75-100g of protein/day to maintain muscle mass. Muscle atrophy is noticeable within a period of just two days of complete inactivity and bed rest (Narici et al., 2020), as also observed in COVID-19 patients with longer ICU stay (Barazonni et al., 2020). In addition, low pre-albumin levels have been shown to be associated with acute respiratory distress syndrome (Wu et al., 2020).

Protein-rich foods like milk and milk products have a vital role to play in reducing the risk of respiratory infections (Makino et al., 2010), regulating satiety (Peuhkuri et al., 2012) and

interestingly exhibiting sleep inducing properties, due to presence of the amino acid tryptophan, plentiful in milk (Muscogiuri et al., 2020). Moreover, cultured milk products and yogurt are good sources of probiotics and can even significantly reduce enteropathogens like *E. coli* and *Helicobacter pylori* (Yang and Sheu, 2012). Though intestinal dysbiosis has been observed in Chinese COVID-19 patients (Xu et al., 2020), no direct linkage or clinical evidence states the beneficial role of gut-microbiota in treatment of SARS-CoV or COVID-19 (Gao et al., 2020). Nevertheless, prebiotics and probiotics could certainly help in associated symptomatic relief such as reducing the duration of diarrhea (Malagon-Rojas et al., 2020) and improving the outcome of respiratory infections (Zhang et al., 2015). Besides, since isolation and quarantine could occasion stress and boredom in patients, Muscogiuri et al. (2020) suggest consumption of foods that contain or promote the synthesis of serotonin and melatonin at dinner like almonds, bananas, cherries, oats.

**Fat:** Sources of fat like cream, butter, cheese sauce, olive oil, or salad dressing improve the energy density. However, a high fat diet can result in an airway inflammatory response, exhibiting bronchial hyperresponsiveness and increased proinflammatory cytokine and neutrophil levels (van Oostrom et al., 2003; Nappo et al., 2002). Even short-term consumption of high fat diet has been shown to reduce immunity levels throughout the body. Barazzoni et al. (2020) state that the patient's respiratory efficiency is also a determinant of fat and carbohydrate ratio accounting for the day's energy needs; where it varies between 30:70 (subjects with no respiratory deficiency) to 50:50 (ventilated patients).

**Omega 3 fatty acids:** Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exert anti-inflammatory effects through pro-resolving mediators (SPMs) and as precursors of anti-inflammatory prostaglandins (Calder, 2020; Weill, 2020). Resolvin, protectins, and maresins (SPMs) are known to resolve the ongoing inflammatory processes and support healing, including in the respiratory tract (Serhan et al., 2015; Serhan et al., 2018; Basil and Levy, 2016). Several studies on animal models of lung injury have shown beneficial effects of individual SPMs from fish oil supplementation in lung injury like reduced lung inflammation and increased bacterial killing (Gao et al., 2017; Wang et al., 2018; Sham et al., 2018; Sekheri et al., 2020; Zhang et al., 2019). Two key meta-analyses highlighted that administration of n-3 fatty acids in combination with other bioactive nutrients led to significantly improved oxygenation, and reductions in ventilation requirements, in length of stay in ICU, in new organ failures, and in mortality (Pontes-Arruda et al., 2008; Dushianthan et al., 2019). Thus, it is likely that patients with ARDS (Acute Respiratory Distress Syndrome) can be treated favorably with n-3 fatty acids, mainly in combination with antioxidants, which act to reduce inflammation and lung injury through their conversion to SPMs, although EPA and DHA do have anti-inflammatory effects in their own right (Calder, 2020). While it is still unclear if fish or fish oil consumption may be beneficial against SARS-CoV-2 infection (Zabetakis et al., 2020), 2–4 g of n-3 fatty acids or even higher have been reported to be physiologically relevant against hypertension, inflammation, and thrombosis in earlier studies (Knapp and FitzGerald, 1989; Knapp et al., 1986). A daily intake of 250 mg EPA + DHA is consistent with global, regional and national expert recommendations (Calder et al., 2020; EFSA, 2010; FAO, 2010; Chinese Nutrition Society, 2013). Omega-3 fatty acids are found in a range of foods, including fish, other seafood, nuts and seeds (such as flaxseed, chia seeds, and walnuts), flaxseed oil, canola oil and fortified foods.

