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Orthomolecular Medicine News Service, July 18, 2021

Vitamin C Levels in Critically Ill Covid-19 Patients

by Michael Passwater

(OMNS July 18, 2021) From the COVID-19 pandemic, we continue to learn about the critical importance of maintaining adequate levels of essential nutrients. When the body is under stress from an illness such as an infection, merely eating an excellent diet may not provide sufficient nutrients to support the immune system. To stave off a fast-moving infection may require higher levels of essential vitamins and minerals. Vitamin C has an essential role in empowering the immune system. Its oxidized form can be recycled by red blood cells (erythrocytes), but a fast-moving illness can overpower this system, causing vitamin C levels to precipitously drop.

A recent study in Spain measured plasma vitamin C levels in 67 critically ill hospitalized adult COVID-19 patients meeting the Berlin criteria for Acute Respiratory Distress Syndrome (ARDS). [1] The results fell into 3 categories: undetectable (<0.1 mg/dL), low (0.1 - 0.4 mg/dL), and "normal" (0.4 - 2 mg/dL). 12 (18%) patients had undetectable plasma vitamin C, 43 (64%) patients had low levels of plasma vitamin C (mean for this group was 0.14 mg/dL with a standard deviation of 0.05), and 12 (18%) patients had vitamin C levels within the normal range (mean for this group was 0.59 mg/dL with a standard deviation of 0.18). In summary, 82% of patients had low or undetectable plasma vitamin C levels, and 18% had values within the reference range, mostly on the low side of the reference range. (Riordon Clinic Bio-Center Laboratory has an established reference range of 0.6 - 2.0 mg/dL for plasma vitamin C). A smaller study of 18 adult COVID-19 patients with ARDS found similar results: 17 (94%) patients had undetectable plasma vitamin C, and 1 (6%) patient had a plasma vitamin C level of 0.24 mg/dL. [2] The assay used in this study had a lower limit of detection of 0.15 mg/dL, above the mean of the low level group in the first study.

Finding low levels of vitamin C in critically ill patients is not new, and has been reported in a variety of studies over the last several decades. In 2017, a study of 44 critical care patients receiving recommended amounts of enternal and parenternal vitamin C (125 +/- 88 mg/day, max

448 mg/day) showed 70% of patients had vitamin C deficiency. [3] Among septic shock patients, 90% had vitamin C deficiency. Borrelli et al published findings in 1996 showing that the lower the plasma ascorbic acid level in septic patients the greater the risk of organ failure and death. [4] Even in presumed healthy people in the USA, vitamin C deficiency is found. In 2003-2004, NHANES samples from noninstitutionalized civilians found a vitamin C deficiency prevalence of 7.1% +/- 0.9%. [5] This was a 44% reduction in vitamin C deficiency from the 1988 - 1994 national study. Smoking and low income were associated with higher rates of vitamin C deficiency. People in a deficient state can avoid acute illness for a time, but have impaired capacity to respond to infections and other stress challenges.

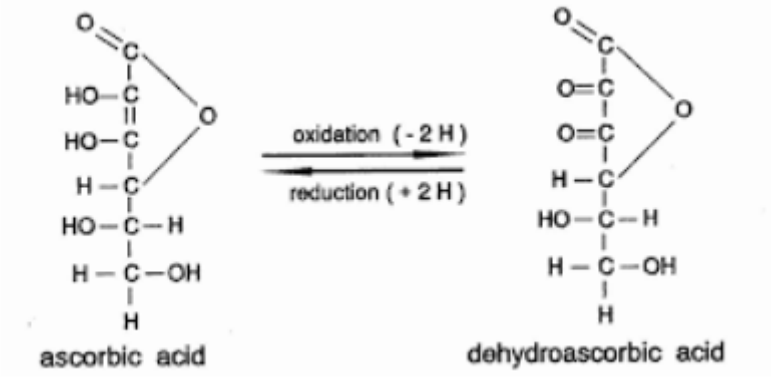
Why do critically ill people require more vitamin C to maintain adequate levels of plasma vitamin C?

