Inflammopharmacology (2023) 31:573–583
https://doi.org/10.1007/s10787-023-01183-3

Inflammopharmacology

REVIEW ARTICLE

Nutritional deficiencies that may predispose to long COVID

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Received: 15 February 2023 / Accepted: 28 February 2023 / Published online: 15 March 2023

Abstract
Multiple nutritional deficiencies (MND) confound studies designed to assess the role of a single nutrient in contributing to the initiation and progression of disease states. Despite the perception of many healthcare practitioners, up to 25% of Americans are deficient in five-or-more essential nutrients. Stress associated with the COVID-19 pandemic further increases the prevalence of deficiency states. Viral infections compete for crucial nutrients with immune cells. Viral replication and proliferation of immunocompetent cells critical to the host response require these essential nutrients, including zinc. Clinical studies have linked levels of more than 22 different dietary components to the likelihood of COVID-19 infection and the severity of the disease. People at higher risk of infection due to MND are also more likely to have long-term sequelae, known as Long COVID.

Keywords Multiple nutritional deficiencies · Lymphocyte proliferation assay · Myeloperoxidase · Glutathione peroxidase isozyme 4 · NADPH oxidase 2

Abbreviations

MND	Multiple nutritional deficiencies
LPA	Lymphocyte proliferation assay
MPO	Myeloperoxidase
GPX4	Glutathione peroxidase isozyme 4
NOX2	NADPH oxidase 2

Introduction

Micronutrient depletion is commonly associated with stress, aging, and infectious disease. Nutrients with solid evidence for stress-induced deficiency include magnesium, zinc, iron, calcium, and niacin (Lopresti 2019). An example of the reverse, deficiency-induced stress, includes cobalamin. On average, 41% of Americans have insufficient levels of cobalamin (vitamin B_{12}), as judged by a lymphocyte proliferation assay (LPA) (Bucci 1994). Low maternal plasma B_{12} and high folate during gestation predict increased HPA-axis stress in the offspring. Higher cortisol responses to stress in children resulting from such pregnancies have been documented during adolescence (median age = 13.6 years) by Krishnaveni et al. (2020). With a higher tendency for stress, these individuals have a greater chance of developing MND. Figure 1 illustrates this interdependence between stress-related deficit in micronutrients and deficiency-induced stress.

What are nutritional deficiencies and how are they determined?

Conventional nutritional science estimates less than 5.7% of people (USA) lack two-or-more essential nutrients (Bird et al. 2017). However, this assessment depends on the criteria employed to define an insufficient level of an essential dietary component. For many nutrients with pleiotropic effects on different organ systems and multiple biochemical pathways, disease in the whole organism manifests in more than one way and at more than one intake level. For example, the dietary requirement for vitamin D to prevent rickets is substantially lower than the requirement to reduce the risk of cancer or for proper immune system functioning (Holick 2020).

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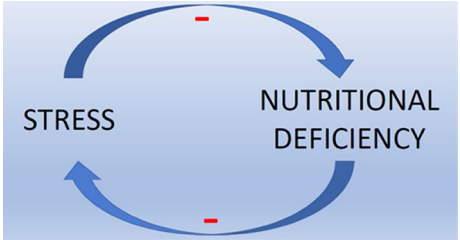

Fig. 1 Cyclic nature of stress and nutritional deficiency

Nutritional deficiency based on the LPA

William Shive, at the Clayton Foundation Biochemical Institute (CFBI), developed a robust method (LPA) for assessing individual deficiencies of many micronutrients based on lymphocyte proliferation (Shive et al. 1986). The CFBI at the University of Texas in Austin has a long and distinguished history of nutritional research. Roger John Williams founded the CFBI. He was a nutritional research pioneer who discovered vitamins B_5 (pantothenic acid), B_6 (pyridoxine), B_9 (folate), LA (lipoic acid), and avidin. Shive's method for rapidly determining deficiency states caused by diet or individual genetic variation finally addresses the concept of 'biochemical individuality' initially proposed by Roger J. Williams (1956). LPA determined the incidence of 19 different nutrient disorders in 833 Americans (Bucci 1994). Based on these data, 98% of Americans have at least one problem; 83% have two-or-more insufficiencies, and 25% have five-or-more nutritional deficiencies (Bucci 1994). MND would predict that a single supplement administered to a patient with multiple inadequacies may not correct disease symptoms resulting from the lack of several. Clinical testing of monotherapy is likely to be confounded by other coexisting deficiencies. Correlation of disease with a selected, single inadequacy is expected to have substantial scatter due to the possibility of MND in many (83%) patients.

