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Interference of Coronavirus with Glucose Metabolism and Its Effect on Affinity of Hemoglobin Binding to Oxygen: A Review

Nadia Gh. AbdulKareem[1] *PhD,* **Fatima A. Mohammad**[2] *PhD*

[1]Dept. of Chemistry and Biochemistry, College of Medicine, Al-Iraqia University, Baghdad, Iraq, [2]Dept. of Chemistry, College of Science, University of Mosul, Nineveh, Iraq

Abstract

Early phases of coronavirus disease-2019 (COVID-19) are characterized by hypoxemic arteries that do not result in gasping, clinical deterioration may occur rapidly if hypoxemia is exacerbated by intra-pulmonary forcing, pulmonary vaso-compression fitness is not managed, and intravascular microthrombi are present with impaired lung diffusion. The goal of this hypothesis is to propose that COVID-19 may interfere with the glycolytic pathway by changing the amounts of intracellular metabolites, especially 2,3-bisphosphoglycerate (2,3-BPG), to aid in the release of oxygen from hemoglobin into the tissues, therefore preventing or treating hypoxia.

As a conclusion, focusing on hypoxia as the primary cause of severe morbidity in COVID-19 patients is thought to result from an increased stability of the relax (R-form) of hemoglobin at the tissue level due to a decrease in glucose metabolite produced from glycolysis process in RBCs (decrease 2,3-BPG concentration in the blood). This theory proposes raising 2,3-BPG levels, which is to free up more O_2 from the R-form of Hb in the tissues.

Keywords COVID-19, glucose metabolism, hemoglobin- oxygen binding, 2,3-bisphosphoglycerate

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List of abbreviations: 2,3-BPG = 2,3-Bisphosphoglycerate, ACE2 = Angiotensin-converting enzyme II, ADP = Adenosine diphosphate, ARDs = Respiratory distress syndrome, ATP = Adenosine triphosphate, CDC = United State centers for disease control and prevention, COVID-19 = Coronavirus disease 2019, ETC = Electron transport chain, Fe^{2+} = Ferrous iron, Fe^{3+} = Ferric ions, GSH = Glutathione, Hb = hemoglobin, HbA = Adult hemoglobin, HbF = Fetal hemoglobin, HIF-2α = Hypoxia-inducible factor 2-alpha, NAD = Nicotinamide adenine dinucleotide, NADH = reduced form of NAD, NADP+ = Nicotinamide adenine dinucleotide phosphate, NADPH = reduced form of NADP, NFB = Nuclear factor kappa B, NFκB = Nuclear factor kappa B, NOS = Nitric oxide synthase, ODC = Oxygen dissociation curve, PDC = Pyruvate dehydrogenase complex, PHD2 = Prolyl hydroxylase domain 2, PPP = Pentose phosphate pathway, RBCs = Red blood cells, ROS = Reactive oxygen species, RNS = Reactive nitrogen species, R-BHB = (R)-beta-hydroxybutyrate, R-form = Relax-form, S1P = Sphingosine-1-phosphate, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, SpO_2 = Oxygen saturation, Sphk1 = Sphingosine kinase 1, T-form = Tense form (deoxy-hemoglobin),

Introduction

Human red blood cells' (RBCs) that have reached maturity, including hemoglobin (Hb) and protected by a plasma membrane, generate energy through anaerobic glycolysis.

Functions of RBCs in human body

1) RBCs account for 84% of all human cells. They release large quantities of reduced glutathione (GSH) into the blood, contributing to the dynamic interorgan-GSH-metabolism, and they provide a cellular defense mechanism against oxidative stress by connecting the GSH cycle to the NADPH-producing pentose phosphate pathway (PPP).

2) Mature human RBCs have the 20S-proteasome, a functioning protein-degrading machinery, and transcription elements that include all the parts of the redox-sensitive nuclear factor kappa B (NFB), hence there is an inverse association between NFB and eryptosis.
3) The function of immune cells in the periphery is only partially regulated by mature Hb hemoglobin bind with gram-negative bacteria's lipopolysaccharide (an endotoxin) and render it inactive.
4) Involvement of circulating RBCs and platelets with bacteria modifies complement receptors to promote pathogen capture, leading to fast clearance of complement-pathogens by phagocytosis in the liver and spleen.
5) Nitric oxide synthase (NOS) activation by protein kinase B is a fundamental physiological function of protein kinase B in RBCs, which regulates RBCs abnormalities. Human RBCs are involved in H_2S turnover in a significant way, which is a point to be stressed [(1)].

