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Hyperglycemia in COVID-19 Inhibits Dehydroascorbic Acid Absorption by Immune Cells Leading to Severe Outcomes

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ABSTRACT

Hyperglycemia in COVID-19 patients is a frequent complication in both diabetic patients and individuals never previously diagnosed with diabetes. High blood glucose has been identified as an important risk factor for poor outcomes such as ICU admission, acute respiratory distress syndrome (ARDS), and death. It is known that certain cell types acquire vitamin C exclusively by transporting the oxidized form of ascorbate, dehydroascorbic acid (DHAA), across the cell membrane using glucose transporters (GLUT). While GLUT are primarily responsible for the uptake of glucose, there is evidence that in disease states most human cells also acquire vitamin C as DHAA via this mechanism. Dysregulation of the immune response in the epithelial or endothelial cells of the lung, including the immune cells that infiltrate the lungs during the disease, is believed to be at the core of severe lung sequelae including ARDS and the cytokine storm. Vitamin C deficiency in one or more of these cell types may be the factor causing dysregulation of the immune response. High plasma glucose inhibits the accumulation of vitamin C in cells that acquire it via DHAA transport, leading to the hypothesis that screening plasma glucose levels early in the course of COVID-19 infection, and treating patients with hyperglycemia to maintain their blood glucose in the normal range, while simultaneously supplementing vitamin C, will prevent the disease from progressing to severe outcomes.

INTRODUCTION

Most individuals infected with the COVID-19 virus will either be asymptomatic, or experience a mild to moderate respiratory illness, and often recover without requiring hospitalization. A small percentage of those infected individuals will experience progression to a severe acute respiratory syndrome (ARDS) and/or death. The peculiar pattern of a patient with mild disease suddenly crashing after many days suggests that some change within their condition triggers dysregulation of the immune response. This change may result from the exhaustion of vitamin C from within one or more cell types. While it appears that a dysregulated immune response is the cause of the severe sequelae, it is unclear which type(s) of cells initiate the extreme inflammatory response and cytokine storm.

A review of hyperglycemia in COVID-19 infection, and ascorbate pharmacokinetics, supports the hypothesis that hyperglycemia may result in vitamin C depletion and immune dysregulation.

HYPERGLYCEMIA IN COVID-19 PATIENTS

Hyperglycemia in COVID-19 patients is a frequent complication in both diabetic patients and individuals never previously diagnosed with diabetes, making it an important risk factor for poor outcomes (Bode et al., 2020). Day-1 average blood glucose was a strong independent variable predicting SARS-CoV-2 radiographic imaging on chest X-ray, and daily average blood glucose was positively correlated with daily chest X-ray findings of ARDS (Iacobellis et al., 2020). Hyperglycemia and diabetes were also identified as independent risk factors for morbidity and mortality in the earlier SARS-CoV-1 outbreak (Yang et al., 2006),

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and comorbid diabetes was found to result in immune dysregulation and enhanced disease severity in a mouse model of MERS-CoV infection (Kulcsar et al., 2019). Several mechanisms have been proposed to explain the high frequency of hyperglycemia in COVID-19 infection, including direct infection of the insulin-producing islet cells (Ilias & Zabuliene, 2020; Ceriello, De Nigris & Prattichizzo, 2020).

It is important to note that the studies to date have generally involved hospitalized patients. Thus, most patients were likely to have been infected many days earlier and may have been asymptomatic or mildly ill for a considerable amount of time without any medical intervention. Little is known of the glycemic status of people prior to seeking medical care for increasingly severe symptoms, such as difficulty breathing. It is plausible that hyperglycemia is frequent in early infection and has simply gone undetected, and that the most effective triage of recently infected patients might be as simple as a fingerstick blood glucose test that could be used to identify those likely to develop severe disease. A pilot study in patients with mild disease suggests this may be accurate (Shen et al., 2021).

An interesting observation is that patients with only moderately elevated blood glucose levels have about the same increased risk for severe outcomes as patients with extremely elevated levels. Even a small incremental increase within the normal range is associated with a substantial increase in risk of ICU admission (Alahmad et al., 2020).

Inhibition of intracellular transport of DHAA also increases steeply with only moderate increases in extracellular glucose concentration (Corpe et al., 2013; Rumsey et al., 1997).

