The Presumptive Role of Oxidative Stress in Long-COVID and Its Potential Treatment with the Glutathione

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Article

The Presumptive Role of Oxidative Stress in Long-COVID and Its Potential Treatment with the Glutathione (3/10)

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Abstract: An increasing consequence of the COVID-19 pandemic is the growing population of individuals with long-covid (LC). Due to its chronic nature, the prevalence of LC greatly exceeds that of acute COVID-19 illness. Additionally, it can affect persons after mild or even asymptomatic SARS-Cov-2 infection. Its persistence and multiple debilitating symptoms negatively impacts the lives and livelihood of tens of millions of individuals and causes an economic burden of $ trillions. Its pathophysiology is not well established, and no accepted treatment is currently available. This review presents evidence of the possible role of oxidative stress (OS) in LC and the potential use of glutathione to address OS and thereby treat LC.

Keywords: COVID-19; long-COVID; oxidative stress; reactive oxygen species; glutathione; glutathione-cyclodextrin complex

1. Introduction

The health impact of the acute COVID-19 ilness is well established. A review by the National Academy of Medicine highlighted that in its wake, an even larger population now suffers from what is best known as "long-COVID" (LC) and officially by its arcane moniker of post-acute sequela of COVID-19 (PASC). It has affected over 60 million worldwide and 15 to 20 million in the United States (US) [1]. As of 2022, Cutler estimated the economic burden in the US to be $2.6 trillion from the combined reduced quality of life, reduced earnings, and medical spending [2].

2. Long-COVID

In a detailed review, Davis et al. outlined the associated immune dysregulation and multiple organ system involvement of LC [3]. The affected organ systems include the cardiovascular, nervous, endocrine, immune, gastrointestinal and reproductive system. LC is a complex condition as defined by Ely et al., that it 1) encompasses new, persistent, or relapsing symptoms following an initial acute COVID-19 infection, 2) may occur immediately or after a delay of weeks or months, 3) may persist for months or years, 4) may initiate new or exacerbate preexisting health conditions, 5) can affect individuals of all ages, 6) is unrelated to the severity of SARS-CoV-2 infection and can occur after an asymptomatic infection, and 7) impairs the daily function of individuals physically, mentally, and emotionally [1]. From the 2024 RECOVER cohort study, the most common symptoms of LC includes fatigue (86%), postexertional malaise (PEM) (87%), postexertional soreness (87%), dizziness (75%), impaired reasoning or "brain fog" (64%), gastrointestinal disturbance (59%), and palpatations (58%) [4]. Due to the persistence of these debilitating symptoms, it has become recognized as a second or "rebound" epidemic [5]. An observational study in England using the database of their national health service (NHS) reviewed the influence of acute COVID severity, SARS-COV-2 variant, illness duration, and hospitalization on cognitive impairment in LC [6]. Significantly, the risk of LC increases with each reinfection and may decrease with vaccinations [7,8]. A timeline of the recognition of LC was presented [8].

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Reviews of the proposed pathophysiologic mechanisms of LC has included the sequelae of direct tissue injury, immune system dysregulation, endothelial dysfunction, mitochondrial metabolic dysregulation resulting in OS, reactivation of harbored pathogens, complement dysregulation, autoimmunity, and functional changes in blood cells [8,9]. Unlike the immediate pathologic injury from the cytokine storm in acute COVID-19, the frequent months-long gap to the onset of LC symptoms, its persistence, and its development even after an asymptomatic infection makes a delayed immune response, autoimmunity, with or without a prolonged antigenic stimulus more likely [10,11]. This has brought into focus the risks of developing neurologic symptoms from COVID-19 that is similar to myalgic encephalitis/chronic fatigue syndrome (ME/CFS) and post-treatment Lyme disease syndrome (PTLDS) [12–14]. Unlike ME/CFS and PTLDS, the sequelae of LC are more complex since they involve the added consequence of tissue injury from acute COVID-19 illness and its influence on exacerbating or precipitating underlying diseases (e.g., of the endocrine, cardiovascular, and pulmonary systems) [3,14]. The similarities and differences between ME/CFS and COVID have been covered in comprehensive reviews [3,13,14]. Overlapping symptoms with ME/CFS include fatigue, post-exertional malaise (PEM), headaches, brain fog, myalgia/arthralgia, orthostatic intolerance from dysautonomia, nausea/diarrhea, and cough [3,8,15]. Symptoms peculiar to long-COVID include decreased or distorted smell and taste, rash, and hair loss. Those peculiar to ME/CFS include painful lymph nodes and tinnitus [14]. Likewise, a comparison of ME/CFS to PTLDS has been presented [16]. There is evidence to support that they all follow a trigger of autoimmunity that stems from the effects of persistent T-cell activation, which in COVID-19, may reflect antigenic stimulation by residual intact viruses or viral remnants [1,3,13,17–19]. Significantly, there is no biomarker to identify LC and it is diagnosed clinically [20]. The estimated cumulative economic cost from loss of quality of life, lost earning, and healthcare cost in the US in 2022 has been updated and recalculated at $3.7 trillion [8].