Cooperativity among hemoglobin, oxygen and 2,3-bisphosphoglycerate (2,3-BPG)

RBCs ability to transport oxygen to tissues is largely determined by the balance between the tense form (T-form) and the relaxed form (R-form) of Hb. Allosteric regulation of oxygen binding efficiency by adenosine triphosphate (ATP) and 2,3-BPG, a glycolytic intermediate unique to RBCs.

A close relationship between the O_2 binding capacity of Hb and the rate of glycolysis in the RBCs was found by studying the Rapoport-Luebering metabolic pathway, which occurs in mature RBCs and produces high concentrations of 2,3-BPG to facilitate liberation of oxygen from hemoglobin to the tissues through decreasing Hb-oxygen affinity [(1)].

Consequently, an increase in 2,3- BPG stabilizes the T-form of Hb and, by increasing the binding of 2,3-BPG, lowers the quantity of free 2,3-BPG and ATP, leading to a further acceleration of metabolism and having significant effects on glycolysis [(1,2)]; whereas, H^+ and oxygen can modulate 2,3-BPG level without large variations in glycolytic flux [(3)].

Hemoglobin's high oxygen-binding capacity allows it to function normally without increasing ambient oxygen levels. Tissue that has almost depleted its O_2 supply becomes acidotic due to increased proton production and elevated amounts of 2,3-BPG, which releases O_2 from Hb. The binding of O_2 to Hb is inhibited by protons and 2,3-BPG [(4)].

With 2,3-BPG, the O_2 dissociation curve (ODC) remains within a safe and usable range. Boosting 2,3-BPG causes a rightward shift in ODC and more cooperation among the quaternary Hb chains. While 2,3-BPG deficiency causes the ODC to move to the left and reduces cooperation [(5)].

Sphingosine kinase 1 activity, hemoglobin and O_2 release capacity

Mature RBCs have an abundance of sphingosine-1-phosphate (S1P), a bioactive lipid biomarker. Twenty-one healthy volunteers showed a quick rise in erythrocyte S1P levels on the first day of low-lying at 5,260 m altitude, which persisted for 16 days with enhanced erythrocyte sphingosine kinase 1 levels (Sphk1). Sphk1-induced S1P upregulation in RBCs protects against hypoxia by increasing O_2 transport to tissues. By increasing the release of glycolytic enzymes into the cytosol and inducing glycolysis, S1P within the cell promotes the formation of 2,3-BPG, which in turn enables the release of O_2. In sum, S1P is shown to be an intracellular hypoxia-responsive bioactive-lipid that promotes RBCs glycolysis and O_2 transport, therefore mitigating the effects of hypoxia on tissue [(6)].

ADP/ATP, NAD+/NADH, and NADP+/NADPH

Pathologies like acute respiratory distress syndrome (ARDS) may develop when cytokine storms alter the cellular amounts of these coenzymes, leading to cell dysfunction and death. Reducing the cytokine storm by adjusting NAD+/NADH ratio in glycolysis, the m-citric acid cycle, beta-oxidation of fatty

acids, and oxidative phosphorylation. Viral infection has been linked to disruptions in the mitochondrial electron transport chain (ETC). In addition, beneficial energy reprogramming is achieved by increasing flux throughout glycolysis to synthesis ATP and by elevating flux done by the pentose phosphate pathway for the synthesis of NADPH. This is achieved by reactivating the pyruvate dehydrogenase complex (PDC) or using fatty acids to circumvent the inhibition of PDC activity that occurs after viral infection. In order to promote the production of proinflammatory cytokines, glucose enters via the hexosamine biosynthetic route and increases O-GlcNAcylation of the transcriptional regulator Interferon IFN-regulatory factor-5 (IRF5) [7].

