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An Orthomolecular Protocol for Long COVID

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ABSTRACT

A significant number of COVID-19 patients suffer from SARS-CoV-2 post-acute chronic sequelae, also known as post-COVID syndrome or long COVID. These patients report a broad range of persistent and debilitating symptoms such as fatigue, brain fog, pain, breathlessness, and dysrhythmias. These chronic symptoms are believed to be a consequence of excessive production of reactive oxygen species (ROS), inflammation, tissue damage, and mitochondrial dysfunction. Patients at higher risk of long-term sequelae are those who experienced severe COVID-19 infection, are immunocompromised and likely have depleted reserves of biological factors and micronutrients necessary for prompt recovery. Based on biochemical principles and studies in conditions that share common traits with long COVID patients such as chronic fatigue syndrome and fibromyalgia, symptom relief and sustained recovery can be expected by administering an orthomolecular protocol consisting of a combination of precursors, cofactors, and biological response modifiers.

INTRODUCTION

A significant number of patients are suffering from Post-Acute Sequelae of severe acute respiratory syndrome Coronavirus 2 infection (PASC), also known as post-COVID syndrome or long COVID. These patients report a broad range of persistent and debilitating symptoms centered around a general sense of fatigue, brain fog, pain, breathlessness, and dysrhythmias. These symptoms can persist for several weeks to months post-infection period (Wood et al., 2021).

There is a lack of systematic reporting on the long-term consequences of COVID-19 with relatively few studies on the subject. However, based on the available evidence, there seems to be a persistence of symptoms with delayed return to the baseline health status. Many patients with a confirmed COVID-19 diagnosis are reported to continue having at least one symptom beyond two weeks following acute infection (Lopez-Leon et al., 2021). PASC is most prevalence among patients who experience severe COVID infection, although many symptoms are still suffered by patients with a milder form of the disease (Bell, 2021; Parker, 2021).

The lack of a known etiology or pathophysiology, the variability in the symptoms, and the lack of external physical signs of the illness contribute to difficulties in developing an effective therapeutic protocol or a rational, targeted, interdisciplinary approach. PASC has often been referred to as an invisible disease, as people may appear healthy and well, but report feeling very ill. This means that there might be a significant number of people suffering from this condition without well-defined solutions.

DISCUSSION

In a population-based probability survey of 593 hospitalized and non-hospitalized adult patients with COVID-19, it was found that patients reporting very severe symptoms from initial infection had 2.25 times higher prevalence of 30-day and 1.71 times higher prevalence of 60-day PASC (Hirschtick, 2021). In this same study, hospitalized respondents had ~40% higher prevalence of PASC of both 30-day and 60-day COVID-19 (Hirschtick, 2021). In a recent systematic review of 250,351 COVID-19 survivors, it was found that over half of the survivors experienced PASC for 6 months after recovery (Groff, 2021). The most frequently reported PASC consequences involved functional mobility impairments, pulmonary abnormalities, and mental health disorders. Since these long-term PASC effects are occur-

ring on a very significant scale; it is important to develop a rational, safe and affordable protocol that can provide relief and effectively address the pathogenetic causes of this condition (Groff, 2021).

According to other studies, risk factors for PASC include having more than five initial symptoms in the original infection, severe COVID-19, increased D-dimer, increased C-reactive protein, increased interleukin-6, decreased lymphocyte count, pre-existing comorbidities, prior psychogenic disorder, and old age among others (Yong, 2021).

MANAGEMENT OF POST COVID-19 FATIGUE AND LONG COVID

Persistence of some of the acute illness physical symptoms, including dyspnea, fatigue, post-exertional malaise, chest pain, and cough, are the most common manifestations of long COVID-19 (Carfi et al. 2020). Patients can also experience gastrointestinal and neurological symptoms (Yong, 2021). Fatigue has been the most common complaint. The mechanisms underlying this post-viral fatigue syndrome in COVID-19 have been proposed to be similar to that of chronic fatigue syndrome (CFS) (Komaroff, 2021).