3. Reactive Oxygen Species (ROS) and Oxidative Stress (OS)

At a physiologic level, ROS regulates aging and activates the innate inflammatory response [21]. This innate response, in turn augments the secondary adaptive immune response [22]. ROS and reactive nitrogen species (RNS) include both radical forms (e.g. superoxide, hydroxyl radical, and nitric oxide) and non-radical forms (e.g. hydrogen peroxide, hypochlorous acid, and peroxynitrite) [22,23]. Although the non-radical species are not directly damaging to cells, they cause oxidative damage when converted to their radical form (usually after reacting with metal ions). As signaling molecules, ROS/RNS regulate or mediate many physiologic functions. These include gene activation, cellular growth, and blood pressure control [23]. The duality of ROS in diseases, whether physiologically beneficial or pathologically harmful, has been outlined [24]. The “Goldilocks” principle of adaptive vs deleterious ROS response using an exercise model has been presented [25]. The level of ROS, which in excess leads to deleterious OS, appears to be the determining factor for transitioning from its beneficial to pathologic effect.

OS occurs when the biological system creates excessive ROS, and to a lesser extent RNS, that alters the normal homeostatic balance between pro-oxidant and anti-oxidant molecules. ROS and RNS are produced in response to external stimuli. OS damage to DNA and other biomolecules that may impair normal functions of tissue cells and lead to human aging and disease [26,27]. Under adaptive physiologic conditions, excessive ROS can be controlled by enzymatic (superoxide dismutase, catalase, glutathione peroxidase - GPx) and non-enzymatic (glutathione) antioxidants. GSH is well-established as the most important cellular antioxidant [26–30]. ROS is primarily generated in mitochondria, but it is also produced in peroxisomes, endoplasmic reticulum, and lysosomes [23].

The influence of peroxisomes in neutralizing ROS was reported in a murine model [31]. Evidence was presented that the loss of peroxisomes in alveolar macrophages results in decreased control of OS leading to impaired lung repair, prolonged inflammation, and persistent pulmonary fibrosis in acute and chronic COVID illness [31,32].

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4. Proposed GSH and OS Influence in LC

The presumptive influence of oxidative stress (OS) in the development of many diseases and the role of excess reactive oxygen species (ROS) and glutathione (GSH) depletion to modulate OS has been presented [33]. A high level of OS is related to a greater severity of acute COVID-19 illness [34]. Although not as conclusive, LC exhibits a similar association with OS [35,36].Of the proposed mechanisms of cognitive dysfunction presented by Al-Aly and Rosen, elevated cytokine levels, endothelial inflammation, platelet and complement activation, and microthrombosis have been associated with OS [35,37].

Monje and Iwasaki detailed the multiple and overlapping ways that COVID-19 may affect the central nervous system (CNS): 1) stimulation microglia response to increased levels of cytokines and chemokines, 2) a direct infection of the CNS, 3) to evoke an autoimmune response against the CNS, 4) reactivation of latent herpesviruses that triggers neuropathology similar to ME/CFS, 5) precipitation of cerebrovascular and thrombotic events that induce ischemia, promote further neuroinflammation, or disruption of the blood-brain barrier function, and 6) a direct neural dysfunction from pulmonary or multi-organ dysfunction following severe COVID-19 [38]. Of the several presumptive pathogenic pathways of LC presented by Al-Aly & Topol, the presence of OS may be responsible for 1) autoimmune or an unchecked dysregulated immune response, 2) mitochondrial dysfunction, and 3) vascular (endothelial) and/or neuronal inflammation that has also been reviewed [10,33,39].

