Opinion

A Potential Role of Coenzyme Q10 Deficiency in Severe SARS-CoV2 Infection

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Abstract

There is a dramatic need for extensive research into the predictors of severe infection with SARS-CoV2 and therapeutic options for infected people. People who suffer from severe illness and higher mortality display a pattern of having specific co-morbidities (diabetes, obesity, hypertension) and are of higher age. Recent research has described methods of viral entry via receptors (ACE2, TMPRSS2) and the hyper-inflammatory state often associated with severe illness (increase in interleukins, increase in TNF-alpha). These discoveries have led to the research of currently available and developing therapies, that are helpful to patients. Deficiencies of specific vitamins and other endogenous molecules of the body should be examined to understand if a pattern exists among the people most severely affected. Coenzyme Q10 (CoQ10) is a fat-soluble substance ubiquitously expressed throughout the body that is important for the generation of ATP and mediation of inflammatory disease. CoQ10 faces a decline with increasing age, genetic predispositions, and ingestion of exogenous compounds that could reduce the level of CoQ10. Deficiencies and subsequent supplementation with CoQ10 recently has displayed encouraging results for the improvement

of a wide variety of diseases. This manuscript is significant as it points to a potential relationship of CoQ10 and the population suffering from severe illness of COVID-19, and further encourages the need for research into measuring the levels of CoQ10 and vitamins to understand if levels predict severe illness and mortality. This could offer new avenues into research in combating this pandemic and potentially future therapeutic options.

Keywords
COVID-19; Coenzyme Q10; antioxidant; SARS-CoV-2; inflammation

1. Introduction

Oxidative stress plays an important role in viral infection through multiple mechanisms, including the reduction of the host antioxidant response [1, 2]. The global scientific community is rapidly trying to delineate the pathophysiology of disease with SARS-CoV2 infection, by identifying associated biomarkers of severe illness in order to discover potential therapeutics. An examination of associations between levels of critical antioxidants such as Coenzyme Q10 (CoQ10), and severity of SARS-CoV2 infection should be examined, as potential associations may indicate markers of disease severity and possibly may have a causative role.

CoQ10 is a fat-soluble molecule that is a member of the ubiquinone family [3]. CoQ10 is ubiquitous in humans and present in most cells, and is both synthesized endogenously and acquired exogenously [3]. The highest levels of CoQ10 are in organs with the highest metabolic demand such as the heart, lung, kidney and liver [3]. CoQ10 has several important physiological roles including acting as an essential cofactor in the electron-transport chain to generate ATP and serving as a lipid antioxidant, neutralizing free radicals thereby preventing ensuing damage to the body [3]. Other researchers have also suggested a deficiency in CoQ10 allows for increased cellular damage from oxidative stress, potentially propagating the cytokine storm hypothesized to be driving severe illness associated with SARS-CoV2 infection [4]. A combination of reactive oxygen species (ROS) and viroporins due to viral infection, may be leading to the stimulation of pro-inflammatory signals, causing the cascade of inflammatory disease in susceptible individuals with COVID-19 pneumonia [5].

Levels of CoQ10 can be diminished for several reasons including advanced age, the effects of compounds interfering with synthesis, and genetic factors. Statins are a major class of compounds highly associated with diminished CoQ10 levels. Statins inhibit HMG-CoA reductase reducing synthesis of cholesterol and levels of CoQ10 due to the inhibition of a common pathway of synthesis [6]. Atorvastatin was found to decrease the level of CoQ10 by 49% within 14 days of treatment [6]. Supplementation with CoQ10 has demonstrated benefit in a variety of diseases. MELAS syndrome, a genetic disease leading to impaired mitochondrial energy production and multi-organ disease, has been treated with CoQ10 [7]. In young women with decreased ovarian reserve, where increased oxidative stress and lower levels of CoQ10 were found to be associated with disease, CoQ10 supplementation significantly improved the number of retrieved oocytes and fertilization rate [8]. CoQ10 may also have benefit in reducing cardiovascular fibrosis associated with aging [9]. CoQ10 levels peak around age 20, followed by an age-dependent decrease over time [10]. The largest tissue

specific decrease at age 80 occurs in the lungs (51.7% from peak) and heart (42.9% from peak) [10]. Mutations of several genes (primarily the COQ genes) involved in CoQ10 biosynthesis can result in a deficiency [11].