There seems to be a persistent inflammatory and excessive reactive oxygen species (ROS) production that affects mitochondrial function among other things (Tereshin, 2021; de Las Heras, 2020; Piotrowicz, 2021). Thus, our proposed protocol concentrates primarily on neutralizing excessive ROS, re-establishing mitochondrial function, and reducing excess inflammation.

ORTHOMOLECULAR NUTRITION AND SUPPLEMENTATION

Since patients who have more severe COVID are more likely to have post-covid syndrome (Hirschtick, 2021), it is likely that they have more extensive tissue damage and therefore have a longerrecovery and repair period. Having more extensive damage is potentially the reason for extended inflammation, increased generation of ROS, and mitochondrial damage (Yong, 2021). Correcting mitochondrial function has produced improved outcomes in other conditions such as chronic fatigue syndrome and other energy-related Illnesses (Nicolson, 2004). It is also hypothesized that improving mitochondrial function may in the alleviation of a variety of symptoms ranging from pain to mobility and energy in post-COVID syndrome.

This article will focus mostly on the use of nutritional concepts, pharmacologic nutritional biochemistry, and metabolic optimization to improve post-COVID syndrome outcomes. Careful selection and consumption of food at optimal intervals, combined with nutrient supplementation in amounts that are established as safe and potentially effective, may provide a solution for many people. Some anti-inflammatory agents are known cause mitochondrial dysfunction and adenosine triphosphate (ATP) depletion by a variety of mechanisms such as an increase in ROS, damage of mitochondrial membrane lipids, and a decrease in glutathione (Salimi, 2019). The role of pharmaceuticals is not within the scope of this article.

Mitochondria are organelles that are present in most cell of the body and produce a substantial portion of the body's total energy. Viral infection triggers mitochondrial damage, accompanied by increased ROS production. ROS, in turn, damages the mitochondrial membranes, mitochondrial deoxyribonucleic acid (mtDNA), and proteins, including those comprising the electron transport chain (ETC), thereby decreasing ATP production. There are dysfunctional pathways that can develop that are related to chronic fatigue. Moreover, an increase in glycolysis causes further mitochondrial damage and contributes to other cellular dysfunctions (Boothet et al., 2012). There are a variety of nutritional-related, or analogs of endogenous substances with biochemical and biological actions that improve physiology. Molecules are mostly of natural origin, have the correct structure and form, and are supplied at the correct amount are termed orthomolecular substances. These orthomolecules may reduce inflammation and mitochondrial damaging ROS, provide lipids for membrane repair and precursors and cofactors needed for the production of oxidative phosphorylation (energy). In individuals experiencing with illness, some of these orthomolecules are frequently scarce; thus,providing individuals with orthomolecules at sufficient quantities and form often facilitates and enhances mitochondrial functioning (Gonzalez et al., 2018).

Two other aspects of the post-COVID syndrome management are to: 1) address excessive inflammation; and 2) minimize free radical formation and propagation. These two aspects are interrelated, and their control is critical in the healing process.

COVID-19 infection and post-COVID syndrome are associated with the involvement of diferent organs and systems, such as lung, liver, kidney, heart, and

gastrointestinal, hematological, and nervous system with a high rate of mortality and induction of multi-organ failure. A recent cohort study of German patients (n=10) who recently recovered from severe COVID-19 infection, found that cardiac involvement was apparent in 78% of patients and ongoing myocardial inflammation presented in 60%, irrespective of infection severity (Puntmann et al., 2020). Fortunately, lung damage with acute respiratory distress syndrome (ARDS), including post-severe acute respiratory syndrome (SARS), tends to improve over time and often resolves (Salamon, 2020).

Post-viral brain involvement presents a temporary brain fog that does not manifest as long-term brain injury. Rather it involves persistent free radical irritation, a decrease in cerebral blood flow probably due to microglial activation, and alterations in temporal blood flow.

