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Nutrition is Associated with COVID-19 Incidence, Severity and Mortality

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Abstract

Earlier research has reported that proper nutrition is critical for reducing infectious disease morbidity and mortality. Malnutrition is very common in COVID-19 populations (up to 85.8% reported-with many studies over 50%) and is associated with significantly higher levels of COVID-19 infection, severity, and death. Low serum albumin, low serum prealbumin, and low and high BMI (Body Mass Index) levels are associated with significantly higher COVID-19 severity. Better overall patient nutrition and supplementation with key immune nutrients such as vitamin D, vitamin C, zinc, Ω-3 fats, and glutamine have been associated with significantly less COVID-19 severity and significantly better outcome. Many other nutrients which have strong anti-viral and/or anti-inflammatory properties show promise in controlling COVID-19 and other infections including vitamins A, vitamin B complex, vitamin E, probiotic bacteria, N-Acetyl Cysteine (NAC), l-carnitine, coenzyme Q10, α-lipoic acid, and phytochemicals from many fruits and vegetables. Many nutritional trials are currently underway, with single or multiple nutrients on COVID-19 patients and COVID-19 susceptible populations. The use of a good general diet, enteral nutrition, and multifaceted supplementation with a wide range of nutrients offers great promise in preventing COVID-19 morbidity and mortality.

• Malnutrition is very common in COVID-19 patients and hospitalized patients in general.

• Better nutrition is associated with significantly better COVID-19 incidence, severity, and mortality rates.

• Severely Ill COVID-19 patients often benefit from early enteral feeding.

• Specific supplemental nutrients such as Vitamins D and C, zinc, selenium, and omega 3 fats are associated with significantly better COVID-19 outcomes.

• Other antiviral and anti-inflammatory nutrients may be useful for controlling COVID-19 and other viral infections including vitamins A, vitamin B complex, vitamin E, probiotic bacteria, N-acetyl cysteine (NAC), l-carnitine, coenzyme Q10, α-lipoic acid, and phytochemicals from many fruits and vegetables.

Keywords: COVID-19; SARS Cov-2; Nutrition; Malnutrition; Vitamin D; Vitamin C; Omega 3 Fats; Zinc; Phytochemicals

Introduction

COVID-19 is characterized COVID-19 (Corona Virus Disease 2019) is caused by SARS Cov 2 (Severe AcuteRespiratory Syndrome Coronavirus 2, which is a RNA respiratory virus which is believed to be transmitted mostly by droplet nuclei in the air [1]. SARS2-Cov2 causes infection by binding the ACE2 (acetylcholine esterase 2) receptors present on the membrane of many cells including the lungs, nasal epithelium, arteries, kidney, heart, and intestines [2-4]. COVID-19 is especially dangerous to older humans as death rates for those over 70 years of age is more than 10%, while less than 0.1% for children and young adults [5]. COVID-19 infection rates in the USA are also significantly higher in African Americans as compared to the USA population as a whole [1,6]. Many recent studies have looked at medical, environmental, population, and nutritional factors involved with COVID-19 incidence, severity, and sensitivity. This review will attempt to make a broad overview of studies of nutritional research and COVID-19 up until April 18, 2021. In addition, selected papers which examine the relationships of nutrition with other respiratory infections like influenza will be described.

Literature Review

Searches were made on such sites as PubMed, Medline, Scopus, and Goggle Scholar for English language papers examining relations between COVID-19 and nutrition/nutritional supplements published up until April 18, 2021. Search terms included COVID-19, SARS COV-2, nutrition, malnutrition, fruits, vegetables, blueberries, cranberries, onions, cruciferous vegetables, kale, broccoli, whey, protein, calories, enteral nutrition, parenteral nutrition, Ω-3 fats, glutamine, arginine, leucine, N-acetyl cysteine, zinc, selenium, iron, calcium, magnesium, vitamins A, B complex, C, D, E, vitamins, whey, yogurt, leaky gut, sarcopenia, curcumin, and others. All papers cited were accepted papers unless noted as a preprint.

Nutritional Screening Status in COVID-19 and Other Patients

There is no one standardized method for measuring malnutrition in hospitalized patients [7]. Nutritional status can be accessed a number of ways. Measuring weight is common way of accessing nutritional status, although many malnourished patients can be overweight, have multiple nutrient deficiencies, and/or experience muscle loss-a condition known as sarcopenic obesity [8]. A review of 14 studies assessing nutritional status in COVID-19 patients reported that the Nutritional Risk Screening (NRS) Instrument has superior sensitivity for measuring malnutrition as compared to standard screening measures [7]. The CONUT score is another good screening method which employs serum albumin level, cholesterol level, lymphocytes, and CONUT-lactate dehydrogenase-c-reactive-protein score is also useful [7]. The Mini Nutritional Assessment (MNA) can detect residual malnutrition and high malnutrition risk in remitting patients [7].

COVID-19 Malnutrition Common

Many studies have reported that malnutrition is very common in

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hospitalized patients in general. Malnutrition of hospitalized patients in general is very common and often unrecognized. Kubrak and Jensen reviewed 110 published studies in acute care patients and reported that malnutrition ranged from 13% to 78% of all hospitalized patients and 42% to 91% of hospitalized elderly [9].

Numerous studies have also reported that malnutrition is common in COVID-19 patients, although malnutrition rates vary considerably depending upon the patient population and screening instrument used. A 2021 review of 14 published studies reported malnutrition levels in hospitalized COVID-19 patients (with varying degrees of severity and varying methods of determining malnutrition) of between 5.4% to 85.8% with an unweighted average of 52.3% for these 14 studies [10].