VITAMIN C ABSORPTION BY CELLS

Ascorbate (ASC), the reduced form of vitamin C, enters cells via the transporters SVCT1 and SVCT2. SVCT1 is mostly associated with the intestinal uptake of ASC and the reabsorption of ASC in the kidneys, thus regulating the ASC concentrations in the bloodstream. SVCT2 is associated with uptake of ASC by many other types of cells. Cellular uptake of vitamin C in the oxidized form (DHAA) is done via glucose receptors. However, the concentration of DHAA in the bloodstream is negligible; DHAA recycling and transmembrane electron transfer by the red blood cells (RBCs) keep vitamin C in the reduced form (Tu et al., 2017), presumably because DHAA is relatively unstable and easily lost to degradation. Due to low concentrations in plasma, DHAA transport has generally been perceived as a minor route of uptake by cells.

When ASC moves from the plasma into extracellular fluids, it is no longer in the presence of RBCs, resulting in increased oxidation within the extracellular fluids (Chen et al., 2008). Decades of accumulated research indicates that DHAA transport is a very important means of acquiring vitamin C in many different cell types. Studies of SVCT1 knock-out animals revealed robust DHAA uptake in the intestines (Corpe et al., 2013), which is not surprising considering that 10-20% of dietary vitamin C is present in the oxidized form. Some important cell types, including RBCs (Tu et al, 2017) and heart muscle cells (cardiomyocytes), depend on DHAA transport exclusively to acquire intracellular vitamin C (Guaiquil et al., 2004). Cartilage-producing cells (chondrocytes) within the synovium possess the ability to transport both ASC and DHAA. These cells have been estimated to acquire 26% of their total vitamin C as DHAA under normal conditions, and 94% as DHAA when the synovial capsule is inflamed in rheumatoid arthritis (McNulty, Stabler, Vail, McDaniel & Kraus, 2005). Localized oxidation of ASC in the vicinity of some cells has been demonstrated, and thus explains the ability of those cells to acquire DHAA even when the surrounding fluid has a low concentration of DHAA in general. A "bystander effect" has been demonstrated whereby immune cells oxidize extracellular ASC which is subsequently absorbed by neighboring cells via GLUTs (Nualart et al., 2003).

Many new and emerging cell regulatory functions of vitamin C have been identified in recent years, and many of them have been attributed to DHAA. A very recent review describes DHAA as, "a possible master regulator of the processes associated with kinase activity, proliferation, and cell death" (Ferrada et al., 2021).

Furthermore, it has been proposed that low plasma levels of vitamin C due to other factors during COVID-19 infection might contribute to poor outcomes (Patterson, Isales & Fulzele, 2021), and low plasma levels of vitamin C will aggravate low DHAA transport.

RESPIRATORY EPITHELIAL CELLS

Epithelial cells may not commonly be perceived as "immune cells," but they do possess a well-characterized immune response to viral infection. The epithelial cells that line the surfaces of the nasal cavity, bronchial network, and alveolar surfaces appear to be the cells that are initially infected in most cases of COVID-19. Whether or not the initial innate immune response in these tissues is "dysregulated" is not entirely clear.

SARS-CoV-2 induces double-stranded RNA-mediated innate immune responses in respiratory epithelial-derived cells in vitro (Neufeldt et al., 2020; Renner et al., 2020). Neufeldt et al., suggests the response is dominated by pro-inflammatory, NF-kB-driven pathways. Blocking the NF-kB mediated inflammatory response may be effective in treating the infection as it has been shown in SARS-CoV-1 infected mice. Intracellular vitamin C down-modulates NF-kB signaling by two different mechanisms, including the direct inhibition of IkappaBalpha kinase β (IKKβ) by DHAA (Cárcamo et al., 2004). Thus, intracellular vitamin C may keep this pro-inflammatory, NF-kB-driven phenotype in check. GLUT2 and GLUT10 transporters exist on the apical surface of epithelial cells of the proximal airways, with their primary function being to maintain low glucose levels in the epithelial lining fluid (ELF) (Garnett, Baker & Baines, 2012). These two transporters are known to have important DHAA transport roles in other tissues (Corpe et al., 2013; Németh et al., 2016). It has been proposed that these transporters in the proximal airways not only provide for recycling of DHAA from the ELF, but are an important source of vitamin C for the epithelial cells. A mechanism for enhanced extracellular oxidation of ASC in the ELF was demonstrated, and it was shown that this mechanism is accompanied by marked intracellular uptake of vitamin C by epithelial cells (Corti et al., 2008). Glucose levels in the ELF are normally much lower than in the plasma, but elevations in plasma glucose result in corresponding elevations in the ELF, and this would in turn be expected to inhibit DHAA uptake by lung epithelial cells.