PROPOSED DIETARY PROTOCOL

Follow a diet rich in whole foods, high in antioxidants, and colorful phytonutrients with anti-inflammatory and detoxifying properties (i.e. organic berries, citrus fruits, spinach, garlic and onions, ginger, broccoli, red bell peppers, etc.). The diet should be low or minimal in refined carbohydrates and processed foods. Eat more vegetables, fruits, and nuts. Merino et al. 2021 showed that a dietary pattern characterized by healthy plant-based foods was associated with an overall 9% lower risk of COVID-19 infection and a 41% lower risk of severe COVID-19. Additionally, hydration is critical. It is recommended to consume 10–15 cups (2.5–4L) of water per day. A good sign of adequate hydration can often be increased frequency of urination, approximately four to six times per day, and improved energy levels.

Hyperglycemia in COVID-19 patients is a frequent complication. High blood glucose has been identified as an important risk factor for poor outcomes such as intensive care unit (ICU) admission, acute respiratory distress syndrome (ARDS), and death (Kitt, 2021). Hyperglycemia may result in vitamin C depletion possibly related to inhibition of ascorbic acid transport across the cell membrane of the leukocytes (Chen, 1983). It has been shown that prolonged hyperglycemia can cause significant decreases in chemotaxis, a fundamental biological process in which a cell migrates following the direction of a spatial cue. These results are consistent with the hypothesis that chronic hyperglycemia may be associated with impaired acute inflammatory response, increased susceptibility to infection, and altered wound repair (Pecoraro, 1987).

The angiotensin-converting enzyme (ACE2) has multiple physiological roles. ACE2 is a negative regulator of the renin-angiotensin system; a facilitator of both amino acid and SARS-CoV transport; and a SARS-CoV-2 receptor. It has been shown that ACE2 expression and activity are associated with obesity (Tejpal et al. 2020), suggesting the role of diet and cardiometabolic health in COVID-19 infection. Dietary patterns have a strong effect on ACE2 levels (Bousquet, 2020). Antioxidant activity and ACE2 inhibition have been found in many foods. Moreover, ACE2 levels in the blood are highly and rapidly sensitive to food intake. There are natural ACE2 inhibitors such as pomegranates, flaxseed, beets, apples, prunes, dark chocolate, garlic, kiwis, and blueberries.

PROPOSED ORTHOMOLECULAR PROTOCOL

Nutraceutical support of mitochondrial function is associated with a reduction in long-term fatigue and inflammation (Hamilton and Jensen, 2021).

High-Dose Intravenous Vitamin C (IVC): 25-50 grams, 2x per week for 4 weeks

The redox, anti-inflammatory, endothelial-restoring, and immunomodulatory effects of high-dose intravenous (IV) vitamin C might be a suitable treatment option (Riordan, 2003). The pathophysiology of COVID-19 is characterized by inflammation and oxidative stress leading to vascular and organ damage, as well as the suppression of adaptive immune responses (Vollbracht and Kraft, 2021). It is likely that the post-acute recovery phase is also accompanied by oxidative stress, inflammation, and thus a deficiency of antioxidants such as vitamin C. It is therefore clinically plausible that vitamin C administration could alleviate fatigue by treating vitamin C deficiency symptoms, and by neuroprotective and vasoprotective effects due to its antioxidant and anti-inflammatory properties.

Vitamin C: 1000 mg, 3x per day (oral)

Scavengers of reactive oxygen species, such as vitamin C can play an important role in minimizing the cytokine storm and preventing tissue damage. In doing so, the level of vitamin C can be rapidly depleted if not replenished (Gonzalez et al. 2020b; Miranda-Massari et al. 2020; Toro et al .2021; Rs et al. 2022). Oral intake should commence after intravenous therapy in order to maintain optimal physiological levels (Gonzalez, 2020a).

Magnesium Citrate: 500 mg, 2x per day

Magnesium (Mg) is a cofactor for over 300 metabolic enzymes that regulate multiple essential functions in central nervous system, endocrine system, and musculoskeletal system among others. Magnesium is insufficient in about 50% of the United States population (Reider, 2020). The supplementation of this mineral has been shown to prevent or treat a variety of disorders or diseases related to the respiratory system (Tang et al., 2020). SARS-CoV-2 may induce a cytokine storm that drains ATP whose regeneration requires phosphate and Mg. Available data show that phosphate and Mg levels are depleted in COVID-19 patients, with phosphate showing a remarkable correlation with its severity (van Kempen, 2021). It has been proposed that magnesium supplementation might help protect against SARS-CoV-2 infection, reduce the severity of COVID-19 symptoms, and facilitate recovery after the acute phase (Trapani, 2022).