Bedock reported that 42.4% of 114 French hospitalized COVID-19 patients were malnourished [11]. Wei reported that 86.2% of 348 Hospitalized Chinese COVID-19 patients were malnourished (39.9% moderate severe malnutrition, 46.3% mild malnutrition) [12]. Larrazabal reported that malnutrition rates in hospitalized COVID-19 patients was 71.8% (255/355 patients), with 23.1% [82/355] being considered severely malnourished by the SGA (Selective Global Assessment Guide) [13]. Rouget reported malnutrition in 30 out of 80 (37.5%) hospitalized French COVID-19 patients with 21 (26%) meeting criteria for severe malnutrition [14]. Zhao reported that of 371 critically ill COVID-19 patients in Wuhan, China, 342 [92%) meet criteria for malnutrition (NRS ≥ 3], and 58 [15.6%) met criteria for severe malnutrition (NRS ≥ 5] [15]. Higher NRS (Nutritional Risk Screening 2002] scores were associated with significantly higher rates of mortality (p<0.001] and increased length of hospital stay (p=0.002] [15]. Each increase in NRS by a factor of 1 was associated with a more than doubled risk of mortality (OR 2.23, 95% CI 1.0-4.6] [15]. Liu's study of 760 hospitalized COVID-19 patients in China reported that 82.6% were at risk from malnutrition (NRS Score ≥ 3], with a mean BMI of 24.0, and with 55.3% with low albumin (<35 gr/l) and 25.5% with low prealbumin (<150 mg/l) [16]. A French study of 108 hospitalized COVID-19 patients reported that 42 (38.9%) had moderate to severe malnutrition and 91 [84.3%) were at risk for malnutrition [17].

Liu reported that 85.8% of 141 Chinese patients over age 65 years were at nutritional risk [17]. Another study of 182 Chinese over age 65 years reported that 52.7% were malnourished and another 27.5% at risk for malnutrition [18]. Severe nutritional risk (NRS ≥ 5] was reported in 61% of 136 critically ill Chinese COVID-19 patients [19]. A Moroccan study of 41 recovering COVID-19 patients who required ICU treatment reported that 19.5% had hypoalbuminemia, 51.2% were low in vitamin D, 14.6% were malnourished, and an additional 65.9% were at risk for malnutrition [20].

Diarrhea and Loss of Appetite Common in COVID-19 Patients

Good nutritional support is also critical for patients recovering from COVID-19. Reduced appetite, chronic diarrhea, chronic nausea and reduced smell are very common in COVID-19 patients and may partially explain the generally poor nutrition status of COVID-19 patients [21]. For example one study of 912 Chinese hospitalized COVID-19 patients reported that 9.87% experienced chronic diarrhea and 24% had significantly reduced appetite [22]. Nutritional support in critical for undernourished COVID-19 patients (both during and after hospitalization) and may include medication to control diarrhea and nausea, use of favorite foods including high calorie high protein foods like cheese, nuts, seeds, and nut butters, and the use of supplemental enteral formulas [23].

Sarcopenia and Cachexia in COVID-19 Patients

Loss of significant amount of lean body mass (Sarcopenia and Cachexia) is common in many diseases and is associated with significantly higher rates of death, infection, more frequent falls, and loss of function [23-27]. Large amounts of muscle loss can occur even in overweight patients-a condition known as sarcopenic obesity [8]. Presence of cachexia and sarcopenia is also common in COVID-19 patients. A 2021 review of 3 published studies involving a total of 587 hospitalized COVID-19 patients reported that 29% to 52% met criteria for cachexia [10,28-30]. Another commentary reported that acute sarcopenia is common in COVID-19 patients during and after their acute phase and many of these patients will require a careful program of medical care, exercise, and nutrition to reverse their acute sarcopenia [31].

Nutrition Important for Rehabbing Recovering Severe COVID-19 Patients

Nutrition is critical for rehabbing patients recovering from severe COVID-19 infection. A Belgian study of 15 patients rehabbing from severe COVID-19 infection reported all 15 were malnourished during their critical infection phase [32]. After a 2 month treatment with supplemental nutrition including a good diet, enteral formulas, and supplements, significant weight gains and significant gains in muscle strength were seen in these patients [32]. Several good general nutritional guidelines for rehabbing patients recovering from COVID-19 have been published [33].

COVID-19 Mortality High in Nations with General Malnutrition

Higher COVID-19 severity and mortality is also reported in nations with high rates of general malnutrition. A 2021 analysis reported that COVID-19 Case Fatality Rates (CFRs) were significantly elevated in low income nations and in nations with 3 or more significant malnutrition indicators including Yemen, Guyana, and the Sub Saharan Africa nations of Angola, Burkina Faso, Chad, Liberia, Mali, Niger, Sudan, and Tanzania [34]. Malnutrition can also increase influenza mortality. During the 1918-1919 influenza pandemic, mortality was significantly increased in parts of India experiencing famine as compared to non famine regions [35].

Better Nutrition Associated Less COVID-19 Incidence, Severity and Death

Earlier research has reported that malnutrition can greatly increase risk of hospital infections in general. For example, a French study of 630 hospitalized patients reported that the odds ratio risk of hospital acquired infections was 4.98 times as great [95% CI: 4.6-6.4] in severely malnourished patients compared with adequately nourished patients [36]. Many recent studies have also reported that overall malnutrition can significantly worsen outcomes in hospitalized COVID-19 patients.

Cinar's study on prognostic nutritional index and mortality in 294 Turkish COVID-19 patients reported that patients in the lower tertile of prognostic nutrition index (PNI-based on serum albumin and lymphocytes) had a 18.2 fold unadjusted greater risk of death (OR 18.2, 95% CI 10.2-64.1) and a 12.2 adjusted greater risk of death adjusted for cofactors (OR 12.2, 95% CI 4.4-28.1) [37]. Other studies also report that better patient nutrition may improve COVID-19 patient survival. Another Turkish study of 397 COVID-19 patients reported that those in the lowest tertile of nutritional PNI had an 18 fold increased risk of death as compared to the lowest PNI tertile (OR 18.57, 95% CI 4.39-

78.65) [38]. A Chinese study of 450 hospitalized COVID-19 patients reported that lower PNI was associated with significantly higher mortality (p<0.001] [39]. Wei reported that lower nutritional status in COVID-19 patients was associated with significantly higher mortality (OR 1.41, 95% CI 1.089-1.825, p=0.009] [12].