2. CoQ10 Anti-Inflammatory and Anti-Oxidant Roles in Disease

CoQ10 has an integral anti-inflammatory role in the body as a free radical scavenger, and has been explored in the treatment of a variety of inflammatory mediated diseases.

Treatment with CoQ10 has been evaluated in several diseases causing critical illness. CoQ10 supplementation improved survival and decreased pulmonary edema in sepsis-induced acute lung injury in rats [12]. Relatedly, in patients with septic shock, CoQ10 levels were found to be lower and correlated with higher levels of inflammatory markers [13].

CoQ10 supplementation has also been evaluated in several inflammatory disease models of platelet aggregation, fibrosis, and chronic inflammatory disease. Inhibition of platelet aggregation by CoQ10 was found to occur through multiple pathways, including the up-regulation of cAMP and PKA, and through the inhibition of vitronectin (CD51/CD61) [14, 15]. CoQ10 supplementation has been found to be beneficial in attenuating fibrosis in the lung and liver in rats through up-regulation of autophagy processes [16]. Supplementation with CoQ10 improves liver and systemic markers of inflammation in people with nonalcoholic fatty liver disease [17].

The utility of supplementation with CoQ10 has also been examined in cardiac and vascular disease. CoQ10 supplementation improves mortality and cardiac markers in people with heart failure [18, 19]. Total cholesterol and low-density lipoprotein levels improve in people with diabetes with CoQ10 supplementation [20]. Supplementation with CoQ10 has been found to improve endothelial dysfunction in people with dyslipidemia [21].

Regarding a potential role in viral infection, CoQ10 has been shown to be lower in patients with acute influenza [22]. A study of sixty-five children with influenza demonstrated that children with H1N1 had significantly lower levels of CoQ10 compared to the group with seasonal influenza [23]. Supplementation with CoQ10 was found to reduce severity of viral myocarditis and reduce mortality in mice, likely through the reduction of oxidative stress [24]. Treatment with CoQ10 in hospitalized elderly patients with community-acquired pneumonia significantly reduced hospital stay and improved time to abatement of fevers [25].

While CoQ10 levels decrease with age and also through the consumption of exogenous agents such as statins, it has also been seen that several genetic diseases result in CoQ10 deficiencies. People with Down syndrome were found to have lower levels of CoQ10, and higher levels of TNF-alpha and IL-6 [26]. Correspondingly, people with Down syndrome have a higher susceptibility to viral and bacterial infections, a higher incidence of autoimmune diseases (diabetes, hypothyroidism), and a higher incidence of acute lung injury [27]. Acute respiratory distress syndrome (ARDS) in people with Down syndrome has been postulated to be due to an imbalance in free radical scavengers [27]. Mutations of the CoQ genes can result in primary CoQ10 deficiency that is associated with low ATP production and the increased presence of ROS [11]. People with primary CoQ10 deficiency can have a range of clinical manifestations including encephalopathy, myopathy, and kidney disease, but many respond well to supplementation with CoQ10 to prevent further progression of disease [11].

3. CoQ10 and COVID-19

Understanding the etiology of why specific members of the population are more susceptible to severe disease necessitating hospitalization with SARS-CoV2 infection is important in the development of therapeutics, and may provide a rapid solution for this globally catastrophic pandemic. An examination of the epidemiological associations has demonstrated the occurrence of severe illness more widely in people of specific age groups possessing certain co-morbid conditions. Mortality and severity of illness of COVID-19 increases dramatically with increasing age [28]. The most common co-morbidities for hospitalized patients with COVID-19 are hypertension, diabetes, and obesity [28]. Although severe disease with COVID-19 often involves respiratory compromise with bilateral interstitial opacities on imaging; notably in the case of severe infection, pulmonary disease is less often a comorbidity [29].