Coenzyme Q10 (CoQ10): 100 mg, 3x per day

Coenzyme Q10 is a fat-soluble substance ubiquitously expressed throughout the body that is important for the generation of ATP and mediation of inflammatory disease. CoQ10 has an integral anti-inflammatory role in the body as a free radical scavenger and has been utilized in the treatment of a variety of inflammatory-mediated diseases (Polymeropoulus, 2020). CoQ10 supplementation has also been used in several inflammatory disease models of platelet aggregation, fibrosis, and chronic inflammatory disease (Mantle et al., 2020). CoQo10 has been found to successfully reduce fatigue and improve performance in both healthy people (Mizuno, 2007) and patients with chronic fatigue (Nicolson, 2004). Furthermore, a prospective, randomized, double-blind, placebo-controlled trial of 12-week duration in 207 patients with myalgic encephalomyelitis/chronic fatigue syndrome, the supplemented group (n=104) using 200 mg of CoQ10 and 20 mg of reduced nicotinamide adenine dinucleotide (NADH) had a significant reduction in cognitive fatigue and an overall improvement in health related quality of life compared to the placebo group (n=103) (Castro-Moreno, 2021). CoQ10 performs several cellular functions of potential relevance to the immune system. CoQ10 has a key role in cellular energy supply, via its role in oxidative phosphorylation within the mitochondria. The immune response has intensive energy requirements and an adequate supply of CoQ10 is required to enable the various immune cell types to optimally function. . There are two forms of CoQ10: ubiquinone (oxidized form) and ubiquinol (reduced form). Ubiquinol supplementation has been shown to improve fatigue in juvenile fibromyalgia (Miyamae, 2013).

Alpha Lipoic Acid (ALA): 300 mg, 2x per day

Alpha lipoic acid, also known as thiotic acid, is a sulfur compound widely distributed in all human cells with important oxidation-reduction (redox) activity that contributes to the regeneration of vitamins C and E and participates in the aerobic energy production (Podda, 1994). ALA has several beneficial effects such as glucose control, excess ROS control, and antioxidant regeneration. These effects may help reduce cell and tissue damage related to COVID-19. Mounting evidence suggests that SARS-CoV-2 infection leads to multiple instances of endothelial dysfunction, including reduced nitric oxide (NO) bioavailability, oxidative stress, and endothelial injury which are thought to be underlying mechanisms in the pathophysiology of COVID-19. Endothelial integrity is critical for micro- and macro-vascular health. ALA has been shown to improve endothelial function by restoring the endothelial nitric oxide synthase activity and reducing oxidative stress. By improving mitochondrial function, ALA can help sustain the tissues' homeostasis and by enhancing glutathione it could indirectly strengthen the immune system (Rochette and Ghibu, 2021). A small prospective randomized controlled clinical trial evaluated the use of ALA in critically ill COVID-19 patients. The mortality in the ALA group was much lower (37.5%) than in the control group (77.8%). However, because the number of patients was small (n=17) it did not reach statistical significance (Zhong, 2019).

Acetyl-L-Carnitine (ALC): 1000 mg, 4x per day

L-Carnitine (3-hydroxy-4-N-trimethyl-aminobutyrate) is a nutrient composed of the essential amino acids lysine and methionine. L-Carnitine is a trimethylated amino acid and functions as a cofactor to convert long-chain free fatty acids to acylcarnitine and transfer them to the mitochondrial matrix. Therefore, ALC plays a central role in the metabolism of fatty acids and its inadequacy will induce feelings of tiredness, lethargy, general fatigue. Many clinical trials have shown the effectiveness of L-carnitine in relieving fatigue caused by the intense treatment of cancer and multiple sclerosis (MS), amongother conditions (Vaziri-harami and Delkash, 2022). Evidence from clinical trials has shown that providing mitochondrial metabolic cofactors CoQ10, lipoic acid, and carnitine through supplementation can lower the

levels of several inflammatory biomarkers (Ambrosi, 2016; Donnino, 2011; Soltani, 2020; Savica 2005). ALC may help alleviate fatigue by supporting the production of mitochondrial energy, interfering with acetylcholine synthesis in the brain, and via anti-inflammatory and antioxidant mechanisms.