Zhao reported that of 371 critically ill COVID-19 patients in Wuhan, China, 342 (92%) meet criteria for malnutrition (NRS ≥ 3], and 58 (15.6%) met criteria for severe malnutrition (NRS ≥ 5] [15]. Higher NRS (Nutritional Risk Screening 2002] scores were associated with significantly higher rates of mortality (p<0.001) and increased length of hospital stay (p=0.002) [15]. Each increase in NRS by a factor of 1 was associated with a more than doubled risk of mortality (OR 2.23, 95% CI 1.0-4.6] [15].

A study of 523 hospitalized Chinese COVID-19 patients (221 or 40.3% admitted to ICU, 115 or 22.0% died) reported that higher NUTRIC score=Nutrition risk in Critically ill score was associated with significantly higher risk death in hospital (for each 1 increase in NUTRIC Mortality OR=1.197, 95% CI 1.091-1.445, p=0.006] [20]. Zhang reported that higher nutritional risk index (NRS ≥ 5) was associated with significant higher death rate in 136 critically ill Chinese COVID-19 patients [19]. Li's retrospective study of 63 hospitalized Chinese COVID-19 patients reported that patients with higher NRS malnutrition scores had significantly worse COVID-19, and significantly higher mortality (p<0.05), as well as higher C-reactive protein and serum precalcitonin levels and lower lymphocyte counts [41].

Lower Albumin Levels and Prealbumin Levels are Associated with Higher COVID-19 Severity and Mortality

Albumin is an abundant protein and many studies have reported that low albumin and/or prealbumin levels are associated with significantly higher rates of mortality, infections, inflammation, and other complications [42-44]. Meta analysis of 19 studies of 4,616 COVID-19 patients reported that lower prealbumin levels were associated with significantly more mortality and/or poorer outcome (SMD=standard mean difference-0.92, 95% CI-1.10,-0.74) [45]. A smaller meta-analysis of 6 studies involving a total of 1,803 COVID-19 patients reported that lower prealbumin levels were associated with significantly more severe disease (WMD-61.80, 98.63,-24.96) [46]. Another review of five studies involving 661 hospitalized COVID-19 patients measuring risk of severity or death, reported all 5 studies showed significantly worse outcomes (all p<0.05) when albumin levels were low [47]. A meta-analysis of 67 studies with 19,760 COVID-19 patients (6,141 with severe disease or poor outcome) reported that serum albumin levels were significantly lower in patients with severe disease or poor outcome (SMD-0.99 gr/l, 95% CI-1.11 to-0.88) [48].

Extra Weight Helpful or Harmful?

Obesity puts patients at risk for many adverse health effects such as cardiovascular disease, diabetes, hypertension, and kidney disease [49]. On the other hand, other studies have reported that moderately higher BMI can significantly reduce influenza death rates [50]. A meta-analysis of 25 studies reported that the risk of community acquired influenza related pneumonia had a J shaped curved relative to BMI relative risk in relation to "normal" BMI of 18.5 to 25.0: underweight (BMI ≤ 18.5, RR 1.9, 95% CI 1.2-3.0), overweight (BMI 25-30, RR 0.89, 95% CI 0.79-0.99), obesity (BMI 30-40, RR=1.03, 95% CI 0.8-1.3), and morbid obesity (BMI 40+RR=4.6, 95% CI 2.2-9.8) [51]. A plot of this data showed that influenza risk started to increase significantly once the BMI level rose to above about 38 to 40 [51].

Many recent studies have examined the relationships between BMI and COVID-19 incidence and severity. Obesity may increase risk for COVID-19 infection in many ways including inducing a chronic pro-inflammation and pro-oxidation state, chronic upregulation of the mTOR system, and by reducing immunity in general [52,53].

Some studies have reported that higher BMI (Body Mass Index or kg/m^2] is helpful to reduce COVID-19 severity or mortality, while many other studies have suggested that extra BMI may increase COVID-19 severity and mortality. Kim's study of 10,861 COVID-19 patients in New York (New York City plus Suffolk, Nassau, and Westchester counties) reported that patients who were underweight (BMI<18.5-OR 1.44, 95% CI 1.08-1.92], obesity class II (BMI 35 to 40-OR 1.25, 95% CI 1.03-1.52) and obesity class III (BMI 40+-OR 1.61, 95% CI 1.30-2.00) had significantly higher death rates due to COVID-19 (53]. Li's study of 523 hospitalized Chinese COVID-19 patients reported that each 1 standard deviation increase in BMI was associated with a 13% reduction of hospital death (HR=0.871, 95% CI 0.795-0.955, p=0.003) (Mean initial BMI was relatively low at 22.8 ± 2.9) (40).

Many studies have reported that higher BMI and/visceral fat levels are associated with significantly poorer COVID-19 outcomes. Huang's meta-analysis of 45,650 COVID-19 patients from 30 studies of BMI defined obesity and 3 VAT (Visceral Adipose Tissue) defined obesity reported that univariate analysis showed that higher fat levels were associated with higher rates of COVID-19 hospital admission (OR 1.76, 95% CI 1.21-2.56, p=0.003), ICU admission (OR 2.19, 95% CI 1.56, 3.07, p<0.001), and death (OR 1.49, 95% CI 1.20-1.85 p<0.001) [54]. Poorer COVID-19 outcomes started to increase in these studies once BMI reached 30 or slightly higher [54]. Another meta-analysis of 16 studies reported that obesity was associated with significantly poorer outcomes in COVID-19 patients (OR=1.78, 95% CI 1.25-2.54, p<0.001) [55]. A study of 200 hospitalized COVID-19 patients in Bronx, New York reported that BMI levels above 35 was associated with a significantly higher COVID-19 rate OR 3.78, 95% CI 1.45-9.83) [48]. An Italian study of 92 hospitalized COVID-19 patients reported that higher BMI was associated with significantly higher rates of need for mechanical ventilation and ICU admission (p<0.01 in both cases) [56]. A French study of 124 consecutive COVID-19 patients reported that severe obesity (BMI defined in this case as BMI 35+) was present in 35 patients (28.2% cases) and that risk of need for mechanical ventilation in patents with BMI over 35 versus less than 25 was 7.36 (OR 7.36, 95% CI 1.63-33.14, p=0.02) [57]. A Chicago, Illinois study of 182 hospitalized COVID-19 patients reported that BMI was significantly higher in COVID-19 patients under age 50 as compared to older patients (among patients without hypertension or diabetes-Mean BMI of 43.1 for patients under 50 years of age and 30.1 for patients 50 years or older. P=0.02) [58].