EGLN1 gene (EGL-9 family hypoxia inducible factor 1)

The hypoxia-inducible factor 2-alpha (HIF-2) protein interacts with the prolyl hydroxylase domain 2 (PHD2) enzyme, which plays a crucial part in the body's capacity to adapt to varying O_2 levels. Important genes involved in cell division, vascular development, and blood cell creation are all under HIF's regulatory wing. It has a crucial role in regulating erythropoietin, the hormone that governs the synthesis of red blood cells. PHD2 enzyme ensures that HIF-2 is destroyed and does not build up in excess. In the presence of sufficient O_2, the PHD2 enzyme becomes very active, speeding up the degradation of HIF-2. In hypoxia, however, PHD2 activity decreases, resulting in slower degradation of HIF-2 and a greater amount of HIF being offered to promote the development of new blood vessels and RBCs. By engaging in these actions will increase the amount of oxygen reaching muscles and organs. The EGLN1 gene helps the body adapt to high altitude, when the air is thin and oxygen levels are low. Because of this, the body adjusts its breathing patterns to produce more red blood cells and blood vessels [8]. Researchers also discovered an adenosine or S1P, in addition to HIF, might alter the glycolytic process in RBCs during hypoxia or high-altitude hypoxia [9].

Because ATP is needed in the first stages of glycolysis by hexokinase and phosphofructokinase enzymes to stimulate glycolytic ATP generation, measuring the amount of ATP produced by RBCs in response to hypoxia is a useful technique. Increased glycolysis caused by hypoxia is mediated by an increase in 2,3-BPG, which causes RBCs to use glucose more quickly. This improves O_2 delivery to hypoxic areas by stabilizing the T-form of Hb. Several researchers have proposed potential mechanisms for RBCs to respond rapidly to hypoxia via PO_2, which is able to regulate multiple RBC activities, including the biosynthesis of ATP, the acceleration of glycolysis, cation exchange and change in pH, metabolic compensation of ATP, cytoskeletal organization, and increase of 2,3-BPG [2,10].

Coronavirus disease (COVID-19) pandemic

In December 2019, a pneumonia outbreak was reported in Wuhan, China. On 31 December 2019; the outbreak was traced to a novel strain of coronavirus, which was labeled as 2019-nCoV by the World Health Organization (WHO) [11,12]. On 11 February 2020, International Committee on Taxonomy of Viruses (ICTV) introduced the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to refer to the virus strain. Earlier the same day, the WHO named the disease caused by the virus strain COVID-19 [13].

The virus causes a highly infectious sickness known as COVID-19. The majority of those infected with the virus will only have mild to moderate respiratory symptoms, but those over the age of 65 years and those with preexisting medical problems are at increased risk for severe sickness, multiorgan damage, or death from the virus [14]. There have been modifications to SARS-CoV-2 throughout time, just as there have been changes to all other viruses. These changes may have an impact on the virus's ability to propagate, the severity of the sickness it causes, or the efficacy of any

vaccinations, treatments, or diagnostic tools developed for it. Keeping an eye on things to catch any major amino acid swaps [15]. Currently, Global Initiative on Sharing All Influenza Data (GISAID), Next strain, and Pango are the accepted nomenclature and tracking methods for SARS-CoV-2 genetic ancestry in the scientific community. They advocated for the use of Greek letters [16].

Variable symptoms result from COVID-19 involve cough, headache, fever, breathing exertions and loss of smell and taste [17-21]. Signs may start 1-14 days after contact with the virus. One third of patients who are infected do not produce noticeable symptoms; whereas, 81% develop mild-moderate symptoms (including pneumonia), 14% show severe symptoms like dyspnea and hypoxia, and above 50% lung involvement on computed tomography (CT) imaging, while 5% develop serious symptoms as respiratory failure, shock, or multiorgan dysfunction [22,23].

Transmission and life-cycle of CoV-2

COVID-19 may spread from person to person via the air. It infects the buccal and respiratory mucosa of those who come into contact with the secretions of infected people. The virus, which has a single-stranded RNA encased in a protein called nucleocapsid (N) and three primary surface proteins called membrane (M), envelope (E), and spike (S), replicates and travels to the lower respiratory tract, where it causes severe pneumonia, in a process called lysis. A pair of proteases, pro-protein convertase furin and transmembrane serine protease 2, cleave spike to allow angiotensin converting enzyme 2 (ACE2) to enter host cells transmembrane serine protease2 (TMPRSS2) ([24]. An illustration of the virus's replication cycle is shown in figure (1) [25].