A diet high in fat including saturated fats and omega-6 fatty acids is known to negatively regulate the immune response. Research indicates that saturated fatty acids and some omega-6 fatty acids like linoleic acid are precursors of pro-inflammatory mediators. Eicosanoids and leukotrienes derived from omega-6 fatty acids counteract the favorable effects of omega-3 intake (Wypych et al., 2017; Innes and Calder, 2018). Charrie et al. (2020) have highlighted the importance of consuming a diet with a high omega 3/omega 6 ratio, as it improves the immune response and exerts an anti-inflammatory effect.

## Intake of micronutrients

Referred to as vitamins and minerals, the micronutrients are required in small quantities. These micronutrients perform an array of roles in the human body including producing enzymes and hormones, proper functioning of macronutrients to regulating the immune response, to name a few. In a recent review, Zhang and Liu (2020) proposed that vitamins A, Vitamin D, B vitamins, vitamin C, omega-3 polyunsaturated fatty acids, as well as selenium, zinc and iron should be considered in the assessment of micronutrients in COVID-19 patients that may have the potential to prevent viral infections and/or benefit infected patients due to their anti-inflammatory and antioxidants properties. Barazzoni et al. (2020), Gleeson et al. (2004), Semba and Tang (1999) too have reported that an adequate intake of iron, zinc, selenium and vitamins A, E, B6, and B12 are vital for the maintenance of immune function and their low levels are associated with adverse clinical outcomes during viral infections. Vitamin C, Vitamin D and zinc have the strongest evidence for immune-supporting roles, that may modulate immune function and reduce the risk of infection (Gombart et al., 2020).

The supporting evidence for the role of the following micronutrients in immunity and enhancing patients' ability to better survive the pathogen exposure comes from studies of frank states of deficiency or suboptimal levels. It may not be practical to measure the extent of each one of the nutrient levels during the pandemic. However, as a preventive measure in order to assure that immune functions are not further compromised, it seems prudent to consume adequate amounts of these nutrients, although studies that define explicit recommended amounts are lacking. ESPEN experts and Calder et al. (2020) suggest ensuring intake of daily allowances for micronutrients for malnourished individuals at risk for or with COVID-19 as a preventive or treatment measure aimed at boosting general anti-infection nutritional defense and potentially reducing impacts of the disease. Nonetheless, a diet comprising a variety of fruits, vegetables, nuts, seeds, predominantly whole grains and pulses along with lean meats, eggs, dairy products and oily fish that are consistent with current country specific dietary guidelines should be advocated.

**Vitamin A:** Popularly known as the anti-infective vitamin, it comprises of fat-soluble retinoids, particularly retinol, retinal and retinyl esters. Several studies have shown that vitamin A supplementation can reduce morbidity and mortality in a number of infectious diseases, particularly measles, measles-related pneumonia, and probably some diarrheal diseases. There may be an impact on malaria and HIV/AIDS infection as well (Semba, 1999; Villamor et al., 2002; Kantoch et al., 20002). Earlier studies have shown higher incidences of respiratory diseases and increased risk of developing bronchopulmonary dysplasia and long-term respiratory disability in children with lower retinol concentrations (Bloem et al., 1990). Vitamin A deficiency reduces cytotoxic activity of natural killer spleen cells and proliferation/maturation/functionality of T lymphocytes and the response against specific antigens due to a polarized Th1 and a reduced Th2