Enteral and Parental Nutrition

Many critically ill COVID-19 patients cannot eat enough food normally and required enteral or parenteral nutrition. Prompt enteral feeding has been shown to significantly reduce morbidity and mortality from many conditions including acute infection, acute pancreatitis, burn injury, cardiac arrest, and traumatic brain injury [59-63].

Early and good quality enteral nutrition for critically ill COVID-19 patients can save lives and promote good recovery. The Australian and New Zealand Critical case society recommends enteral feeding within

24 hours for critgically ill patients unable to take in sufficient oral nutrition [64]. A Michigan study reported that early enteral nutrition in 155 mechanically ventilated COVID-19 patients who received enteral nutrition within 24 hours received significantly more protein [1.04 Vs. 0.85 g/kg, p=0.003] and calories[17.5 Vs. 15.2 kcal/day/kg, p=0.015] during their hospital stay and had a statistically insignificant 21% reduction in mean length of hospital stay [18.5 Vs. 23.5 days, p=0.37] as compared to patients patients who did not received enteral nutrition within 24 hours [65]. Early enteral and parenteral feeding may also be needed in critically ill children with COVID-19 [66].

Many hospitalized COVID-19 patients are receiving enteral or parenteral nutrition. A study of 44 consecutive Chinese hospitalized critical COVID-19 patients reported that 30 (68.2%) received enteral nutrition and 3 (6.8%) received parenteral nutrition on the first day of admission [67]. Only 22 out of 33 (66.7%) patients receiving enteral or parenteral nutrition met their energy requirements, with mean daily enteral intake of only 1,300 calories in enteral patients who survived and 675 calories in parenteral fed patients who survived [67].

Chinese recommendations for COVID-19 patients suggest screening all patients for nutritional risk [68]. Any patients with a Nutritional Screening Risk Score (NRS) of ≥ 3 should receive oral nutritional supplements [68]. They also suggest an enteral underfeeding strategy of about 20 kcal/day/kg of calories and 1.0-1.2 g/day/kg of protein a day for ventilated patients or other severely ill patients, increasing to 25-30 kcal/day/kg and 1.2-1.5 g/kg/day as patients improve [68]. Parenteral nutrition should be used with caution [68]. Oral or intravenous Ω-fatty acid emulsions-of about 10 gram day can also be given to reduce inflammation and reduce risk of infections and death [68]. The ESPEN (European Society for Parenteral Enteral Nutrition) guidelines are fairly similar to the Chinese guidelines [69]. These guidelines recommend enteral nutrition at 1.2-2.0 gr/day/kg, a high single dose of 500,000 IU Vitamin D, sufficient levels of micronutrients and antioxidants, and at least 500 mg daily of EPA (EicosaPentanoic Acid) and DHA (DocaHaxaenoicAcid) [69].

French researchers recommend beginning enteral (preferred) or parenteral nutrition with 24 hours of COVID-19 admission (barring such problems as bowel ischemia or intestinal bleeding) [70]. Feeding may start to low rates the first few days but should be built up to 25-30 kcal/kg/day and 1.2-1.3 g/protein/day as the patient improves [70]. For more detailed description of guidelines for enteral and parenteral nutrition care of COVID-19 patients-please read Martindale [71] and Chapple [72]. Much more research on nutritional care for COVID-19 patients is needed. For a good review of nutritional research and research needs for COVID-19 patients, please see Mechanik [73].

Enteral feeding can be performed by either nasogastric tubes or PEG feeding-with PEG feeding being generally preferred for long term feeding [74]. A snorkeling mask which allows for both enteral feeding and non-invasive feeding of COVID-19 patients has been developed by the Italian company Isinnova SRL [75]. Inserting PEG feeding tubes are a rapid and relatively safe procedure [76,77]. For a concise review of PEG placement in COVID-19 patients, please consult Goyal [77]. While enteral feeding can significant reduce morbidity and mortality from many infections, non-infectious disease and trauma-it is important to use correct technique and management to avoid common problems like aspiration, infections, line clogging, and diarrhea [76]. It is also important to check to see if the PEG machine is providing the proper amount of formula over time, as some studies have reported that clogging of lines and serious formula underdelivery occurs in many as 23 to 35% of PEG fed patients [76].

Immunonutrition Enteral Formulas for COVID-19 Patients

Immunonutrition enteral formulas contain combinations of extra amounts of critical nutrients such as Ω-fats, short chain fatty acids, partially digested whey protein, arginine, glutamine, zinc, nucleotides, and extra amounts of vitamins A, B complex, C, E, and D [78]. Some researchers have suggested that such immunonutrition enteral formulas be used for COVID-19 patients [78]. Good studies on the effects of immunonutriton formulas on COVID-19 are needed [79]. Much earlier research has documented that such immunonutrition enteral formulas can significantly reduce risk of infections and other complications in critically ill patients. For example, a 2003 review of 26 published studies reported that use of immunonutrition enteral formulas in acutely ill patients were associated with significantly lower rates of many infections including pneumonia (OR 0.54, 95% CI 0.35-0.84, p=0.007) and bacteremia (OR 0.45, 95 CI 0.35-0.84, p=0.0002) [80]. In addition, use of enteral immunonutrition formulas were associated with significant reductions with time on mechanical ventilation (mean 2.25 days, 95% CI 0.5-3.9, p=0.009], ICU length of stay (mean 1.6 days, 95% CI 1.2-1.9 days, p<0.0001), and total hospital stay (mean 3.4 days, CI 2.7-4.0 days, p<0.0001) [80].