IMMUNE CELLS

The white blood cells (WBCs) and RBCs that circulate in the bloodstream differentiate from the same hematopoietic stem cells in the bone marrow. The WBCs (immune cells) differentiate into two major categories, the myeloid and lymphoid lines. The myeloid line further differentiates into several sub-types, including granulocytes and monocyte/macrophages, and the lymphoid line comprises a range of lymphocyte subtypes including several types of T cells and B cells (Orkin & Zon, 2008).

Infiltrations of granulocytes, monocyte/macrophages, and lymphocytes into the lungs of COVID-19 patients have all been reported and associated with the hyper-immune response in severe disease (Nathan, 2020; Rockx et al., 2020; Munster et al., 2020).

Intracellular ascorbate concentrations in circulating lymphocytes, monocytes and granulocytes have been reported to be 3.5, 3 and 1.5 mM, respectively, in normal, healthy subjects (Ang et al., 2018), which are 10 to 20-fold greater than levels in plasma. Vitamin C has been shown to prevent dysregulation of both lymphocyte and granulocyte function (Anderson, 1982), and down-modulates the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling responses (Cárcamo, Bórquez-Ojeda & Golde, 2002). GM-CSF signals for increased transport of DHAA, possibly by increasing the expression of GLUT transporters in the cell membrane (Vera, Rivas, Zhang & Golde, 1998). These findings point to vitamin C as a regulator of cytokine redox-signal transduction in host defense cells, and its potential role in controlling inflammatory responses.

Both GLUT1 and GLUT3 are reportedly expressed on the plasma membrane of circulating WBCs (Maratou et al., 2007). The IC50 of glucose on DHAA transport for these two transporters is reportedly 10 mM (180 mg/dL) and 4 mM (72 mg/dL), respectively (Rumsey et al., 1997). Thus, plasma glucose values frequently found in COVID-19 patients are consistent with significant inhibition of DHAA absorption by WBCs.

GRANULOCYTES

Resting granulocytes in the bloodstream of normal people maintain a high basal level of intracellular vitamin C that is about 10 times the concentration in the plasma. Whether or not these basal concentrations are the result of ASC transport by SVCTs remains controversial. Some studies suggest that these cells have no functional transporters for ASC, while others have demonstrated ASC transport (Vera et al, 1998; Washko, Wang & Levine, 1993). Preferential DHAA transport by granulocytes in these studies is consistent. It is known that granulocytes that become activated in disease states rapidly increase their intracellular concentrations above basal levels by twice or more; and it has been demonstrated and well-accepted that granulocytes acquire these extremely high intracellular vitamin C concentrations by transporting DHAA (Vera et al., 1998; Washko et al., 1993).

MONOCYTES/MACROPHAGES

Human monocytes appear to be similar to granulocytes in their uptake of vitamin C, except that their basal concentrations are higher, and monocytes were found to have an even greater capacity to take up DHAA. This greater uptake is related to more facilitative glucose transporters on the monocyte cell membrane, and the uptake is stimulated by GM-CSF (Vera et al, 1998). Monocytes infiltrate into the lungs, and differentiate into macrophages in the tissue. Little is known of vitamin C transport in tissue macrophages.

A relatively recent finding related to monocyte vitamin C transport is also interesting. In U937 cells (a model cell line used to study the behavior and differentiation of monocytes), DHAA at concentrations compatible with those present at inflammatory sites inhibited SVCT2 transport of ASC (Fiorani et al., 2014). Hence, even if these cells express functional ASC transporters, they may not be able to acquire vitamin C via this pathway at inflammatory sites. If their DHAA transport is simultaneously inhibited by high glucose, a "perfect storm-like" situation may exist wherein both mechanisms of vitamin C accumulation are inhibited.

LYMPHOCYTES

A study in an immortalized lymphoblast cell line suggests that lymphocytes are capable of transporting both ASC and DHAA, but that the transport of DHAA is the primary mechanism, and the capacity of DHAA transport greatly exceeds the capacity of ASC transport (Ngkeekwong & Ng, 1997). More recently, normal human T-cells were shown to have functional SVCT2 and ASC uptake, but extensive DHAA uptake was also demonstrated (Hong et al., 2016). Normal lymphocytes (both T-cells and B-cells) have been shown to take up DHAA at a very rapid rate and contain a high intracellular level of total vitamin C (Stahl et al., 1985). In experiments on mouse T cells, these cells internalized more vitamin C when they were activated, due to enhanced glucose transporter GLUT-1 and GLUT-3 expression that persisted up to 48 h after activation. Blocking oxidation of ASC in the culture medium with a reducing agent almost completely inhibited the enhanced vitamin C uptake (Maeng et al., 2009). Thus, DHAA uptake appears to be a very important mechanism for acquiring vitamin C in lymphocytes, particularly in activated cells.