Mixed Phospholipids: 1000 mg, 3x per day

Evidence indicates that diminished mitochondrial function through loss of efficiency in the electron transport chain caused by oxidation occurs during fatiguing illnesses. Lipid Replacement Therapy (LRT) administered as a nutritional supplement of phospholipids (phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidyletanolamine) with antioxidants can prevent oxidative membrane damage, and LRT can be used to restore mitochondrial and other cellular membrane functions via delivery of undamaged replacement lipids to cellular organelles. Recent clinical trials using patients with chronic fatigue have shown the benefit of LRT plus antioxidants in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue. The LRT seems to work by protecting mitochondrial and other cellular membranes from oxidative damage as well as removing and replacing damaged lipids (Nicolson and Ellithorpe, 2004).

Astaxanthin (ASX): 12 mg, 4X per day

Astaxanthin is a red pigment related to the carotenes present in some algae with powerful antioxidant and immune-modulating properties. Specifically, ASX supports the regulation of cyclooxygenase-2 (COX-2) pathways and the suppression of cytokines (Ahmadi, 2021). It has been shown to exert a protective effect by regulating the expression of pro-inflammatory cytokines interleukin beta (IL-1β) interleukin 6 and 8 (IL-6, IL-8), and tumour necrosis factor alpha (TNF-α). ASX has been shown to prevent oxidative damage and attenuate exacerbation of the inflammatory responses by regulating signaling proteins and pathways such as nuclear factor kappa B (NF-κB), nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), and the Janus kinase/signal transducers and activators of transcription (JAK/STAT).This evidence provides a rationale for considering natural astaxanthin as a therapeutic agent in COVID-19 infection to reduce inflammation propagated by the cytokine storm (Talukdar et al.2020). Growing evidence suggests a specific association between the therapeutic effects of astaxanthin and its antiapoptotic properties which are of particular interest in COVID-19 given the known damages caused by ROS-mediated apoptosis. Therefore, astaxanthin looks promising to prevent the progression of multi-organ damage. (Fakhri, Yosifova, Aneva, et al., 2019).

Vitamin E (Tocopherols and Tocotrienols): 400 IU, 4x per day

Vitamin E has the potential be utilized to prevent oxidative damages associated with the SARS-CoV-2 pathogenesis due to its free radical scavenging effects (Samad et al., 2021). In addition, some studies suggest that vitamin E has antiplatelet and antithrombotic effects (González-Correa, 2005; Dowd, 1995), which might be useful considering that coagulopathies are a common complication in severe COVID-19 cases. In addition, a literature evaluation of 12 randomized controlled trials (246 participants in the intervention arms and 249 participants in control arms), found that serum levels of C-reactive protein (CRP), an inflammatory biomarker, were significantly lower in patients taking vitamin E (α-tocopherol or γ-tocopherol); thus supporting the notion that vitamin E may have anti-inflammatory properties (Saboori, 2014).

N-Acetyl Cysteine (NAC): 600 mg, 2x per day

N-Acetyl Cysteine (NAC), a precursor of the potent antioxidant glutathione has been used in clinical practice to treat critically ill septic patients and more recently for COVID-19 patients. In a 36-week open-label clinical trial conducted in eight older adults and eight young adults, a combination of NAC with glycine was supplemented. Supplementation in older adults help corrected red blood cell glutathione, glutathione deficiency, oxidative stress, and mitochondrial dysfunction (Kumar et al., 2021). Based on the results of multiple comprehensive measurements, NAC supplementation also helped improve inflammation, endothelial dysfunction, insulin resistance, genomic-damage, cognition, strength, gait speed, and exercise capacity (Kumar et al., 2021). Given the antioxidant, anti-inflammatory, and immune-modulating properties of NAC, it may be a potentially beneficial, safe, and feasible adjunctive treatment or prevention option for SARS-Cov-2 infection (Shi and Puyo, 2020).