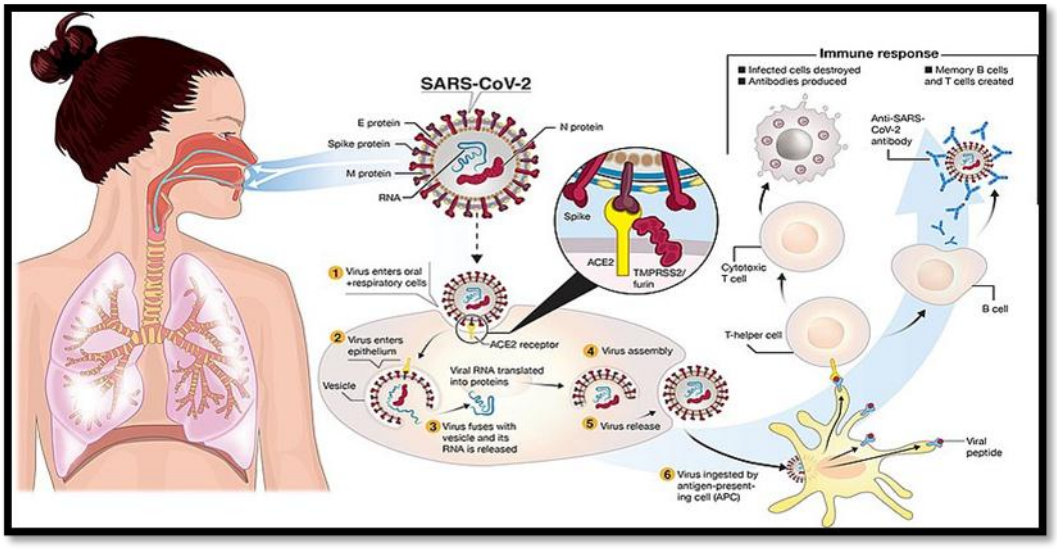

Figure 1. Transmission and replication cycle of SARS-CoV-2 causing COVID-19 [25]

COVID-19 testing methods

For the detection of virus's nucleic acid use the following methods:

1. Real-time reverse transcription polymerase chain reaction (rRT PCR)
2. Transcriptional mediated amplification
3. Reverse-transcription loop mediated isothermal amplification (RT LAMP) by nasopharyngeal swab [26-28].

Comorbidities

According to the United State centers for disease control and prevention (CDC), the most common major respiratory co-occurring conditions are severe to moderate asthma, preexisting chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary fibrosis [23].

Hypoxemia in COVID-19 patients

Patients with COVID-19 have a particularly difficult challenge in the form of hypoxemia. Hypoxemia in COVID-19 patients has been attributed to a variety of factors, including the virus itself, a hyperimmune response to the virus, a cytokine storm that damages lung tissue and alveoli, and even direct viral injury [13].

Hypoxia in COVID-19

1. Since the pathogenic processes listed below account for the multi-organ morbidity and mortality seen in COVID-19, it is clear that Abdelzaher and his coworkers are correct in attributing these devastating effects to an overactive immune system rather than the infection itself [29]. The hyper-inflammatory storm caused by the overactive immune system caused cells to penetrate and damage many organs (the lungs, the kidneys, and the heart, for example). As can be seen in figure (2), the virus is known to cause a cytokine storm and lung inflammation by activating T-lymphocytes and macrophages in appropriately [7].
2. The blood flow is disrupted because the immune system is out of whack and causing blood clots (both small and large).
3. Acutely worsening O_2 uptake is severe hypoxemia brought on by a cytokine storm and micro-thrombosis in the pulmonary circulation [29].

Another phenomenon known as 'happy' hypoxemia mean a noticeable arterial hypoxemia without relative signs of respiratory distress [30].

