Opinion

A potential role of Coenzyme Q10 deficiency in severe SARS-CoV2 infection

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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 (Figure 1) (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).

Levels of CoQ10 can be diminished for several reasons including advanced age, the effects of compounds interfering with synthesis, and genetic factors predisposing to lower levels. One major class of compounds that are highly associated with diminished CoQ10 levels are statins. Statins inhibit HMG-CoA reductase reducing synthesis of cholesterol and levels of CoQ10 due to the inhibition of a common pathway of synthesis (4). Atorvastatin was found to decrease the level of CoQ10 by 49% within 14 days of treatment (4). CoQ10 levels peak around age 20, followed by an age-dependent decrease over time (5). The largest tissue specific decrease at age

80 occur in the lungs (51.7% from peak) and heart (42.9% from peak) (5). Mutations of several genes (primarily the COQ genes) involved in CoQ10 biosynthesis can result in a deficiency (6).

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 (7). Relatedly, in patients with septic shock, CoQ10 levels were found to be lower and correlated with higher levels of inflammatory markers (8).

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) (9,10). CoQ10 has been found to be beneficial in attenuating fibrosis in the lung and liver in rats through up regulation of autophagy processes (11). Supplementation with CoQ10 improves liver and systemic markers of inflammation in people with nonalcoholic fatty liver disease (12).

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 (13, 14). Total cholesterol and low-density lipoprotein levels improve in people with diabetes with CoQ10 supplementation (15). Supplementation with CoQ10 has been found to improve endothelial dysfunction in people with dyslipidemia (16).

Regarding a potential role in viral infection, CoQ10 has been shown to be lower in patients with acute influenza (17). 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 (18).

Although CoQ10 levels decrease with age and also through the consumption of exogenous agents such as statins, it has been seen that several genetic diseases also 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 (19). Further, 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 (20). Acute respiratory distress syndrome (ARDS) in people with Down syndrome has been postulated to be due to an imbalance in free radical scavengers (20). Mutations of the CoQ genes can results in primary CoQ10 deficiency that is associated with low ATP production and the increased presence of reactive oxygen species (ROS) (5). 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 (5).

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 severe illness to be occurring more widely in people of specific age groups and possessing

certain co-morbid conditions. Mortality and severity of illness of COVID-19 increases dramatically with increasing age (21). The most common co-morbidities for hospitalized patients with COVID-19 are hypertension, diabetes, and obesity (21). Although severe disease with SARS-CoV2 often involves respiratory compromise with bilateral interstitial opacities on imaging, notably in the case of severe infection, pulmonary disease is less often a comorbidity (22). An inverse correlation is seen with age and BMI, as it appears that younger people who were hospitalized were more often obese (23). 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 COVID-19 infection. 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 (21). The severe complications of COVID-19 including ARDS are thought to be due to a hyper-inflammatory state (24). 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.

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 either preventing oxidative stress, attenuating coagulation, mitigating a hyper-immune response, or inhibiting viral replication of entry directly. The deficiencies associated with disease may involve other antioxidants such as Vitamin C and E. Large studies should 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. 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. The potential of CoQ10 as a therapeutic in COVID-19

If an association is confirmed, a causative mechanism could further be explored and CoQ10 may potentially become a protective therapy in the future. Dosing to replenish levels of CoQ10 in deficiency could be initiated between 100mg to 200mg daily to have physiological impact (25). 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.

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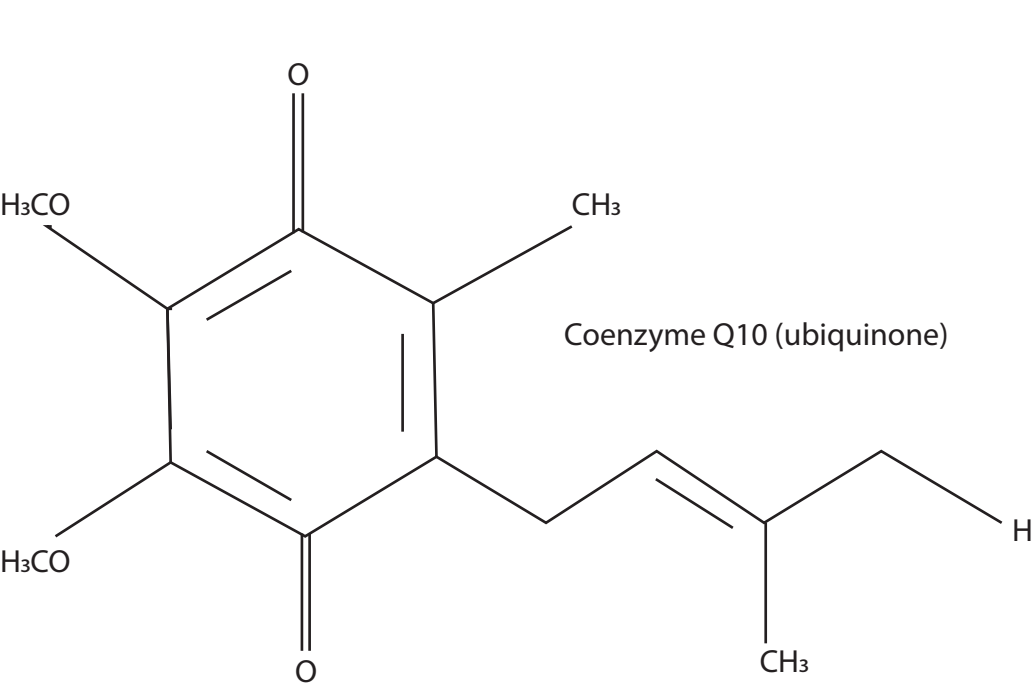
Figure 1

The molecular structure of Coenzyme Q10 (CoQ10)


O
H₃CO
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Coenzyme Q10 (ubiquinone)
H₃CO
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