Glutathione (GSH): 1000mg liposomal, 4x daily

Glutathione is an endogenous compound made from the amino acids glycine, cysteine, and glutamic acid. It is produced by the liver and involved in many processes, including protein manufacturing, tissue repair, metabolic detoxification, and also acts as potent intracellular

antioxidant. Some researchers have indicated that GSH is poorly absorbed when administered orally, primarily due to the action of the intestinal enzyme, γ-glutamyl transpeptidase (GGT) which actively degrades GSH (Zhang, 2005). However, intravenous administration, liposome encapsulated GSH, and other formulations have increased bioavailability (Buonocore, 2016). Some observational and research analyses have suggested that glutathione deficiency is a plausible explanation for some of the morbidity and mortality associated with COVID-19 (Polonikov, 2020; Silvagno 2020). Given this information, it has been proposed that GSH supplementation may be beneficial in COVID-19. GHS can mitigate the inflammatory response, specific for SARS-CoV-2, and dependent on its binding to its receptor ACE2, increased GSH levels may prevent and subdue the disease (Guloyan et al. 2020).

Omega 3: 1000 mg, 3x per day

Omega-3s are polyunsaturated fatty acids (PUFAs). Dietary sources include fish oils, algae, and phytoplankton and it's also present in some plants. Omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, are known to be incorporated throughout the body into the bi-phospholipid layer of the cell membranes leading to the production of fewer pro-inflammatory mediators. Omega-3 upregulates the activation of immune cells specifically macrophages, neutrophils, T-cells, B-cells, dendritic cells, natural killer cells, mast cells, basophils, and eosinophils. Omega-3 fatty acids regulate membrane fluidity and membrane lipid assembly (Hathaway et al., 2020). Supplemental forms should be molecularly distilled.

Systemic Proteolytic Enzymes (SPE): 3x per day, on empty stomach

Enzymes break the chain-like molecules of proteins (polypeptides) into shorter fragments (peptides) and eventually into their smaller basic components known as amino acids. Enzymes such as lysozyme, catalase, bromelain, and papain are known to function as immunomodulators and work to combat oxidative stress (Rathi et al., 2021). SPE may be capable of breaking down the spike protein. SPE may induce the unfolding of recombinant spike and envelope proteins by reducing disulfide stabilizer bridges (Akhter et al., 2021). In a prospective randomized controlled cohort study of 429 COVID-19 patients with at least one chronic disease and moderate-to-severe respiratory symptoms, investigators compared routine care versus QCB (quercetin, vitamin C, bromelain) supplementation. Quercetin is a bioflavenoid that activates or inhibits the activities of a number of proteins in vitro. The supplementation group had significantly greater decreases in C-reactive protein (CRP) and ferritin, as well asand increases in platelet and lymphocyte counts (Önal et al., 2021). Another review of 10 studies found that the use of bromelain was effective in reducing pain, inflammation, and stiffness in patients with osteoarthritis (Brien, 2004). Another study in a group of 116 children with sinusitis showed that those who used bromelain alone had symptom relief in a shorter period than with the other therapies used (Braun, 2005). Taken together, these studies suggest that both quercetin, with SPE properties, and bromelain may help reduce inflammation and symptoms associated with COVID-19.

Palmitoylethanolamide (PEA): 600 mg, 2x per day

PEA is an amide of endogenous fatty acid of the N-acylethanolamine family with immunomodulatory, anti-inflammatory, neuroprotective, and pain-relieving effects (Noce et al., 2021). PEA is a cannabimimetic compound that performs a wide variety of biological functions to counteract chronic pain and inflammation (Gatti et al., 2012). An antiphospholipid syndrome secondary to SARS-CoV-2 infection can occur from cytokine storm resulting in phospholipids consumption. In a case study, PEA was used successfully in a 45-year-old COVID-19 female with antiphospholipid syndrome (Roncati et al., 2021).