Association of nutritional disorders with COVID-19 disease

Figure 2 illustrates the relationship between COVID-19 disease, the incidence of nutrient disorders, and the effect of nutritional supplements. The first two columns in this figure include nutrients or conditions (i.e., fructose intolerance and insulin dysfunction) known to be assessed by Shive's LPA. The incidence of disorders determined by LPA in a group of 833 Americans, expressed as a percentage, is included immediately following the name of the nutrient or condition (Bucci 1994). The third column of Fig. 2 contains nutrients, where LPA has not assessed the deficiency prevalence. Column three includes available data for the frequency of insufficiency determined by other methods. Based on a comprehensive evaluation of peer-reviewed literature in April 2022, those nutrients that had one-or-more credible publications linking them with the risk and severity of COVID-19 are indicated by a green checkmark (√). Those nutrients that exacerbate the risk of COVID-19 disease or are toxic in excess have a red checkmark (√). Cobalamin (vitamin B_{12}) is particularly noteworthy, since the incidence of B_{12} deficiency correlates with COVID-19 disease (Wee 2021), but B_{12} supplements increase the risk of disease severity (Dalbeni et al. 2021). Most nutrients under consideration, 22 out of 29, have evidence to support the notion that their levels affect COVID-19 disease. Two micronutrients, zinc and selenium, are known to be toxic in excess (Fosmire 1990; Barceloux 1999).

Literature relating different nutrients with COVID-19 disease: cobalamin/vitamin B_{12} (Wee 2021; Elham 2021; Galmés et al. 2020; Dalbeni et al. 2021; Clemente-Suárez et al. 2021; van Kempen and Deixler 2021); calcium (Zhou et al. 2020; Osman et al. 2021; Yang et al. 2021; Zeng et al. 2021; El-Kurdi et al. 2020); zinc (Galmés et al. 2020; Dharmalingam et al. 2021; Zeng et al. 2021; Heller et al. 2021; Maares et al. 2022; Notz et al. 2021; Du Laing et al. 2021; Chillon et al. 2022); thiamin/vitamin B_1 (Al Sulaiman et al.