1. Increased consumption

   White Blood Cells, such as neutrophils and monocytes, actively take up ascorbic acid from plasma (fluid portion of blood) to achieve intracellular levels of 1 mM, 50-100 -fold higher than the typical vitamin C level of plasma. When stimulated to produce an oxidative burst, these white blood cells will pull in more vitamin C to increase intracellular concentrations ten-fold to 10 mM. If there is not enough vitamin C available, the white blood cell's oxidative burst intended to kill an invading pathogen may destroy the WBC itself instead. Cytokines, inflammation, fever, and other biological stresses of illness also increase the metabolic demand for vitamin C throughout the body. [6]

2. Decreased recycling of dehyroascorbic acid (DHAA) back to ascorbic acid (AA)

   Healthy blood plasma must contain antioxidants to counteract the effects of oxygen. Ascorbic acid (AA) is a major antioxidant which serves to maintain the reductive capacity of circulating blood. [7] AA has a short half-life of minutes in human blood before being oxidized to dehydroascorbic acid (DHAA). Humans cannot make their own ascorbic acid. However, survival is possible with meager milligram amounts of AA intake due to recycling of the oxidized DHAA back to AA within red blood cells (RBCs) in the circulatory system and between astrocytes and tanycytes with GLUT1-DHAA receptors and neurons with SVCT2-AA receptors in the central nervous system. RBCs are the most numerous cell type in the body, and have a large number of GLUT1 receptors that preferentially take in DHAA. With 20-30 trillion RBCs circulating in a healthy person, DHAA in the blood can be recycled to AA every 3 minutes in a healthy person.



Vitamin C (Ascorbic Acid is oxidized to Dehydroascorbic acid, which can be reduced back to ascorbic Acid (vitamin C)

The recycling process is primarily dependent on glutathione peroxidases (GPx, a family of antioxidant selenoproteins), and to a lesser extent on NADH and NADPH oxidoreductases within the red blood cells. Damage or destruction of the RBCs, damage to or shortage of the intracellular reducing agents, or hypoxic conditions impairs or halts the recycling process. [8,9] Additionally, as the reductive capacity of plasma decreases, the amount of DHAA lost to irreversible oxidation to 2,3-diketo-L-gulonic acid further depletes the body's pool of AA. To maintain AA levels in the body as intracellular recycling decreases, intake of AA must increase.

In addition to maintaining antioxidant capacity, RBCs are responsible for the management of the three gases of life, O2, CO2, and NO, throughout the body. [10] RBCs (erythrocytes), are produced from erythroid precursor cells in the bone marrow, and circulate for approximately four months. They are biconcave discs, with very flexible membranes to allow them to flow smoothly throughout the body's 60,000 miles of blood vessels. Capillaries in the body's extremities become so narrow that the RBCs flow single file, underscoring the necessity of cell membrane flexibility.

New research reveals that RBC membrane components, interferon, and selenoproteins are targets of the SARS-CoV-2 virus, and along with NAD are all depleted by the virus. [11-15]

In addition to GLUT1 receptors, RBC membranes also can express ACE2 receptors, which are well established as a cellular entry point for the SARS-CoV-2 virus. CD147 and the RBC structural protein Band3 have also been shown to serve as attachment points for the virus. Mature RBCs do not have a nucleus and cannot support viral replication. However viral attachment and entry can disrupt the RBC's ability to transport and transfer oxygen to tissues, as well as destroy selenoproteins which in turn disrupts DHAA - AA recycling. RBC membrane disturbances and loss of antioxidant capacity results in a more spherical and less flexible RBC, and oxidation causes phosphatidyl serine and other lipids to flip from the inner side of the membrane to the outer side of the membrane. These changes inhibit the RBC from bending and twisting to travel through the small capillaries of the circulatory system, and accelerate the RBC's clearance from circulation by the reticuloendothelial system monocytes in the spleen and liver. Immature RBC precursor cells have a nucleus, numerous ACE2 receptors, and can support viral replication. Invasion of these cells by the SARS-CoV-2 virus is even more damaging. Release of RBC precursor cells into the blood stream in response to hypoxia, can intensify the disease by causing immunosuppression and serving as a rich source of selenocysteine and other nutrients for the rapidly replicating virus. The virally induced structural, functional, and metabolic damage to RBCs helps explain cases of COVID-19 presenting with hypoxia disproportional to the degree of pneumonia present.