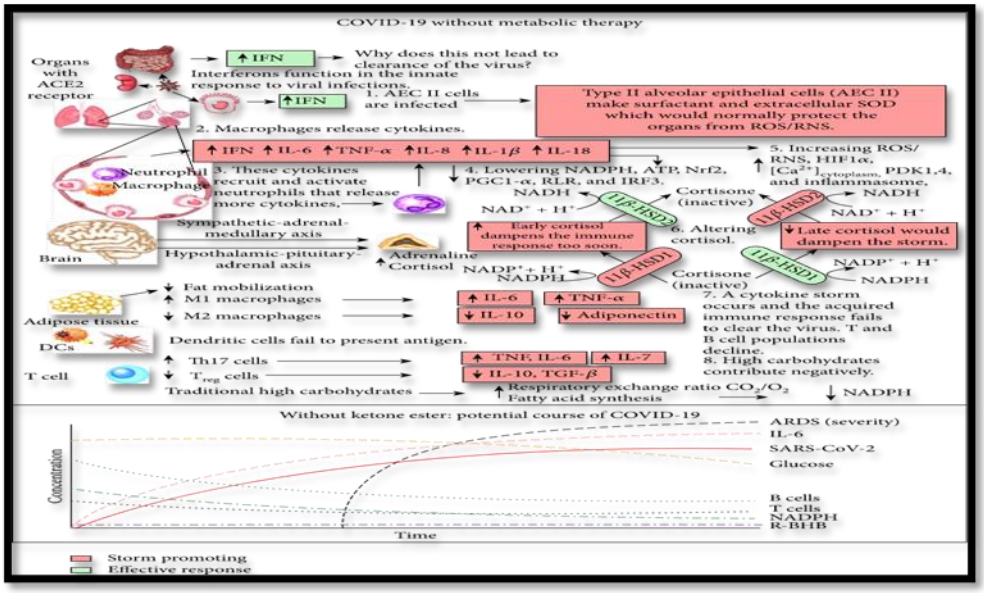

Figure 2. Mechanisms of ARDS and mortality after SARS-CoV-2 infection [7]

Modification in oxyhemoglobin dissociation curve

Find hypoxemia through determination of O_2 saturation (SpO_2) by pulse oximetry. But with COVID-19, it is important to be careful with how interpret the SpO_2 readings. Reduced partial pressure of CO_2 ($PaCO_2$) from hypoxemia-induced tachypnea and hyperpnea shifts the sigmoid shape of the oxyhemoglobin dissociation curve to the left [30,31], as shown in figure (3).

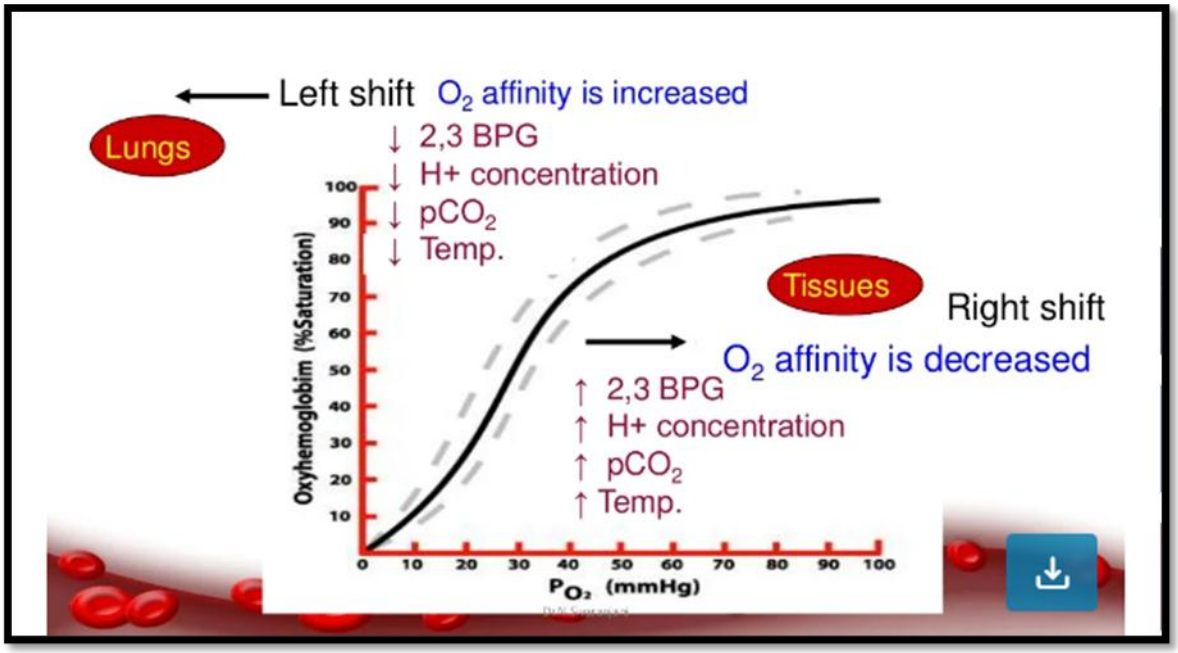

Figure 3. Factors affecting oxygen dissociation curve [32]

Free iron

Hemolysis induces a redox reaction because free iron, especially ferrous iron (Fe^{2+}) is released into the tissue. Since free iron is very harmful to cells and tissues, the body creates a transport molecule called ferritin. COVID-19 obstructs the system that supplies the blood with O_2 [4].