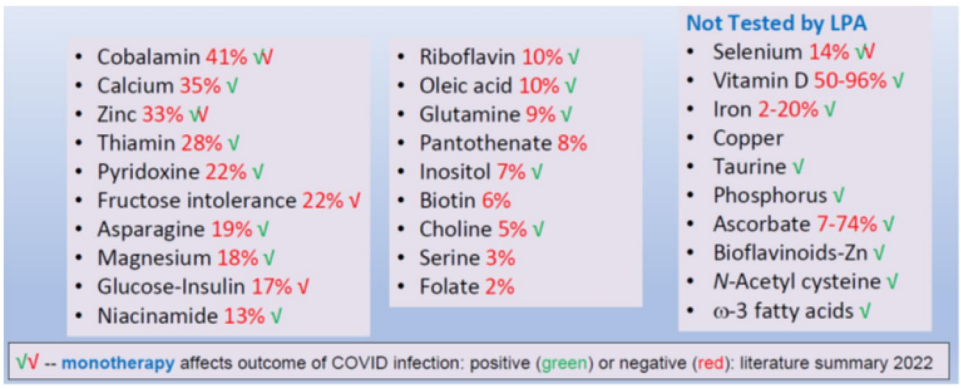

Fig. 2 Relationship between nutrient disorders and COVID-19 disease

2021; Branco de Oliveira et al. 2021); pyridoxine/vitamin B_6 (Kumrungsee et al. 2020; Galmés et al. 2020); fructose (Vazirani 2021); magnesium (Jose et al. 2021; Zeng et al. 2021; Trapani et al. 2022; Eskander and Razzaque 2022; van Kempen and Deixler 2021); glucose (Shauly-Aharonov et al. 2021; Wang et al. 2021; Ardestani and Azizi 2021); niacinamide/vitamin B_3 (Raines et al. 2020); riboflavin/vitamin B_2 (Akasov et al. 2022); oleic acid (Clemente-Suárez et al. 2021); glutamine (Matsuyama et al. 2021; Cengiz et al. 2020; Soliman et al. 2022); inositol (Espinola et al. 2021; Bizzarri et al. 2020; Laganà et al. 2020); choline (Olivari et al. 2020; Freedman et al. 2020; Bizzarri et al. 2020); selenium (Galmés et al. 2020; Im et al. 2020; Dharmalingam et al. 2021; Clemente-Suárez et al. 2021; Fakhrolmobasheri et al. 2022; Khatiwada and Subedi 2021; Schomburg 2022; Heller et al. 2021; Moghaddam et al. 2020; Notz et al. 2021; Du Laing et al. 2021; Zhang et al. 2020; Skesters et al. 2022); cholecalciferol/vitamin D (Galmés et al. 2020; Grant et al. 2020; Im et al. 2020; Clemente-Suárez et al. 2021; van Kempen and Deixler 2021; Weir et al. 2020; Kaya et al. 2021); iron (Galmés et al. 2020; Nai et al. 2021; Habib et al. 2021; Drakesmith et al. 2021; Taneri et al. 2020; Dharmalingam et al. 2021; Zeng et al. 2021; Clemente-Suárez et al. 2021); taurine (Iwegbulem et al. 2022; van Eijk et al. 2022); phosphorus (van Kempen and Deixler 2021; Seers and Davenport 2020); ascorbate/vitamin C (Liu et al. 2020; Hemilä and de Man 2021; Holford et al. 2020; Galmés et al. 2020; Clemente-Suárez et al. 2021; Biancatelli et al. 2020); bioflavonoids (Derosa et al. 2021; Biancatelli et al. 2020; Español et al. 2021; DI Pierro et al. 2021; Landis et al. 2022); *N*-acetyl cysteine (Shi and Puyo 2020; Assimakopoulos et al. 2021; Mohanty et al. 2021; De Flora et al. 2020; Zhou et al. 2021; Jorge-Aarón and Rosa-Ester 2020; Wong et al. 2021; Andreou et al. 2020; de Alencar et al. 2021; Kapur et al. 2022); ω-3 fatty acids (Clemente-Suárez et al. 2021; Das 2020; Goc et al. 2021); retinoic acid/vitamin A (Galmés et al. 2020); folate (Galmés et al. 2020; Meisel et al. 2021; Doaei et al. 2021); copper (Galmés et al. 2020; Dharmalingam et al. 2021; Zeng et al. 2021; Andreou et al. 2020); iodine (Fröhlich and Wahl 2021); nickel (Dharmalingam et al. 2021); lithium (Dharmalingam et al. 2021); chromium (Zeng et al. 2021); manganese (Zeng et al. 2021); albumin (El-Kurdi et al. 2020); potassium (Liu et al. 2021; Alfano et al. 2021; Noori et al. 2022); sodium (Gheorghe et al. 2021).

The contribution of zinc and selenium deficiency to morbidity and mortality from COVID-19 disease

There is a clear correlation between zinc or selenium deficiency with morbidity and mortality from COVID-19 infection (Heller et al. 2021; Moghaddam et al. 2020; Maares et al. 2022; Notz et al. 2021; Du Laing et al. 2021). The humoral response, production of antibodies after SARS-CoV-2 vaccination, also correlates with free zinc, but not total serum zinc concentrations (Chillon et al. 2022). Although correlation does not necessarily prove causation, the essential role of zinc in the production of 10% of all proteins (Read et al. 2019) and of selenium in DNA biosynthesis or alkyl-hydroperoxide detoxification (Muller et al. 2007) would argue that there is a mechanistic explanation.