response (Iwata et al., 2004). While humoral immunity is little affected by vitamin A deficiency (VAD), cell-mediated immunity is markedly impaired. The ratio of T-cells bearing CD4+ and CD8+ antigens, the percentage of native CD4+ T-lymphocytes, serum immunoglobulin G, as well as splenic B lymphocytes are lower in VAD children as compared to the controls. Vitamin A supplementation enhances the inflammatory responses accompanied by decreased Th1 and increased Th2 response as well as increased mucosal responses showing its positive impact on immunity (Albers et al., 2003). Given the positive impact of Vitamin A on immunity, individuals with suspected or confirmed COVID-19 should ensure adequate intake of vitamin A in their diets (from plant, animal and/or fortified foods). Preformed vitamin A are found in foods of animal origin (liver, fish oils, milk, eggs, etc.) while the plant-based foods provide provitamin A (leafy green vegetables, orange and yellow vegetables, tomato products, fruits, and some vegetable oils) (IOM, 2001). Both provitamin A and preformed vitamin A must be metabolized intracellularly to the active forms of vitamin A (Ross, 2010). In addition to the consumption of a well-balanced diet, it is safe and effective to consume a multivitamin and mineral supplement that provides 100% of the RDA for Vitamin A for age and gender and follows the recommended upper safe limits set forth by expert authorities of the country (Calder et al., 2020).

**B-vitamins:** These water-soluble vitamins work as coenzymes, have specialized roles including involvement in intestinal immune regulation, thereby contributing to gut barrier function and reducing inflammation by suppressing pro-inflammatory cytokines. Owing to its anti-oxidative effects, thiamine reduces the oxidative stress induced activation of NF-kB (Marik et al., 2020). In their comprehensive review, Yoshii et al. (2019) have summarized that deficiency of Vitamin B12 has been shown to decrease phagocytic and bacterial killing capacity of neutrophils, and deficiency of vitamin B6 has led to low blood T lymphocyte numbers, thymus and spleen atrophy, and impaired lymphocyte proliferation and T lymphocyte-mediated immune responses.

Among the B vitamins, B6, B12 and folate are important in antiviral defense, supporting the activity of natural killer cells and CD8+ cytotoxic T lymphocytes (Calder et al., 2020). Given that deficiency of B vitamins may weaken host immune response, supplementation with B vitamins to the virus-infected patients should be considered (Zhang and Liu, 2020). While a few studies in hospitalized patients have shown a positive relation between deficient thiamine status and risk of COVID 19 infection (Crook et al., 2014; O’Keeffe et al., 1994), another study conducted by Im et al. (2020) on a small number of hospitalized COVID 19 patients showed no deficiency in vitamin B1 and B12 levels. The MATH+ protocol postulated by Marik et al. (2020) includes thiamine as one of the core components of the treatment strategy along with methylprednisolone, ascorbic acid and heparin. Donnino et al. (2016), suggest a dosage of thiamine at 200 mg IV 12 hourly for a week, with a subsequent oral thiamine administration. Shakoore (2020) has highlighted the significance of riboflavin, niacin, pyridoxin, folic acid and cobalamin use in prevention, alleviation and treatment of SARS-CoV-2 infection.

Supplementation that meets 100% of the age and gender specific RDA for the B-vitamins should be advocated in addition to consumption of a well-balanced diet (Calder et al., 2020). Although Vitamin B6 and folate are found in a wide variety of foods like fish, organ meats, eggs, dairy products, nuts, beans, dark green leafy and starchy vegetable, and fruit (other than citrus), Vitamin B12 is only naturally present in animal products (fish, meat, poultry, eggs, milk, and milk products) and certain fortified foods (IOM, 1998).



**Vitamin C:** Vitamin C has a crucial role in various aspects of the immune system (Carr and Maggini, 2017). Being a highly effective antioxidant, it protects important biomolecules (proteins, lipids, carbohydrates, and nucleic acids) from damage by oxidants generated during normal cell metabolism and through exposure to toxins and pollutants (Carr and Frei, 1999). It is a cofactor for a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes and for the lysyl and prolyl hydroxylases required for stabilization of the tertiary structure of collagen, and is a cofactor for the two hydroxylases involved in carnitine biosynthesis, a molecule required for transport of fatty acids into mitochondria for generation of metabolic energy (Carr and Maggini, 2017; Mandl et al., 2009; England and Seifter, 1986). Previous studies have shown that deficient individuals were highly susceptible to potentially fatal infections such as pneumonia and that scurvy (deficiency of vitamin C) often followed infectious epidemics in populations (Hemila, 2017) and respiratory infection in individuals (Carr and McCall, 2017), particularly lower respiratory tract infections (Hemila, 1997). Acting as a weak antihistamine (Field et al., 2002), vitamin C also offers relief from flu-like symptoms (sneezing, runny nose, swollen sinuses, etc.) which are also reported with COVID-19. The use of ascorbic acid has been accepted in the latest MATH+ protocol, supported by the evidence (Front Line Covid-19 Critical Care Alliance, Nov. 12, 2020) that it helps reduce the cytokine storm and improve lung function.