Specialized Pro-Resolving Mediators (SPM): 500 mg, 3x per day

Specialized pro-resolving mediators are a group of endogenously produced lipid substances that promote resolution of inflammation. They consist of lipoxins, resolvins, maresins, and protectins and represent a novel class of bioactive lipids that are generated by enzymatic oxygenation of n-3 and n-6 polyunsaturated fatty acids (PUFAs) after the initial stages of the inflammatory cascade. SPM may enforce the pro-resolutive axis of inflammatory processes. This might also help improve chronic courses associated with inflammation of heart and lung tissue (Regidor et al., 2021). They can also regulate macrophage infiltration, cytokine production, and stimualte pro-resolving macrophage phenotypes (Balta et al. 2021).

SUMMARY OF SAFETY AND OTHER CONSIDERATIONS

The list of biological response modifiers that have been discussed within this protocol (micronutrients, cofactors, peptides, fatty acids and botanicals) is not exhaustive. Rather, this protocol serves to provide a practical overview of several biological response modifiers and suggest their role in the practical management of COVID-19. There are many other factors that might contribute to recovery (i.e., probiotics). High-dose intravenous vitamin C followed by oral supplementation is very safe and well tolerated. Some people have limited tolerance to oral supplements, usually related to a weakened gastric or intestinal mucosa. Therefore, supplementation should be adjusted based on individual tolerance. As some people may not tolerate supplementation with all 14 supplements mentioned within this protocol, is important to plan a strategy that fits the specific needs of each individual patient. First, oral supplements are better tolerated when consumed with-meals and it always better to start with fewer products to ensure tolerance before adding other oral products.

Although the first five supplements (vitamin C, Mg, CoQ10, ALC, ALA, and phospholipids) have different physiological functions and mechanisms of action, they all work to support cell energy production. The next four supplements (ASX, vitamin E, NAC and GSH) also have a variety of distinct physiological actions and share antioxidant properties. The last group (omega-3, proteolytic enzymes, PEA and SPM) share anti-inflammatory effects.

Some patients with recent trauma, post viral infection with SARS-Cov-2 or post-COVID-vaccine adverse effects may have elevated levels of D-dimer, coagulation factors, and inflammatory markers. Patients that are on anticoagulants and/orhave history of coagulation disorders should be cautious with medications which have antiplatelet effects like aspirin. Also note that alpha-tocopherol (vitamin E) and acetylsalicylic acid have been shown to increase gingival bleeding (Liede, 1998). However, mixed tocopherols have not shown this effect. Omega-3 possesses inhibitory effects in platelet function and some clinicians are concerned about possible risk of bleeding.

Laboratory testing can be very useful for guiding and targeting supplementation to help focus on particular insufficiencies.. Some of these laboratory tests may include measuring inflammatroy markers, serum nutrient levels, mitochondrial function markers, and coagulation markers among others. In the future, metabolomics or comprehensive metabolic profiling could give important insight into the patterns of metabolites related to the biochemical dysfunctions of concern.

There are other interventions that may improve outcomes but that require more specialized medical supervision. Some of these include, Hyperbaric Oxygen Therapy (HBOT), Photobiomodulation (PBM), Low-Level Laser Therapy (LLLT), Exosomes and mesenchymal stem cells (MSC).

CONCLUSION

The post-acute recovery phase of COVID-19 is assumed to be accompanied by oxidative stress, inflammation, and mitochondrial dysfunction which causes physical and mental fatigue. Chronic fatigue syndrome and fibromyalgia-like clinical manifestations following COVID can be very challenging to treat; nevertheless, they can be effectively treated when applying a proper therapeutic protocol. This protocol should consist of a combination of synergistic nutrients and co-factors that are known to have actions that mitigate the oxidative, inflammatory, and energy issues that are common in COVID-19 infection. The proposed protocol should have positive effect on diminishing chronic fatigue and other persistent long COVID symptoms.

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