When O_2 saturation was increased for a given PaO_2, the hypocapnia phase was entered. In spite of a low PaO_2, a healthy SpO_2 may be maintained. It has been hypothesized by Liu et al. [30] that elevated levels of ferric ions (Fe^{3+}) and heme serum concentrations cause inflammation and ferroptosis in COVID-19, which in turn leads to the production of a high concentration of serum ferritin to bind Fe^{3+} and prevent tissue damage. This kind of contact between the virus and the heme group of Hb is called direct viral interaction.

Intrapulmonary shunt causes hypoxemia in COVID-19 patients because of increased edema, which increases lung weight, alveolar disassembly and further degradation cannot be reversed by increasing the proportion of inspired oxygen. The release of endogenous vasodilator prostaglandins, bradykinin, and cytokines may also play a role in the inefficiency of lung perfusion regulation, which is linked to the advancement of inflammation [30].

Angiotensin-converting enzyme 2 (ACE2)

The pathophysiology of COVID-19 infection includes a dysregulated renin-angiotensin system since ACE2 is the primary efficient

receptor employed by SARS-CoV-2 for cell entry [33]. Serum angiotensin II levels were correlated with viral load and lung injury in COVID-19, according to another research [30].

As a net consequence of COVID-19 pathogenesis is the intravascular micro-clot formation due to imbalance between procoagulant and fibrinolytic action in acute inflammation and endothelial hurt [34-36]. So, the uncovered basement membrane masked with debris of fibrin, deadly cells, and complement activation yields, collectively denoted as hyaline membranes which might not consent adequate time for RBCs to equilibrate their O_2 uptake. A diffusion restriction may occur in COVID-19 [37-39].

Some individuals infected with SARS-CoV-2 exhibit a severe innate immune response, complete with a cytokine storm and ARDS, which contributes to the high fatality rate associated with this virus. Low energy metabolism altered redox state, oxidative damage, and cell death all define this phenomenon at the molecular level. Exogenous ketones may enhance cell efficiency and metabolic flexibility to give considerable immunological regulation. As a result of the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during a virus-stimulated cytokine storm, many enzymes involved in central metabolism, such as the pyruvate dehydrogenase complex, are injured, downregulated, or inactivated, thereby reducing metabolic flexibility. This leads to an energy and redox disadvantage lowering B and T cell production and culminates in increased cytokine generation and cell death. While a ketogenic diet has been shown to protect mice from influenza virus infection via a protective (T) cell response, therapies that increase (R)-beta-hydroxybutyrate (R-BHB) levels, such as the use of ketogenic food or various forms of exogenous ketones, may aid host protection against respiratory viral infectivity, by lowering inflammation. To discover new protective mechanisms against viral infection, it is crucial to investigate metabolic methods, as seen in figures (4 and 5) [7].

COVID-19 and glucose metabolism

Metabolic renewal, such as the switch to aerobic glycolysis, promotes the replication of SARS-CoV-2 and the host cellular response. The generation of 3-phosphoglycerate is involved in the regulation of proinflammatory cytokines like IL-1, which is elevated in COVID-19 infected individuals [40] (Figure 6). Figure 6 suggesting a direct link to glucose metabolism and emphasizing the importance of glucose metabolism in virus-induced cytokine storm that results in low oxygen supply to lung cells due to inflammatory events [41-43]. Therefore, limiting viral replication and reducing inflammation by enhancing the function of the adaptive immune system may be facilitated by regulating hyper-glycolysis in acutely COVID-19 infected individual [44,45].