Due to the low storage capacity of the body for the water-soluble vitamins, a regular and adequate intake is required to prevent hypovitaminosis C (plasma vitamin C < 23  $\mu\text{mol/L}$ ) and vitamin C deficiency (<11  $\mu\text{mol/L}$ ). Epidemiological studies have indicated that vitamin C deficiency are relatively common in otherwise 'healthy' individuals, even in Western world as a result of poor dietary habits, life-stages and/or lifestyles either limiting intakes or increasing micronutrient requirements, various diseases, exposure to pollutants and smoke, and economic reasons (poor socioeconomic status and limited access to nutritious food) (Schleicher et al., 2009; USDCDCP, 2012, Maggini et al., 2008; Huskisson et al., 2007). Carr and Maggini (2017) concluded that Vitamin C prophylactically prevents infection when the diet provides at least adequate, if not saturating plasma levels (i.e., 100–200 mg/day), that optimize cell and tissue levels. However, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased metabolic demand. Calder et al. (2020) have also recommended an additional intake of at least 200 mg/day above the RDA for vitamin C for healthy individuals and higher intakes of 1–2 g/day to restore normal blood levels and support optimal immune function in individuals who are sick, beginning at the onset of symptoms. Fruits and vegetables, particularly, citrus fruits, tomatoes, tomato juice, potatoes, red and green peppers, kiwifruit, broccoli, strawberries, brussels sprouts, and cantaloupe are major sources of vitamin C (USDA, 2019).

**Vitamin D:** Referred to as the sunshine vitamin, it is a fat-soluble vitamin that is naturally present in only a few foods, however produced endogenously when ultraviolet rays from sunlight strike the skin to trigger vitamin D synthesis. Several mechanisms through which optimal Vitamin D can reduce risk of infections include inducing the genes for cathelicidins and defensins that can lower viral replication rates (Liu et al., 2006; Adams et al., 2009; Laaksi, 2012; Herr et al., 2007; Agier et al., 2015) and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing

concentrations of anti-inflammatory cytokines (Huang et al., 2020; Sharifi et al., 2019; Cantorna et al., 2015; Jeffery et al., 2009).

Calder et al. (2020) have recommended a daily intake of 2000 IU/day (50 microgram/day) that is above the RDA but within the recommended tolerable upper safety limits. Based on their narrative review, Grant et al. (2020) recommend that individuals at risk of influenza and/or COVID-19 should consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d with a goal to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). Higher vitamin D3 doses might be useful for those who become infected with COVID-19. Numerous recent studies have shown a relation between the insufficient levels of Vit D with occurrence (Israel et al., 2020) and severity of COVID-19 infection (Karahana and Katkat, 2020; Radujkovic et al., 2020; Jain et al., 2020). Administration of Vitamin D3 could form a part of the treatment modality in hospitalized patients (Maghbooli et al., 2020; Avolio et al. 2020; Castillo et al., 2020) and specifically in elderly populations (Annweiler, 2020). It is found in flesh of fatty fish, fish liver oils, and in small amounts in eggs, mushrooms, milk and dairy products, or foods fortified with vitamin D (IOM, 2010; USDA, 2019).