Immune enteral formulas/dietary supplements may be especially useful for elderly patients since immune systems tend to get less effective in older individuals due to a number of factors including 1) higher rates of malnutrition and lower average nutrient intake and absorption in elders, 2) declining T cell function, and 3) aging associated inflammation of "inflammaging" [79].

Less Sugar Consumption and Blood Sugar Control in Diabetics Helpful

Proper blood sugar control is critical in diabetic patients in the COVID-19 era. Various studies have reported that severity and mortality of COVID-19 and measures of inflammation and hypercoagulability is significantly greater in patients with diabetes and/or high hemoglobin A1C levels [81]. Limiting sugar consumption and getting moderate exercise has also been suggested as ways to boost immunity and limit COVID-19 morbidity and mortality [82,83]. Univariate analysis of World Nations reported that higher sugar consumption, higher malnutrition rates, and higher rates of physical inactivity are all related to significantly higher rates of COVID-19 death (granted there could be many cofactors that can also affect national COVID-19 death rates) [82].

Specific Nutrients may Improve COVID-19 Survival

Vitamin D

While good overall nutrition is essential to recover from COVID-19 and other serious infections, specific nutrients or combinations of nutrients may be especially helpful [84]. Vitamin D deficiency is very common in children and adults, especially in humans who do not receive supplementary dietary vitamin D and/or have darker skin which is less efficient in producing vitamin D from sunlight. A large study of 3,170 US Adults over age 60 years old reported that vitamin D deficiency is found in 76% of European Americans and 96% of African Americans [85]. Vitamin D deficiency is very common in children and adults, especially in humans who do not receive supplementary dietary vitamin D and/or have darker skin which is less efficient in producing vitamin D from sunlight. Vitamin D plays helps improve immunity by many ways including binding to and modulating expression of B cells, T cells, and antigen processing cells [86]. A number of studies have reported that Vitamin D can reduce risk of many infections. For example, a meta analysis of 11 placebo-controlled trials involving 5,660 patients reducing the risk of respiratory tract infections such as influenza and non influenza pneumonia by 36% (OR 0.64, 95% CI 0.49-0.84] [87]. Many human and animal studies have reported that vitamin D deficiency is associated with significantly greater risk of ARDS (Acute Respiratory Distress Syndrome) [88].

Significantly higher rates of both COVID-19 infection and mortality are seen in darker skinned people living in countries such as Britain and the USA, and the worst COVID-19 outcomes may be due to the generally poorer Vitamin D status of dark skinned people [89,90]. Other factors which may increase COVID-19 risks in darker skinned people include crowding, socioeconomic disadvantages, and the fact that minority populations often live in areas with relatively high outdoor levels of PM2.5, NO2, and other air pollutants [6,90,91].

Vitamin D deficiency is also common in COVID-19 patients. A review of 14 studies examining relationships between vitamin D and COVID-19 reported that vitamin D deficiency (below 30 nmol/L of 25(OH) D levels) was reported in 42 to 82% of COVID-19 cases and 6.6 to 65% healthy controls [92]. Vitamin D deficiency is also associated with significantly poorer COVID-19 outcomes. A meta-analysis of 27 published studies reported that vitamin D insufficiency was associated with increased hospitalization (OR=1.81, 95% CI 1.41-2.21) and increased mortality from COVID-19 (OR=1.82, 95% CI 1.06-2.580 [93]. A 2021 meta-analysis of 14 studies with 91,120 patients reported that low vitamin D was associated with significantly higher risk of contracting COVID-19 (OR=1.80, 95% CUI 1.72-1.88) [92]. Another 2021 meta-analysis 10 papers with 361,934 participants reported that vitamin D deficiency was associated with increased risk of COVID-19 incidence (OR 1.43, 95% CI 1.00-2.05) [94]. A study of 560 Chinese COVID patients reported in multiple logistic regression that male sex, increasing age, and vitamin D deficiency were also associated with greater COVID-19 risk [95]. Another study reported that both regular low dose and high dose bolus [80,000 IU Vitamin D] was associated with significantly lower mortality in 77 elderly COVID-19 patients aged 84 to 93 years [96].

Magnesium, vitamin D and B12

As noted above, the majority of USA adults are vitamin D deficient [85]. At least 30% of US adults have a magnesium deficiency as measured by intracellular magnesium [97]. Magnesium is involved in over 600 enzymatic reactions and plays important roles in respiratory and vascular physiology [98]. Magnesium depletion can lead to oxidative stress, endothelial deficiency, and cytokine storm [86,99]. Magnesium is also required to activate vitamin D [86]. A Singapore study involving 43 hospitalized COVID-19 patients reported that a low dose supplementation regime with 1000 IU/d vitamin D, 150 mg/d magnesium oxide, and 500 µg/d vitamin B12 was associated with an 87% reduction of the need for oxygen therapy [17.6 Vs. 61.5%, OR 0.13, 95% 0.03-0.59, p=0.006] and an 80% reduction in the need for ICU treatment (OR 0.20, 95% CI 0.04-0.93) [100].

Vitamin C

Many studies have reported that supplemental vitamin C is helpful for preventing or treating many human infections including viruses, bacteria, and Candida [101,102]. Vitamin C has many anti-inflammatory, immunomodulating, viricidal, antoxidant, and antithrombotic properties [102]. Vitamin C, and also vitamins A, D, E, also help downregulate cytokines to help prevent cytokine storm common in critical phases of COVID-19 [102-105]. While SARS-CoV2-COVID-19 downregulates the expression of type-1 interferons (a major anti-viral defense mechanism), while vitamin C upregulates type-1 interferons [106,107].

A review of 31 studies with 7,095 adults and 1,532 children reported that use of supplemental vitamin C was associated with significantly shorter length of cold infections (Mean-9.4% decrease in colds, 95% CI-13% to-6%) [101]. Three controlled trials reported that supplemental vitamin C prevented pneumonia, and 2 studies reported a treatment benefit of vitamin C for pneumonia [101].