Interestingly, it was demonstrated that administration of an intravenous glucose load resulted in a prompt and very significant decrease of lymphocyte ASC level in normal subjects. The rate of its decline correlated closely with the rate of change of plasma glucose levels (Chen et al., 1983).

DISCUSSION

Ever since vitamin C was chemically identified and first synthesized in the 1930's, there has arguably been no other substance so controversial in the field of human health and medicine. Suggestions that it can prevent or cure a myriad of different diseases have flourished and floundered. Anecdotal stories, as well as documented case reports, have occasionally described remarkable successes. Indeed, there are at least two such remarkable reports in treating COVID-19 patients with intravenous ascorbate (Waqas Khan et al., 2020; Gonzales et al., 2020), and other such reports in treating patients with non-COVID-19 related sepsis and ARDS (Bharara et al., 2016; Fowler et al., 2017). One retrospective trial reported remarkable results in treating severe sepsis (Marik et al., 2017).

That a particular tissue, cell type, or subcellular compartment might be deficient in vitamin C, even when the body as a whole is replete, is not a novel concept. Studies on the rare genetic disease Arterial Tortuosity Syndrome, known to be caused by mutations in the gene for GLUT10, indicate that the lack of this functional DHAA transporter results in deficiency of vitamin C within the endoplasmic reticulum of these patient's fibroblasts. This deficiency is thought to result in poor production of collagen and elastin, not so different than in scurvy, yet these patients have normal plasma ascorbate levels (Németh et al., 2016). Diabetic patients have demonstrably low ascorbate levels in the RBCs, which is attributed to hyperglycemia interfering with DHAA transport. At least one study links this ascorbate deficiency in the RBCs to microangiopathies (e.g., retinopathy, nephropathy, neuropathy), the serious sequelae of diabetes (Tu et al., 2015).

This manuscript presents evidence related to the intracellular uptake of vitamin C in a variety of cell types important in COVID-19 disease, to support a few simple concepts:

1. The intracellular concentration of vitamin C is important in regulating the immune responses in these cells;
2. A continuous consumption of vitamin C in these cells, combined with inhibition of uptake due to hyperglycemia, could lead to a critically low threshold in one or more of these cell types;
3. Critically low thresholds could be the triggering event in dysregulation of the immune response, explaining the sudden transition from a mild disease to a potentially fatal one; and,
4. Early intervention consisting of blood glucose monitoring, correction of hyperglycemia, and vitamin C supplementation, might prevent this sudden transition to a disease with severe outcomes.

As of the date of publication (May, 2021), the pandemic in the USA appears to be waning, but there are still tens of thousands of new cases being reported daily – which is likely to continue for some time. It is an opportunity to investigate the glycemic status of newly diagnosed cases, and the potential therapeutic value of this hypothesis. This pandemic will probably not be the last serious outbreak of disease caused by closely-related coronaviruses.

In regard to treating seriously ill COVID-19 patients with intravenous vitamin C (IVC), this intervention might be more successful with more stringent glucose control in patients. Hyperglycemia resulting from stress, and hyperglycemia induced by glucocorticoid treatment, are both prevalent in critically ill patients with ARDS and sepsis (COVID-19 induced and otherwise). Guidelines for managing these ICU patients generally advise against aggressive blood glucose control. The Surviving Sepsis Campaign (Rhodes et al., 2017) recommends an upper target blood glucose ≤ 10mM (180 mg/dL). This is in part because even a single hypoglycemic episode is believed to be more dangerous than a chronic hyperglycemic state in these patients. Also, because aggressive glucose control has not shown great differences in outcomes, and because there are so many other more dangerous factors to manage in these patients. This may be true and wise in the absence of IVC therapy. But, since plasma glucose values in the range of 10 mM (180 mg/dL) are consistent with significant inhibition of DHAA absorption, more stringent blood glucose management may be necessary for successful IVC intervention.

CONCLUSION

Hyperglycemia may have a profound inhibitory effect on the absorption of vitamin C in some cell types. Deficiency of vitamin C in one or more of these cell types could be the trigger for the transition of COVID-19 patients from a mild-to-moderate disease state to a far more serious one. In critically ill patients, benefits of IVC intervention might be improved by more stringent blood glucose management. The combination of aggressive blood glucose management with vitamin C therapy needs further evaluation.

COMPETING INTERESTS

The author is the founding member of ReCverin LLC, a manufacturer and distributor of vitamin C products for consumers.

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