Zinc is a gatekeeper of immune function (Wessels et al. 2017). The knowledge that insufficient dietary zinc produces an elevated risk of infection dates to the early 1960s (Prasad 2001). Evidence suggests zinc deficiency causes cell-mediated immune dysfunction (cytokine storm), cognitive impairment (brain fog), and depression (Prasad 2013; Nowak et al. 2005). Zinc deficiency also is associated with retarded wound healing (Kogan et al. 2017), various types of cancer risk (Skrajnowska and Bobrowska-Korczak 2019), and heart failure (Rosenblum et al. 2020). Much of the pathology associated with suboptimal zinc is also associated with the sequelae of COVID-19, known as Long COVID.

Zinc and COVID-induced loss of smell and taste

Zinc supplements post-infection reduce the duration of anosmia, but not all symptoms resulting from SARS-CoV-2 infection (Abdelmaksoud et al. 2021). A likely explanation for the effect of zinc in shortening the duration of anosmia during COVID-19 disease involves the initial site of infection and the role that zinc plays in olfaction. The nasopharyngeal area is a common site for the first encounter with SARS-CoV-2. Loss of olfaction is an expected early symptom of COVID-19. As SARS-CoV-2 proliferates, it would result in local depletion of zinc, since many proteins (10%) and viral replication both require zinc ions. Localized zinc depletion would deprive olfaction of this essential metal ion. There are two steps in the detection of odorant molecules that require zinc. The first is the cleavage of conjugates that mask odorant detection, and the second is the conjugation of odorant molecules that terminates detection and prevents saturation of the olfactory receptor. The gene for the odorant metabolizing enzyme UDP-glucuronosyltransferase (UGT), elevated during zinc deficiency (tom Dieck et al. 2003), is linked to COVID-induced loss of smell (Shelton et al.2022). The odorant metabolizing enzymes, UGT, and β-glucuronidase are essential for the sense of smell (Neiers et al. 2021). Zinc activates the membrane-associated β-glucuronidase (Yamaguchi et al. 1990). High zinc concentrations can completely inactivate UGT and β-glucuronidase (Schöllhammer et al. 1975). These effects of zinc on β-glucuronidase and UGT can explain the paradoxical association of anosmia with zinc

deficiency (Pisano and Hilas 2016) and high-zinc resulting from the intranasal administration of zinc solutions (Alexander and Davidson 2006). Anosmia and dysgeusia are commonly associated with COVID-19 (Zahra et al. 2020) and dietary zinc deficiency (Pisano and Hilas 2016).

Selenium has a dual role in the progression of COVID-19 disease

Keshan disease is a highly fatal disorder first recognized in 1935 and ultimately linked to the consumption of crops grown in low-selenium soils (Chen 2012). Excess dietary selenium is also toxic. The effects of chronic exposure resulting from the consumption of crops grown in high-selenium soils (Lower Cambrian outcrop areas in Southern Shaanxi, China) are documented (Barceloux 1999; Du et al. 2018). Zhang et al. (2020) have pointed out that infections by SARS-CoV-2 and other viruses are more prevalent in those regions of China with low selenium soil content. Selenium deficiency also results in congestive cardiomyopathy, heart failure, cardiomegaly, increased risk of cancer, infection, inflammatory disease, diabetes, retarded wound healing, and infertility, while excess selenium results in brittle hair and brittle, thickened, stratified nails or loss of both hair and nails (Hariharan and Dharmaraj 2020; Fairweather-Tait et al. 2011). In the extreme, selenium deficiency or excess can result in death.

Figure 3 lists three selenium-containing enzymes (in red) essential to life based on gene-knockout experiments in mice (Muller et al. 2007). Glutathione peroxidase isozyme 4 (GPX4) is an enzyme capable of detoxifying alkyl-hydroperoxides, membrane-bound phospholipid-hydroperoxides, and dioxetanes, like those formed during the immune response to pathogens with reactive oxygen species (Belikov et al. 2015; Di Mascio et al. 2019). Thioredoxin reductase is essential for activating ribonucleotide reductase to form the deoxynucleotide precursors for DNA biosynthesis and T-cell proliferation (Sengupta and Holmgren 2014; Muri et al. 2018).