**Vitamin E:** Vitamin E, a fat-soluble antioxidant found in higher concentrations in immune cells than any other cells, is known to be effective in modulating immune function. This is particularly due to its protective effect against oxidation of polyunsaturated fatty acids which are enriched in membranes of immune cells, resulting from their high metabolic activity, making them prone to oxidative damage (Coquette et al., 1986; Hatam and Kayden, 1979). Vitamin E deficiency and supplementation have been demonstrated to affect the immune system and inflammation in opposite directions through various regulatory roles including alterations in membrane integrity and signal transduction, modulation of inflammatory mediators and cell cycle (Lewis et al., 2018). Animal and human studies have demonstrated that vitamin E deficiency impairs both humoral (antibody production) and cell-mediated (particularly that of T cells) immune functions (Han and Meydani, 2006). Modulation of immune function by vitamin E has clinical relevance, as it affects host susceptibility to bacterial and viral infection (Pae and Wu, 2017; Meydani et al., 2018). There may be an age-specific requirement for vitamin E in order to maintain optimal immune response (Bou Ghanem et al., 2015). Similar to the recommendations for vitamin A, Calder et al. (2020) have suggested consumption of 100% of the RDA for Vitamin E from a supplement in addition to the intake of a well-balanced diet. Nuts, seeds, vegetable oils, green leafy vegetables as well as fortified foods are significant sources of Vitamin E (USDA, 2019).

**Zinc:** Although a trace mineral, it plays an essential role in development and proper functioning of cells of the immune system (both the innate and adaptive systems). Even marginal deficiency of zinc has been shown to impair formation, activation and maturation of lymphocytes, weaken the innate host defense, lead to dysfunctioning of both humoral and cell-mediated immunity, as well as to disrupt the intercellular communication via cytokines (Gammoh, 2017; Tuerk and Fixel, 2009; Mares and Haase, 2016). Zinc deficient children are more prone to increased diarrheal and respiratory morbidity (Roth et al., 2010; Aggarwal et al., 2007) and zinc supplement could reduce measles-related morbidity and mortality caused by lower respiratory tract infections (Awotiwon et al., 2017). Previous studies have shown that zinc supplementation effectively impaired the replication of several types of RNS viruses, including the severe acute respiratory syndrome (SARS) coronavirus in Vero-E6 cells (Velthuis et al., 2016). Calder et al. (2020) recommend that

a daily intake in the range of 8–11 mg/day be met to support optimal immune function which should be met by a well-balanced diet in conjunction with a multivitamin/trace-element supplement if necessary. McCarty and DiNicolantonio (2020) have suggested that an increased zinc intake of 30–50 mg/day might be beneficial in the control of RNA viruses including influenza and coronaviruses. However, supplementation with zinc above the RDA is not recommended for prevention of COVID-19 (NIH, 2020). Case reports of COVID-19 patients have suggested that zinc doses between 115 to 184 mg Zn/day for 10 to 14 days (Finzi, 2020) and 220 mg Zn daily for 5 days (Sattar et al., 2020) have helped in patient recovery. This warrants further research, owing to the small number of patients studied. Oysters, crab, lobster, red meat, poultry, beans, nuts, whole grains, fortified breakfast cereals, and dairy products are good sources of zinc; however, the bioavailability of zinc from grains and plant foods is lower than that from animal foods (IOM, 2001; USDA, 2019).

**Selenium:** Selenium is required in trace amounts. The availability of selenium in our food is dependent on the geology, selenium soil content and soil pH (Zhang et al., 2020). The biological effects of selenium are exerted through its incorporation into selenoproteins that are involved in the activation, proliferation, and differentiation of cells that drive innate and adaptive immune responses (Huang et al., 2012; Rayman, 2012; Avery and Hoffmann, 2018). Se and selenoproteins are also involved in immunoregulation, which is crucial for preventing excessive responses that may lead to autoimmunity or chronic inflammation (Zhang et al., 2020). Adequate levels of selenium prevent excessive cytokine activation in infectious and inflammatory conditions (Huang et al., 2020; Conti et al., 2020). Apart from impairment of the host immune system, epidemiological studies in humans and certain animal models have shown that selenium deficiency can result in reproducible genetic mutations of otherwise benign variants of RNA viruses to virulence, especially in the deficient host under oxidative stress (Guillin et al., 2019; Harthill, 2011). Beyond the intake of a well-balanced diet, a multivitamin and trace-element supplement that supplies 100% of the age and gender specific RDA for selenium is recommended (Calder et al., 2020).