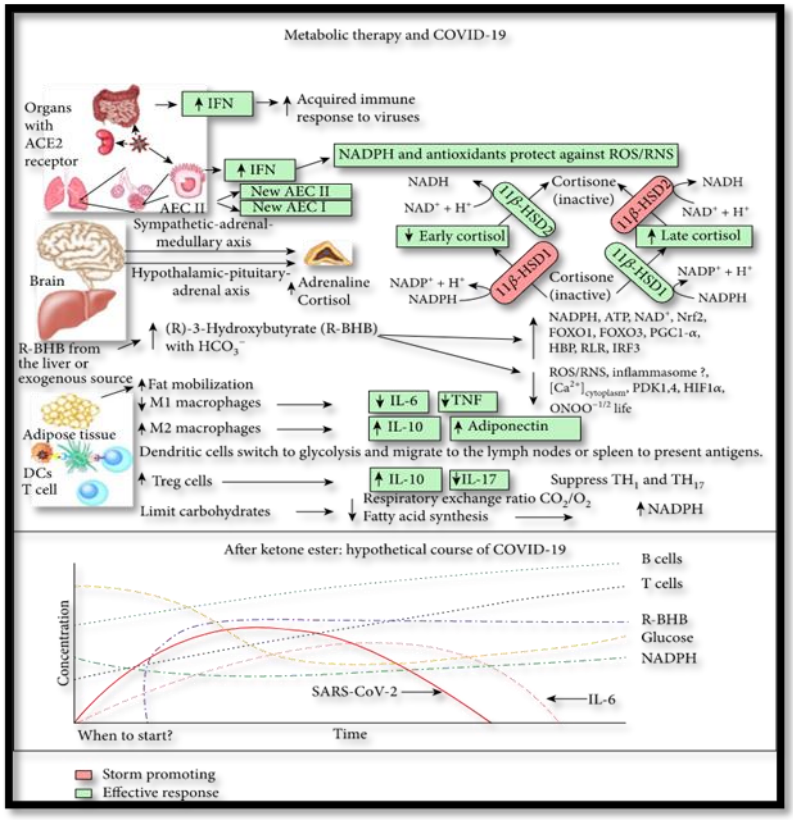

Figure 4. Mechanisms and time course of SARS-CoV-2 infection when using a ketone-based metabolic therapy [7]

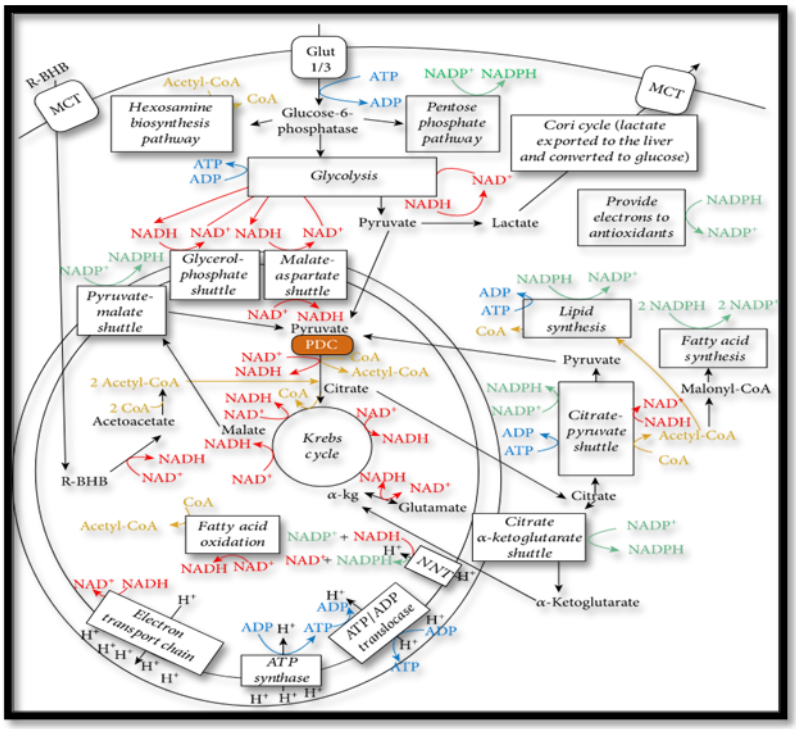

Figure 5. The major pathways of central metabolism and reactions that alter the ratios of coenzyme couples [7]