Glutamate cysteine ligase	*Gclc*$^{-/-}$	embryonic lethal
Glutathione peroxidase 4	*Gpx4*$^{-/-}$	embryonic lethal
Thioredoxin 1	*Txn1*$^{-/-}$	embryonic lethal
Thioredoxin 2	*Txn2*$^{-/-}$	embryonic lethal
Thioredoxin reductase 1	*Txnrd1*$^{-/-}$	embryonic lethal
Thioredoxin reductase 2	*Txnrd2*$^{-/-}$	embryonic lethal
Mn superoxide dismutase	*Sod2*$^{-/-}$	neonatal lethal

Non-lethal: *Cat, Gpx1, Gpx2, MrsA, Mt1, Mt2, Mt3, Prdx1, Prdx2, Prdx6, Sod1, Sod3, Ttpa, Ogg1*

Fig. 3 Enzymes essential to life; their gene designation; and phenotypic outcome of gene-knockout experiments in mice. Enzymes in red require an essential selenocysteine

Selenium deficiency would have a differential effect on the immune response and SARS-CoV-2 proliferation, since replication of the virus involves RNA biosynthesis (RNA-dependent RNA polymerase) in contrast to lymphocytes and polymorphonuclear neutrophils (PMN), which rely on DNA biosynthesis (Yin et al. 2020). Because of this, low selenium produces a disadvantage to the immune response relative to SARS-CoV-2 replication. Selenium deficiency would also increase the collateral damage to host cells during infection by limiting the host-protective effect of GPX4 (Martinez et al. 2021).

The first stage of immune response: proliferation

There are three stages of the immune response to infection by a pathogen, illustrated in Fig. 4. In the first stage, immunocompetent cells that can respond to viral antigens must proliferate to mount an adequate response to invaders that are also increasing in number. The role of many essential nutrients is evident in the first stage of the immune response. Zinc is an integral component of a wide range of proteins (10% overall) necessary for cell replication and is specifically involved in human DNA polymerases and other essential DNA-binding enzymes (Evanics et al. 2003; Petrucco and Percudani 2008). Selenium is necessary for the biosynthesis of deoxynucleotides for DNA replication and the proliferation of immunocompetent cells (Sengupta and Holmgren 2014; Muri et al. 2018). Glutamine is a regulator of DNA replication and cell multiplication and is an essential component of purine and pyrimidine biosynthesis (Zetterberg and Engström 1981; Cory and Cory 2006). Phosphate depletion markedly inhibits DNA synthesis and cell division (Alexander et al. 2022; Engström and Zetterberg 1983; Houillier and Salles 2021). Many other essential nutrients are required in adequate amounts to support the rapid response of the immune system to a pathogen threat. It is not surprising that most of the commonly encountered deficiencies (Fig. 2) have evidence linking them to the development of severe COVID-19 disease. Without an adequate increase in the pathogen-specific and auxiliary cells of the immune system, it will be overwhelmed by a rapidly increasing pathogen.

The second stage of response: innate immunity

The second stage of immune response is the direct destruction of the pathogen by polymorphonuclear neutrophils (PMN) and T lymphocytes. This cytotoxic defense system exposes the pathogen to reactive oxygen species (ROS).