An inverse correlation is seen with age and BMI, as it appears that younger people who were hospitalized were more often obese [30]. Statins are among the most widely prescribed medications in the United States in 2020, and would likely be more commonly prescribed to patients with disorders such as hypertension, diabetes, and obesity, frequently seen with severe SARS-CoV2 infection [31]. If decreased levels of CoQ10 are determined to increase susceptibility to severe COVID-19 pneumonia, people may consider stopping statins in the short-term during the pandemic to reduce risk.

Further, the finding of increasing age being associated with lower CoQ10 levels correlates well with the connection between age and severe illness in COVID-19, as the disease significantly affects individuals of older age more often while causing mild illness in the vast majority of children [30]. The severe complications of COVID-19 including ARDS are thought to be due to a hyper-inflammatory state [32]. Given the widespread role of CoQ10 in mitigating oxidative stress in the affected organ systems, interplay with inflammatory mediators, and the possibility that the demographic of severely affected people are at risk of CoQ10 deficiency, CoQ10 may be a marker of those susceptible to severe disease with COVID-19 and may be a causative agent for disease progression to the pathological hyper-inflammatory state (Figure 1).
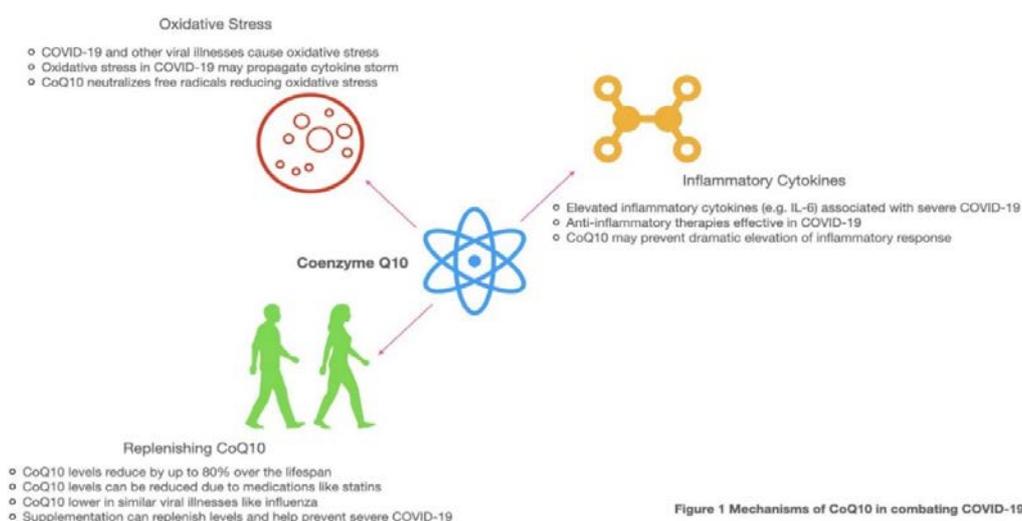

Oxidative Stress
- COVID-19 and other viral illnesses cause oxidative stress
- Oxidative stress in COVID-19 may propagate cytokine storm
- CoQ10 neutralizes free radicals reducing oxidative stress

Inflammatory Cytokines
- Elevated inflammatory cytokines (e.g. IL-6) associated with severe COVID-19
- Anti-inflammatory therapies effective in COVID-19
- CoQ10 may prevent dramatic elevation of inflammatory response

Coenzyme Q10

Replenishing CoQ10
- CoQ10 levels reduce by up to 80% over the lifespan
- CoQ10 levels can be reduced due to medications like statins
- CoQ10 lower in similar viral illnesses like influenza
- Supplementation can replenish levels and help prevent severe COVID-19

Figure 1 Mechanisms of CoQ10 in combating COVID-19

Figure 1 Mechanisms of CoQ10 in combating COVID-19: 1 Scavenging free radicals and reduction of oxidative stress; 2 Mitigation of damaging inflammatory cytokines; 3 Replenishing levels in aging individuals whose levels of CoQ10 decrease with age.