Recent studies have demonstrated a linkage of selenium with COVID-19 infection and disease progression. A sufficient and a more than sufficient selenium dose has been found to be positively associated with the recovery rate. Selenium as selenite has proven beneficial even for conditions requiring critical care. The basal selenium status in different parts of China has been shown to be associated with COVID-19 recovery rate (Moghaddam et al., 2020). Good sources of selenium are brazil nuts, seafoods, organ and muscle meats, dairy products, cereals and other grains (Sunde, 2006; IOM, 2000).

**Iron:** Numerous studies have reviewed the role of iron in immunity and host susceptibility to infection. However, the relationship between iron deficiency and susceptibility to infection remains complex, as iron is used both by the host and pathogens. On one hand, iron overload can impair immune function and can favor damaging inflammation and pathogenic growth, as well as causing oxidative stress that promotes harmful viral mutations, although several host immune mechanisms have developed for withholding iron from a pathogen (Wessling-Resnick, 2018; Ganz and Nemeth, 2015; Ward et al., 2011; Ganz, 2018; Nairz et al., 2018). On the other hand, iron deficiency can impair host immunity and has been reported as a risk factor for the development of recurrent acute respiratory tract infections (Jayaweera et al., 2019; Mao et al., 2014). Cavezzi et al. (2020) and Taneri et al. (2020) have highlighted the possible role of iron in the hyper-inflammatory and infectious state of COVID-19. A dysregulated iron metabolism with hyper-

ferritinemia and hemoglobinopathy along with hypoxia might heighten the inflammatory state and augment the mortality risk (Edeas et al., 2020). Studies of pooled mean hemoglobin and ferritin levels in COVID-19 patients have demonstrated that the severe cases had lower pooled hemoglobin levels but higher ferritin values, as compared to moderate cases (Fan et al., 2020; Richardson et al., 2020). Furthermore, COVID-19 survivors have been found to have lower mean levels of ferritin compared to non-survivors (Taneri et al., 2020). To maintain ideal immune function, consumption of 100% of the RDA for iron (age and gender specific) from a multivitamin and multimineral supplement in addition to the intake of a well-balanced diet has been recommended (Calder et al., 2020). Based on current knowledge, however, higher doses should be avoided and deficiency should be treated with care.

Dietary iron can be obtained both from plant and animal sources; however, heme iron has higher bioavailability than nonheme iron, and other dietary components have less effect on the bioavailability of heme than of nonheme iron (Hurrell and Egli, 2010). Plants (nuts, beans, vegetable) and iron-fortified foods contain nonheme iron only, whereas meat, seafood, and poultry contain heme iron (Wessling-Resnick, 2014).

**Copper:** Copper supports natural killer cell activity, promotes T lymphocyte responses and the functions of neutrophil, monocyte and macrophage (Percival, 1998; Li et al., 2019; Besold et al., 2016). Copper deficiency in both animals and humans has been reported to impair immune functions, increase susceptibility to bacterial/parasitic challenges, recurrent respiratory tract infections, decreased lymphocyte proliferation and IL-2 production, all of which is reversed with copper administration (Mao et al., 2014; Hopkins and Failla, 1997). Turnlund et al. (2004) have reported that a copper intake of 7.8 mg/day altered immune function and reduced oxidative stress although it is unknown if these changes were favorable. In lieu of lack of recommended dietary intake of copper against COVID-19, meeting 100% of the RDA through a supplement along with a well-balanced diet is recommended (Calder et al., 2020). Shellfish, seeds and nuts, organ meats, offal, wheat-bran cereals, whole-grain products, and chocolate are richest sources of copper; the absorption of which is inversely proportional to the amount of copper in the diet (Collins and Cooper, 2014; IOM, 2001).

## Hydration

During fever, the body loses water rapidly as a result of sweating, vomiting and/or diarrhea, in addition to the obligatory water losses through urine, stool, skin and the respiratory tract. Fluid losses can be up to 900 ml (30 ounces) every 24 hours, with additional 90 ml lost through coughing and breathing (Reithner, 1981). Throughout the day an adequate consumption of fluids is recommended to stay hydrated which also helps to thin the respiratory secretions that can otherwise lead to a build-up in lungs and subsequent pneumonia. It is recommended to consume about 3 liters of fluids every day as plain water, clear beverages, fresh fruit juices, and nourishing fluids like milk-based drinks as well as oral rehydration solutions when needed for vomiting or diarrhea. A variety of drinks as per the likes and dislikes of the patient can be incorporated to avoid palate fatigue (ASPEN, 2020; Handu et al., 2020; BDA, 2020). However, the recommendations vary for elderly and renal/cardiac patients. To manage a dry mouth, at least 60-80ml of fluids should be sipped every 15 minutes, avoiding drinking directly before or during meals to avert satiation.