Vitamin C has a low cost, and a good safety profile and can be given to patients who have good kidney function at high levels of 2-8 grams orally and 6-24 grams intravenously daily [102]. Vitamin C levels are often low in many COVID-19 patients and these benefits could benefit from oral or parenteral vitamin C supplementation [102]. A Chinese study reported that mean plasma vitamin C concentration of 31 COVID-19 patients was only 2.00 mg/L-which is almost 80% less than the 9.23 mg/L seen in 51 healthy controls, and much lower than the reference range of 6-20 mg/L for vitamin C [103]. After treating COVID-19 patients with intravenous 100 mg/day/kg vitamin C, mean vitamin C levels rose to 13.23 mg in the COVID-19 patients [104].

Many COVID-19 nutrient trials are now underway. As of April 10, 2021, Clinical Trials. Gov reported 60 ongoing trials involving supplementation of COVID-19 patients with vitamin C with or without other nutrients [105]. Many of these studies have involved studies with 3 or more supplemental nutrients. [105-109]. Only a few of these studies have been published as of April 10, 2021. An Iranian study of severe COVID-19 patients reported that 30 patients given IV 6 grams vitamin C daily had significantly lower temperature at day 3 (p=0.001] and higher peripheral blood capillary oxygen levels as compared to the 30 patients not given vitamin C (p=0.014] [110]. Mortality was similar in both groups and median length of hospital stay was actually longer in the group given vitamin C [8.5 days versus 6.5 days, p=0.028] [110]. A 4 way analysis treated 214 COVID-19 patients with ascorbic acid 8,000 mg day, 50 mg zinc gluconate, both, or neither and reported fairly similar times to 50% improvement in all 4 patient groups [111]. A retrospective Chinese study of 6 severe and 6 critical COVID-19 patients reported that treatment with IV Vitamin C (mean 162 mg/kg/day for severe and 177 mg/kg/day for critical was associated with many significant improvements including better 3 day c-reactive protein, better lymphocyte and CD4+ cell levels, better PaO_2/FiO_2, and significantly lower organ failure assessment values [112]. A case series of 17 intubated COVID-19 patients reported that IV Vitamin C was associated with a significant decrease in inflammatory markers such as ferritin and D-dimer [113].

Other research has suggested that combinations of vitamin C, curcumin, and glycyrrhizic acid may have the potential regulate immune response by acting on NOD-like and Toll-like pathways to promote interferon production, activate T and B cells, and regulate inflammatory processes [114,115]. Future research papers on Vitamin C should yield interesting results, especially if combined with other nutrients in multi-faceted studies [116].

Vitamin A

Vitamin A has strong anti-infection, immunomodulating, and mucosal barrier support which may be useful for treating COVID-19 and other viruses [117]. A clinical trial is currently underway in Iran which treats COVID-19 patients with fairly high doses of vitamin A-25,000 IU daily plus 600,000 IU Vitamin D once, and Vitamin E 300 IU twice daily [105].

Vitamin E

Vitamin E also has strong anti-infection, anti-oxidant and anti-inflammatory properties and may be a useful part of nutrition treatment for COVID-19 [117,118].

B Vitamins

B vitamins play many anti-infective and anti-inflammatory roles [117,118]. About 25 Worldwide clinical studies involving supplementation with one or more B vitamins in COVID-19 patients were being conducted-according to Clinical Trials.gov on April 15, 2021 [119].

Selenium

Selenium has multiple anti-oxidant, anti-inflammatory (including preventing cytokine storm), and immunostimulatory properties that might be useful in controlling viruses like COVID-19 [120]. Selenium levels are low in many areas of the world including the Wuhan area of China [121]. Selenium has been shown to inhibit SARS-COVID 2 proteases *in vitro* [120]. A German study of 33 COVID-19 patients reported that serum selenium was significantly lower in COVID-19 patients who died versus those who survived (Mean 40.8 ug/l for non-surviving COVID-19 cases, 50.3 µg/l Selenium for COVID-19 survivors, and 84.4 µg/l for healthy controls [121]. A Chinese analysis reported that cure rates for severe COVID-19 were significantly higher in regions with relatively high selenium intake and higher hair selenium levels as compared to lower selenium Chinese regions [122] (of course, cofounders can exist).

Zinc

Zinc is involved in many immune processes including, improving innate and acquired immune response, T and B cell development, maintenance of good mucosal integrity, and impairing viral replication of RNA viruses such as SARS-Cov2 [84,123,124]. A number of studies have reported that zinc deficiency is common in COVID-19 patients and lower zinc levels are associated with significantly poorer COVID-19 outcome [84]. An Indian study reported that zinc levels were significantly lower in 47 COVID-19 patients (mean 74.5 ug/dL-54% were below the usual zinc cutout of 70 µg/dL) as compared to 45 healthy controls (mean 105.8 µg/dL) [125]. A recent large preprint study of 3,473 Hospitalized New York City COVID-19 patients reported that reported a 37% reduced risk of mortality in the 1,006 patients given zinc plus ionophore (hydroxychloroquinine) at the rate of 50 mg PO once or twice daily [OR 0.63, 95% CI 0.41-0.91] [126]. (Several other good zinc ionophores include pyrrolidine dithiocabrmate, hinokitol, resveratrol, quercetin, and epigallocathechin-gallate [126]). A small study of 29 Japanese COVID-19 patients reported that zinc levels below 70 µg/dL were associated with significantly worse disease [127].

Iron

Some studies have linked severe COVID-19 with lower blood hemoglobin and ferritin levels [128]. On the other hand, high ferritin levels have been linked to cytochrome storm and worse COVID-19 outcomes [129]. More study on iron nutrition and metabolism and COVID-19 are needed.

Calcium

Hypocalcemia is common in COVID-19 patients, with one study reporting 16 out of of 20 [80%) COVID-19 patients [130]. Calcium plays critical roles in immune function, respiratory health, and bone health [130]. A Chinese study of 67 hospitalized COVID-19 patients reported that calcium levels were significantly lower in patients with poor outcomes (mean of 2.01 mmol/L poor outcome versus 2.10 mmol/L good outcome, p<0.001] [131].