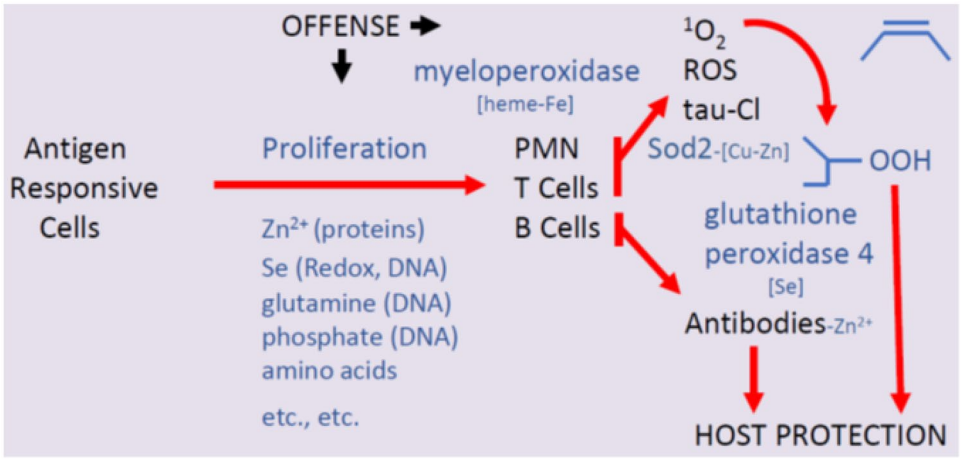

Fig. 4 Overall summary of nutrient roles in pathogen response

Myeloperoxidase (MPO) plays a role in the second stage of the immune response by producing hypochlorous acid/hypochlorite (ClO^-, $pK_A = 7.5$), singlet oxygen, and *N*-chlorotaurine (tau-Cl) (Aratani 2018; Kanofsky 1989; Schuller-Levis and Park 2003). In addition to the production of ROS localized in regions of infection, PMN, in combination with T lymphocytes, use a variety of cytotoxic mechanisms to fight infection, including the release of antimicrobial peptides and the expulsion of their nuclear contents to form 'extracellular traps' (Mayadas et al. 2014; Reusch et al. 2021; Witter et al. 2016). Although MPO is not essential to the innate immune response, MPO, PMN, and monocytes play a significant role in the pathology associated with severe infection (Shrivastava et al. 2021; Matsushita et al. 2015; Peyneau et al. 2022). ROS produced by MPO are not an essential component of the host defense response, since genetic deficiency in MPO only renders an individual less capable of clearing pathogenic organisms. However, it does not significantly increase the risk of severe infection unless the individual has diabetes (Nauseef 1988). Severe COVID-19 disease is associated with elevated levels of MPO (Shrivastava et al. 2021). The T cell GPX4 is essential for preventing T cell death by MPO-induced ferroptosis with concomitant loss of effective immune response (Matsushita et al. 2015).

MPO is a heme–iron-containing enzyme implicated in the pathology of chronic inflammation that, in the presence of hydrogen peroxide and chloride ions, will destroy its heme prosthetic group to generate free iron (Maitra et al. 2013). NADPH oxidase 2 (NOX2) requires essential heme–iron, FAD (riboflavin/vitamin B_2 derived), and NADPH (niacinamide/vitamin B_3 derived) cofactors to produce superoxide (Magnani et al. 2017). Unlike MPO-deficiency (Nauseef 1988), loss of NOX2 results in immunodeficiency and recurrent infections (Noreng et al. 2022). Inability to produce NADPH due to glucose 6-phosphate dehydrogenase (G6PD) deficiency renders an individual prone to infections, presumably due to reduced activity of NOX2, and susceptible to oxidative stress due to reduced activity of glutathione peroxidases (Luzzatto et al. 2020; Mallouh and Abu-Osba 1987). G6PD deficiency also increases the risk of COVID-19 disease (Vick 2020).

Superoxide produced by NOX2 is converted to hydrogen peroxide by superoxide dismutase (Winterbourn et al. 2016). Superoxide dismutase activity in PMN and lymphocytes depends on prosthetic copper and zinc cofactors (Vucić et al. 1997). Human catalase requires a heme–iron and NADPH (niacinamide/vitamin B_3 derived) cofactors and detoxifies hydrogen peroxide by its conversion to water and oxygen (Goyal and Basak 2010). Glutathionylation of catalase by NOX2 can result in PMN death (Nagarkoti et al. 2019).

MPO synthesizes ClO^- and tau-Cl from hydrogen peroxide, chloride, and taurine (Aratani 2018; Kanofsky 1989; Schuller-Levis and Park 2003). Hydrogen peroxide and alkyl-hydroperoxides can react with ClO^- and other oxidants (e.g., metal ions and peroxynitrite) to form singlet oxygen (Miyamoto et al. 2007; Kanofsky 1989). ClO^- is a highly reactive oxidant that can degrade the tetrapyrrole rings of hemoglobin, cause vitamin B_{12} and nitric oxide deficiency, compete with oxygen for hemoglobin binding, and is thought to be responsible for the induction of cytokine storms (Camp et al. 2021; Goud et al. 2021). ClO^- reacts rapidly with glutathione to give products that glutathione reductase cannot reduce (Carr and Winterbourn 1997). Tau-Cl is a somewhat less reactive oxidant than ClO^- with a longer lifetime and more extended range of action but similar detoxification chemistry by glutathione (Schuller-Levis and Park 2003; Kim and Cha 2014; Carr et al. 2001). Tau-Cl has anti-inflammatory effects by mitigating the inflammatory impact of ClO^- (Marcinkiewicz and Kontny 2014; Kim and Cha 2014). Singlet oxygen is the most reactive of the ROS. Despite the limited life of PMN-generated singlet oxygen due to its decomposition by radiative decay ($\lambda = 1270$ nm