In addition to elucidating the interactions of SARS-CoV-2 with the RBCs and RBC precursor cells, recent genetics, proteomics, metabolomics, and lipidomics research has identified specific interactions leading to interferon and selenoprotein destruction and suppression. These studies have also identified nicotinamide phosphoribosyltransferase, nicotinamide, and nicotinamide riboside as therapeutic options to boost innate immunity and counteract NAD depletion by the virus.

Importance of adequate niacin, glutathione/cysteine (NAC and alpha lipoic acid), and selenium

The findings of recent studies on the effect of nutrient deficiencies in COVID-19 add empirical evidence in support of hypotheses published early in the pandemic. In March of 2020, Yufang Shi and team in China recommended the use of niacin (vitamin B3) whenever lung damage was detected by CT scan. [16] Miller, Wentzel, and Richards in South Africa pointed to the importance of NAD+ deficiency. [17] Over a decade ago, Ethan Will Taylor proposed the oxidative stress-induced niacin sink (OSINS) model for HIV, another RNA virus. [18] Taylor, along with Hiffler, Vavougios, Polonikov and others also suggested glutathione and selenium as central in the etiology of SARS-CoV-2 disease. [19-21] Additionally, a German study showed an inverse association between COVID-19 mortality or severe illness and selenium and selenoprotein P levels. [22] And in the USA, two cases of severe COVID-19 were successfully treated with oral and intravenous glutathione, N-acetyl-cysteine (NAC), and lipoic acid have been published. [23]

Conclusion

SARS-CoV-2 is an RNA virus capable of causing systemic, life-threatening disease in humans. Severe disease is characterized by hyper-inflammation, hyper-coagulation, and hypoxia. The virus produces proteins that knockdown two major pillars of the innate immune system, interferon and selenoproteins. Selenoprotein knockdown impairs antioxidant capacity and hemostasis (anticoagulation and clotting). The virus also damages RBC structure, which combined with loss of antioxidant capacity, impairs management of oxygen, carbon dioxide, and nitric oxide throughout the body. Additionally, consumption of NAD by the virus depletes cells of a vital energy source.

Restoring and maintaining healthy levels of ascorbic acid, selenocysteine, vitamin D, and NAD is critical in the battle against SARS-CoV-2. In treatment, as well as in research, it is important to remember that nutrients do not work optimally alone. Selenium, vitamin D, magnesium, and vitamin K2 are interdependent. Vitamin C, selenium, and vitamin E are interdependent. Niacin and NAD are also dependent on adequate intracellular selenoproteins and vitamin C levels. Single nutrient studies and interventions will miss essential synergies and confounding variables regardless of the sample size.

In critical illness, large doses of vitamin C can be helpful in resuscitation efforts. In the setting of septic vascular collapse, intravenous co-administration of vitamin C and cortisol helps the body repair damaged blood vessels quickly. Ongoing large doses of vitamin C are needed to fuel white blood cells, regain antioxidant capacity throughout the body, and counteract its rapid consumption. Frequent dosing to maintain a steady state is better, because ascorbic acid has a short half-life. Early intervention is better, because activated white blood cells are dependent on a high level of ascorbic acid. Taking gram quantities with each meal, and increasing intake to bowel tolerance during illness, is helpful. When ill, it is necessary to take ascorbic acid throughout the day, much more than can be absorbed in one sitting.

New research techniques, and new viruses improve our understanding of biochemistry and biology, and reinforce a longstanding concern - inadequate nutrition remains global and public health enemy #1.

Recommended adult doses to reduce risk of serious infection: [24-30]

- Vitamin C, 500-1000 mg, 3 times daily (more to bowel tolerance if sick)
- Vitamin D, 5,000 IU/day
- Vitamin K2, 100 mcg/day

- Niacin / niacinamide 200 - 1000 mg/d (in divided doses, start with smaller doses, increase over weeks)
- Magnesium 400 mg/d (in malate, citrate, chelate, or chloride form)
- Zinc, 20 mg/day
- Selenium 200 mcg/day

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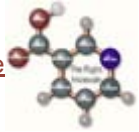

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