Further elucidation of the presumptive mechanism of LC was reported in an exhaustive prospective clinical analysis of 113 COVID-19 vs 39 healthy controls followed for up to a year after initial confirmation of acute SARS-CoV-2 illness [40]. Over 6500 biomarkers were analyzed. This study observed that LC patients exhibited an enhanced complement activation during the acute illness that persisted at 6-month follow-up [40]. Furthermore, LC patients had evidence of persistent thromboinflammation with its characteristic endothelial activation of vWF and thrombin cascade, platelet aggregation, and prolonged T-cell activation [18,41]. As previously mentioned, like ME/CFS, the presence of cytomegalovirus or Epstein-Barr virus antibodies is a possible risk factor of long-COVID [39,42]. However, data collected from the large RECOVER cohort study did not find a clinically useful biomarker to identify LC [20]. Finally, there currently is no accepted treatment for LC [3]. Significantly, the role of GSH in inhibiting antibody and complement-mediated immunologic cellular injury and the possible role of GSH in acute COVID-19 illness has been presented [43–46]. By reducing the presumed influence of OS to stimulate the pathophysiologic process of LC, GHS may indirectly reduce the degree and persistence of LC symptoms.

Many illnesses are associated with clinical markers. However, not all markers influence disease pathophysiology. Two critical questions must be answered. First, how influential is OS in the development of LC? Next, if OS is critical, can the antioxidant, GSH, counter the effect of OS in LC? As yet, the use of antioxidants in disease management has been disappointing. This is likely from use of weak antioxidants or of costly and inconvenient ones. The use of GSH has been well studied and is hampered by the lack of an effective and efficient delivery system. N-acetylcysteine (NAC) requires enzymatic conversion into GSH, oral GSH has low bioavailabilty, and intravenous GSH is costly and inconvenient. There is a novel product that may overcome these limitations – GSH that is sequestered in γ-cyclodextrin to produce the GSH-cyclodextrin (GC) complex. A small study using the G-C complex in young, healthy adults demonstrated its effect on reducing the level of malondialdehyde (MDA) (a product of lipid peroxidation) [47]. As a marker of OS, the reduction of MDA in those individuals presents indirect evidence of reducing OS. Significantly, γ-cyclodextrin can cross the blood-brain barrier (BBB) [48]. Rigorous studies with the complex will be needed to determine its efficacy and to determine the role of GSH in management of LC through its modulation of OS.

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5. Conclusions

LC has affected the lives of tens of millions of individuals in the US with a total economic burden of well over $2 trillion. However, treating LC faces many obstacles. Among them are that it: 1) is not a disease but a syndrome with a constellation of dozens of variable symptoms affecting almost all organ systems, 2) lacks a universally accepted definition, 3) is mostly self-reported, 4) has no unique biomarker, and 5) as yet has no identified and accepted underlying cause. Although LC eventually resolves, debilitating symptoms of those with LC negatively impacts individual lives and livelihood for many months. There are many questions that need to be studied and answered before targeting OS in the treatment of LS. First, is OS a marker or influencer of LC? Next, if OS is an influencer, can GSH reduce OS in LC? Finally, can the G-C complex effectively deliver GSH? Advantages of the complex are that it 1) is not a costly monoclonal antibody, 2) is a commercially available non-prescription product, 3) delivers GSH directly and does not require enzymatic conversion, 4) crosses the BBB, and 5) has no reported significant adverse side effects. The influence of OS in LC and use of GSH to treat it awaits studies using the complex. If confirmed, the application of GSH with the complex may be a cost-effective approach to the management of the socio-economic and healthcare crisis of LC. Given the complex and variable nature of LC, addressing OS has its limitations, however, studies with the use of GSH should help identify its role in treating LC.

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Abbreviations

The following abbreviations are used in this manuscript

BBB	Blood-brain barrier
GSH	Glutathione
GPx	Glutathione peroxidase
G-C	Glutathione-cyclodextrin
LC	Long-COVID
ME/CFS	Myalgic encephalitis/chronic fatigue syndrome
MDA	Malondialdehyde
NAC	N-acetyl cysteine
OS	Oxidative stress
PEM	Post-exertional malaise
POTS	Postural orthostatic tachycardia syndrome
PTLDS	Post-treatment Lyme disease syndrome
ROS	Reactive oxygen species
RNS	Reactive nitrogen species

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