and 1200 nm) it reacts at diffusion-limited rates with various intra- and extra-cellular components to form hydroperoxides and dioxetanes (Hackbarth et al. 2022; Stief 2003; Di Mascio et al. 1990; 2019; Skovsen et al. 2005). Singlet oxygen is also thought to potentiate thrombolysis (Stief 2007). GPX4 (an essential selenium enzyme) is required to prevent death by ferroptosis from the alkyl-peroxides and phospholipid-peroxides formed by singlet oxygen (Stockwell et al. 2020; Yang and Stockwell 2016).

The third stage of response: antibody production

Activated B lymphocytes will differentiate into antibody-producing plasma cells (Nutt et al. 2015). Chillon et al. (2022) have shown that the antibody response to vaccination with SARS-CoV-2 antigens correlates with free zinc but not with total zinc levels (99.999% protein-bound). The average level of free zinc in human serum is about 0.2 µM (0.09–0.42 nM), only 0.0015% of the total zinc, 11.5–15 µM (Chillon et al. 2022; Alker et al. 2019; Maares et al. 2022). The difference between serum free zinc in COVID-19 survivors is, on average, about twice the concentration of free zinc in patients that do not survive infection (0.4 vs. 0.2 nM) (Maares et al. 2022). Males tend to have slightly higher free zinc levels (0.23 vs. 0.21 nM) than females (Chillon et al. 2022; Maares et al. 2019).

IgG antibodies have a weak metal-binding site (copper or zinc) in their Fc region (Glover et al. 2015; Mehta et al. 2021; Yamanaka et al. 2016). Zinc binding to the metal site of IgG antibodies results in protein aggregation and prevents copper-induced degradation (Glover et al. 2015; Mehta et al. 2021). IgG is only one of many zinc-binding proteins in the blood, such as other immunoglobulins (IgM and IgA), albumin, α2-macroglobulin, haptoglobulin, fibrinogen, ceruloplasmin, complement C4, prealbumin, and C-reactive protein (Yamanaka et al. 2016). These proteins, together with other zinc-binding nutrients in the blood, such as the bioflavonoid quercetin, will maintain the 'free' zinc levels to facilitate cellular uptake by the ZIP transporters (Singh et al. 2021; Dabbagh-Bazarbachi et al. 2014; Haase and Rink 2014). Free zinc is a potent inhibitor of the SARS-CoV-2 main protease at nanomolar concentrations and is an inhibitor of viral replication (Panchariya et al. 2021). Adverse effects on antibody production at higher free zinc concentrations may explain the observation of maximum response during hypozincemia (Xu et al. 2022). There may be an optimal and dynamic range of free zinc for antibody response to SARS-CoV-2 that may not correspond to other aspects of the immune response.

Summary

Nutritional deficiencies predispose individuals to severe infection by SARS-CoV-2. COVID-19 disease further exacerbates dietary deficiencies. Stress before or after illness also lowers the stores of essential nutrients. Although zinc (33%) and selenium (14%) are prevalent deficiencies, there are more than 22 different nutritional factors (MND) reported to influence infection outcomes. People at higher risk of infection due to MND are also more likely to have long-term sequelae (Long COVID).

Acknowledgements No grant support was used to prepare this manuscript.

Funding Not applicable.

Data availability Enquiries about data availability should be directed to the author.

Declarations

Conflict of interest The author declares that he has no conflict of interest, financial or otherwise.

Consent for publication Not applicable.

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