Glutamine, N-Acetyl Cysteine, Carnitine, Coenzyme Q10, and α-Lipoic Acid, Supplementation with amino acids, coenzyme Q10, and α-Lipoic acid many be helpful in preventing or ameliorating COVID-19. Glutamine is the most abundant amino acid in the body and has many immune promoting effects [132]. A Turkish study of 60 hospitalized COVID-19 patients reported that patients given 10 grams of glutamine three times daily with meals was associated with significantly shorter hospitalization times (Mean 8.9 days for 30 patients with glutamine supplements versus 10.4 days for 30 patients without glutamine supplements, p=0.005) [133].

N-acetyl cysteine (NAC) is a peptide which is a precursor for the important anti-oxidant peptide glutathione [134]. NAC may improve COVID-19 survival through their anti-inflammatory and immunomodulating effects and by limiting cytokine storm [135,136]. One study of 262 older Italian adults reported that supplementation with 600 mg NAC twice daily was associated with a 69% reduction in influenza like symptoms (p=0.001) [137]. Some researchers have suggested that anti-inflammatory and immune modulating nutrients such as l-carnitine, α-lipoic acid, and coenzyme Q10 can be useful in treating viral infections [138].

Omega 3

Omega 3 or Ω-3 fats include ALA-alpha-linolenic acid, EPA eicospentaenoic acid), DHA (docosahexaenoic acid), and the related λ-fatty acids such as λ-linolenic acid from evening primrose oil [139]. Omega 3 fats can improve immunity and infection survival by several mechanisms including reducing the inflammatory and septic responses, coagulation reduction, and arrhythmia improvement [139-141]. Omega 3 fatty acids may also modulate viral infection by counteracting the viral activation of the SREBP (Sterol Regulatory Element Binding Protein) and by modulating cell membrane rafts where ACE2 is mainly expressed [140]. Cell culture studies have reported that Ω-3 fats, especially eicospaentaenoic acid (EPA) and α-linolenic acid (ALA), were able to effectively block binding of the SAR-Cov2 viruses to the ACE2 receptor [141-142].

Omega 3 fats are found mainly in fish/fish oil/flax/evening primrose oil and smaller amounts in soybean, flax oil, meat and butter [140]. A study of 38 nations reported that most people receive far below the recommended minimum Ω-3 intake of 0.2% of total energy (corresponding to about 670 mg day for a 3,000 calorie diet) [140]. Only a few studies have examined the effects of supplementing omega 3 fats with COVID-19 outcomes. An Iranian double-blind study of 128 critically ill COVID-19 patients reported that low dose fish oil [1 capsule containing 400 mg EPA and 200 mg DHA daily] reported that 1 month survival was significantly improved in the patients receiving low dose fish oil (21% Vs. 3%, p=0.003] [143]. In addition, creatinine and BUN parameters were significantly improved in the patients given fish oil [143]. A case series was presented of 3 patients who recovered from COVID-19 infection when given 2 grams of icosapent ethyl (a form of EPA) daily by nasogastric tube [144]. A recent short review also suggested that parenteral fish oil could be useful to treat COVID-19 patients due to their wide ranging anti-infective and anti-inflammatory properties [145].

Phytonutrients may be Helpful in Controlling COVID-19

Phytonutrients are chemicals produced by herbs, vegetables, and fruits that often have beneficial biological properties. Some researchers have speculated that higher consumption of fruits and vegetables in general may be useful in controlling COVID-19 [146,147]. A study of overall food consumption rates and COVID-19 mortality in 158 World Nations Reported that increasing consumption of fruits ($p=0.047$) and increasing consumption of legumes and beans ($p=0.046$) were both associated with significantly lower COVID-19 mortality, while increased consumption of sugar sweetened beverages was associated with significantly higher COVID-19 mortality ($p<0.001$) [148]. Other researchers have suggested treating/preventing COVID-19 with a variety of herbs/fruits vegetables which have anti-inflammatory and anti-infective properties including quince, apple, citrus fruits, grape, carrot, tea, pomegranate, parsley, and nettles [149]. Other studies have suggested that specific phytochemicals (many are polyphenols) may be useful for controlling COVID-19 [146,147]. Some researchers have suggested that cruciferous vegetables (broccoli, cauliflower, cabbage (often fermented), kale, arugula etc) contain chemicals such as glucoraphanin and sulforaphane may reduce risk of COVID-19 by up regulating the nrf2 central antioxidant system [150,151]. Other research has suggested that vegetables in onion family such as onion and garlic contain organosulfur and flavonoid compounds which have anti-inflammatory and immunomodulatory effects which may be useful in controlled COVID-19 [152,153]. An *in silico* study reported that 7 phenolic phytochemical compounds were able to reduce ACE2 binding including quercetin, curcumin, naringenin, luteolin, heperidin, mangiferin, and gallic acid [154,155]. In addition, 7 alkaloids and terpenoids, including berberine and piperine were also able to bind to the ACE2 receptor *in vitro* [154].

Resveratrol is a phytochemical found in many plants including grapes, blueberries and cranberries [156]. Resveratrol may be able to reduce the damage caused by COVID-19 infection through its anti-inflammatory and anti-thrombotic properties [156]. In addition, a cell culture study reported that resveratrol was found to inhibit the replication of SARS-Cov2 in culture Vero cells [157].