4. Exploring the Role of CoQ10 in COVID-19

A potential association may exist between reduced levels of CoQ10 and the population of people most severely affected by COVID-19. The causative mechanisms of creating a susceptibility to severe illness remain unclear, though they could be a result of a reduced ability to preventing oxidative stress, attenuating coagulation, mitigating a hyper-immune response, or inhibiting viral replication or viral entry directly. The deficiencies associated with disease may involve other antioxidants such as Vitamin C and E. Exploring whether correlations exist between known antioxidants such as CoQ10 and inflammatory cytokines can help further understand the pathophysiologic process and find new therapeutic solutions.

Patients with influenza were found to have significantly lower levels of CoQ10 when compared to healthy controls [22]. Further, Il-2 and TNF-alpha were found to be negatively correlated with levels of CoQ10 in influenza patients [22]. Large studies should continue to measure CoQ10 levels along with vitamins and lipids of infected people with COVID-19 at the time of presentation to examine whether correlations predict clinical outcomes and correlate with the levels of inflammatory cytokines and molecules such as IL-2, IL-6, TNF-alpha and D-dimer. Studies have demonstrated relatively higher levels of Il-6 in patients with severe COVID-19 [33]. The cytokine storm hypothesis has prevailed as the leading hypothesis for the development of complications resulting in severe COVID-19, with a focus on IL-6 [34]. The evaluation of anti-inflammatory therapies has been investigated in patients with severe COVID-19, with corticosteroids showing significant therapeutic benefit and reduction in mortality [35]. Recently, the JAK1/2 inhibitor baricitinib, when combined with remdesivir, was shown to reduce median recovery time by one day [36]. As such, CoQ10, which mitigates the hyper-immune response may play an integral role in the susceptibility and development to severe COVID-19. Clinical outcomes of COVID-19 in individuals with genetically predisposed CoQ10 deficiency should also be examined.

Given the complexity of SARS-CoV2 infection and heterogeneity in disease presentation, the reasons for severe illness are likely multifactorial. CoQ10 may serve as a marker correlated to severe illness, and potentially as a causative agent for susceptibility to worse clinical outcomes.

5. Conclusions

If an association is confirmed, a causative mechanism could further be explored and CoQ10 may potentially become a protective therapy in the future. Studies using CoQ10 supplementation found that daily doses of between 100mg to 200mg significantly improved inflammatory markers [37]. Based on these results, dosing to replenish levels of CoQ10 in deficiency could be initiated between 100mg to 200mg daily to have physiological impact [37]. While supplementation with CoQ10 is generally well-tolerated, adverse effects have included gastrointestinal upset, abdominal discomfort, allergic reaction and headache [38]. As is the case with many disease states, more impactful benefits can be made when treatments are used as prophylaxis. If lower levels of CoQ10 are correlated with severe COVID-19 illness, supplementation of deficient individuals may potentially offer a therapeutic solution to reduce the burden of disease and improve the state of this pandemic.

Author Contributions

VM Polymeropoulos completed all work for this manuscript.

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Competing Interests

Author VM Polymeropoulos was employed by Vanda Pharmaceuticals.

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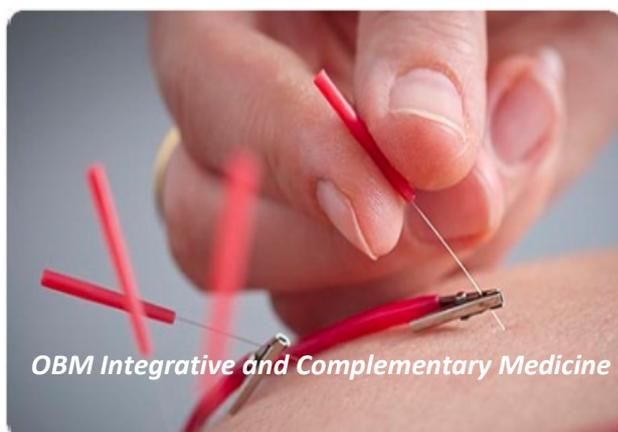
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