## Meal frequency and consistency

The upsurge in nutrient requirements due to fever can sometimes be met through increasing the frequency of meal consumption. The Academy of Nutrition and Dietetics suggest that small frequent meals/snacks also assist in managing nausea and shortness of breath. In patients where breathing and chewing at the same time is difficult, nutrient-dense beverages including oral nutritional supplements could replace solid foods to efficiently increase energy intake (Handu et al., 2020). Oral nutrition supplements such as protein powders and meal replacement shakes containing at least 150 calories and 15-30g of protein per 160 ml should be chosen.

## Flavorings

Loss/altered taste and smell in COVID-19 patients can be managed by improving the flavor of plain foods by adding herbs, spices and honey/sugar and consuming food at cold/room temperature that are hot. In order to avoid the monotony, a gap of few days should be aimed for before repeat offering of foods, as tastes may continue to transform (ASPEN, 2020; BDA, 2020).

## Physical activity

Good nutrition along with physical activity, regular sleep and necessary medication together support recovery from the illness. WHO recommends that all healthy adults aged 18-64 years (irrespective of gender, race, ethnicity or income level) should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. This includes leisure time physical activity such as walking, dancing, gardening, hiking, swimming, cycling, occupational, household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities (WHO, 2011). While at present there are no specific guidelines on exercise or physical activity for COVID-19 patients with mild symptoms, the British Dietetic Association (2020) and ESPEN experts (Barazonni et al., 2020) discourage excessive sedentary behaviors like prolonged hours of sitting and reclining and screen time. Simple, gentle non-strenuous exercises like walking inside home or in the home garden, stair climbing, stretching and balancing exercises could help make breathing easier while maintaining agility and the immune system. Yoga and traditional Tai Ji Quan-Qigong exercises can be helpful also, and do not necessitate any special equipment (Chen et al., 2020). Patients should perform physical activity only as per their tolerability and exercise capacity. Trials are ongoing to test exercise as a modality for prevention/treatment of COVID-19 symptoms (McCall et al., 2020).

## Conclusions

The current pandemic has over stressed the healthcare system in taking care of the more severe cases of individuals with COVID-19 honing the focus to urgent clinical attention with an oversight on nutritional care. Further, to deal with this crisis, a majority of the COVID-19 patients--confirmed or suspected--with mild symptoms are managing their symptoms at home with frequent follow ups from the health care team. The emerging literature suggests a detrimental effect of malnutrition, suboptimal nutrient status and also the significance of nutrition in plausibly influencing the outcomes of patients with COVID-19. The link between the role of diet in combatting viral infections, including COVID-19, is suggested in the existing evidence that diet

has a profound effect on immunity and disease susceptibility. Additionally, nutrients are determinants of the composition of the gut microbiota that subsequently influences the characteristics of immune responses in the body.

Although studies addressing the role of specific nutrients in COVID-19 are still at an early stage, available evidence suggests that meeting the needs of an array of macro and micro-nutrients (energy, proteins, fats, vitamins A, D, E, C, B vitamins, iron, selenium, zinc, etc.) by diet and/or supplementation has the ability to positively affect the immune system. This is through several mechanisms like activation of cells, modification in the production of signaling molecules thereby decreasing the emergence of more pathogenic strains of viral diseases, and functional gene expression. The importance of hydration, meal frequency and consistency, incorporation of seasoning to improve palatability for plausible management of the associated symptoms along with physical activity have also been highlighted. Human clinical studies focusing on duration, dosage, combination and forms of macro-and micro-nutrients in different populations are required to elucidate the role of diet and nutrition in preventing or improving clinical outcomes of COVID-19.

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