Quercetin is a flavenol phytochemical found in many plants including onions, cruciferous vegetables, tomatoes, and blueberries. Quercetin can block the ACE2 receptor and reduce the level of SARS-Cov2 and other coronaviruses into the cell [155]. Combinations of quercetin with vitamin C exert a synergistic anti-viral effect [158]. Biancatelli et al. suggest trials of vitamin C with quercetin for high COVID-19 risk populations-with or without other nutrients and/or other COVID-19 treatments such as Remdesivir and convalescent plasma [158]. Besides quercetin, many other flavenols from fruits and vegetables have strong anti-inflammatory anti-viral properties by many mechanisms including inactivating the S protein on the glycoprotein surface of SARS-Cov2 and destabilizing the SARS-Cov2 ACE2 binding site [159]. The safety profile of most flavenols is excellent and flavenols in food, food supplements, and drugs should probably be employed in future COVID-19 studies [159,160]. Curcumin has a wide range of anti-inflammatory, anti-thrombotic, and antiviral effects and may also modify ACE2 receptor repression [161,162]. It has been observed that COVID-19 rates are relatively low in South East Asian Nations which consume relatively high amounts of curcumin [161]. Seaweeds possess many phytochemicals which have strong antiviral, antioxidant, anti-inflammatory effects which may be helpful in controlling COVID-19 [163]. It has been suggested that the relatively low rate of COVID-19 in Japan may be due to the high amounts of seaweed in the Japanese diet [163].

Other research has reported that many oils such as olive, cocounut, eucalyptus, lavender, oregano, and tea tree oils and many herbs such as astragalus, Echinacea, liqourice root, cinanamon, Ashwaganda, shiitake mushrooms, and many others have antiviral and/or antinflammatory properties which may be useful for preventing or treating COVID-19 [164].

Mediterranean Diet may be Useful for COVID-19

Several papers have suggested that the Mediterranean diet-rich in fish, olive, oils, nuts, fruits and vegetables and having strong anti-inflammatory and anti-thrombotic properties which-may be useful for reducing COVID-19 morbidity and mortality [165].

Probiotics and Leaky Gut

Probiotic bacteria like Lactobacillus and Bifidobacterium in the intestines have broad immunostimulatory and broad antiviral, antibacterial, and antifungal activity and supplemental probiotics have also been suggested as way to prevent and treat COVID-19 and other fungal infections [166,167]. One study suggested that levels of gut plasma permeability factors was significantly higher in COVID-19 patients than controls, and interventions to reduce gut permeability (such as probiotics, glutamine, and avoiding GI allergens and toxins) may be useful in COVID-19 patients [168].

Lactoferrin and Whey

Lacteroferrin is a glycoprotein found in mammalian milk (and is human milk is about 10 times more concentrated than cow and goat milk) which has broad anti-viral and anti-bacterial properties and has been suggested as a supplement to prevent and treat COVID-19 [169,170]. Human whey protein has been reported to strong effects of inhibiting SARS-Cov2 replication in Vero E6 and A549 cell lines [170-173].

Conclusion

Use Proper nutrition offers great promise in preventing and treating COVID-19 and other viral infections. Nutrition is often an overlooked factor in hospitalized patients. General malnutrition is very common in hospitalized COVID-19 patients-with various studies reporting levels of malnutrition between 5.4 and 85.8% depending upon specific hospitalized populations and definitions of malnutrition. Many studies have reported that malnutrition is associated with significantly more COVID-19 infection rates, severity and mortality. Dietary supplementation with a number of specific nutritional factors have been associated with better COVID-19 outcomes including, vitamin D, vitamin C, zinc, Ω-3 Fats, and glutamine. Many other supplements and phytochemicals have promise in preventing and treating COVID-19 and other viral infections, including vitamins A, vitamin B complex, vitamin E, probiotic bacteria, N-acetyl cysteine (NAC), l-carnitine, coenzyme Q10, α-lipoic acid, and phytochemicals from many fruits and vegetables. Much more research is needed to determine the levels of nutrient deficiencies in COVID-19 patients and also on the use of many nutrients, preferably in combination, to reduce COVID-19 morbidity and mortality.

Both low and high BMI may be associated with higher rates of COVID-19 severity and with death rates in a typical U-shaped fashion. The BMI cutoff point associated with significantly higher COVID-19 severity (around BMI 30 or slightly higher) appears to be lower than a similar cutoff point for influenza (around BMI). Further investigation and analysis on BMI weights and other nutritional markers as they relate COVID-19, influenza, and other respiratory pathogens might yield important information on the relationships between bodyweight, immunity and infections. Since many patients with COVID-19 and other infectious diseases may be deficient in many nutrients, multifaceted nutritional studies may be needed for optimal treatment and single nutrient supplement protocols will probably not produce statistically improved results. Ideally large studies with good controls and strong statistical power involving multiple nutrient interventions would be very useful to determine ideal nutritional strategies to prevent and treat COVID-19, influenza, and other respiratory infections. Several prospective studies are currently underway to examine the effects of supplementation of multiple nutrients on COVID-19 morbidity and mortality. For example, a Spanish study led by Dr. Arturo Yanez is currently examining the effects of a 2 × 2 × 2 nutritional analysis involving supplementation with 1] 4,000 IU Vitamin D/d Vs. placebo, 2] 1,000 mg omega DHA/EPA/d Vs. placebo, and 3] 1,000 mg. Vitamin C, vitamin B complex, and Zinc Acetate 100 mg/d Vs. placebo-on COVID-19 severity and mortality in about 1,500 COVID-19 patients.

Many of the interventional studies have employed relatively low doses of nutrients (such as 400 mg of EPA and 200 mg DHA in the Doaei study). Large studies are needed to determine optimal doses of supplement combinations to use. Somewhat larger levels of supplements may be useful in reducing COVID-19 morbidity and mortality, although there may be some toxic effects of large doses of some nutrients.

For the present, the best advice to patients at risk for or having COVID-19 is probably a advise broad based general diet, with adequate protein and omega 3, sufficient water, and wide range of fruits and vegetables. A good set of food supplements which include Vitamins A, B complex, C, D, E and zinc would probably also be useful. More research is needed to determine optimal supplement doses.

One limitation to this review is that it covered papers published only up to April 18, 2021. There will certainly be more good research papers and insights about the relationships between COVID-19 incidence, severity, and death rates published after April 18, 2021. Hopefully, the review will help to stimulate more research and clinical concern about COVID-19 and (mal) nutrition.

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