Fetal and adult hemoglobin in correlation to glucose metabolism

Adults have adult Hb (HbA1, or 2α2β), whereas fetuses have fetal Hb (HbF, or 2α2γ). Fetal RBCs (f-cells) contain HbF, and because of its role in the transfer of O_2 from the mother's circulation to the developing baby's tissues, HbF concentrations in the newborn's blood remain increased for another two to four months. HbF has a greater affinity to O_2 than maternal HbA1, because HbF contains 2 γ subunits while HbA1 contains 2β. In fact, since 2,3-BPG improves oxygen release from Hb, certain intracellular molecules may bind to Hb and alter its binding affinity for O_2. Because the subunit of HbA1 is positively charged, 2,3-BPG (which has negative charges) interacts with it considerably more strongly than it does with HbF (which binds to oxygen with a higher affinity) [29,46,47] as shown in figure (7).

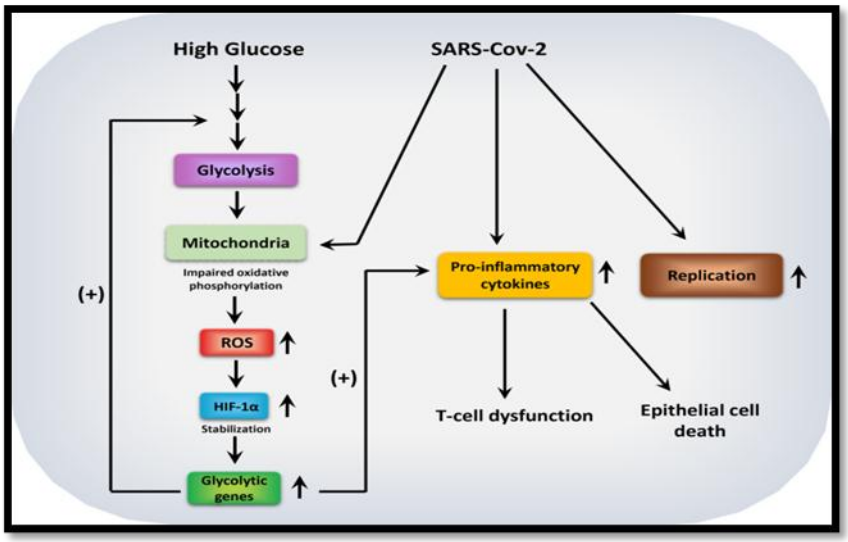

Figure 6. Glucose metabolism potentiates SARS-Cov-2 replication, cytokine storm and lung epithelial cell death [41]

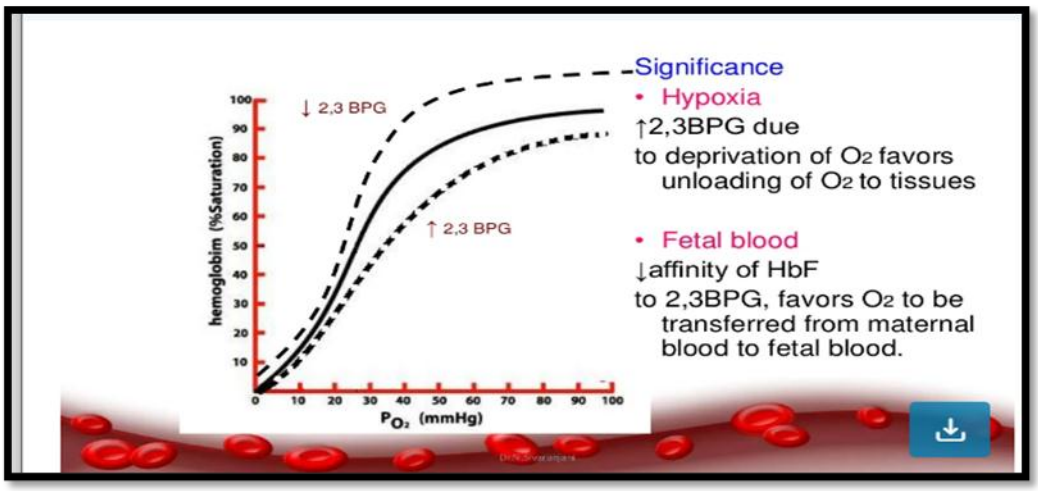

Figure 7. Effect of fetal hemoglobin and 2,3-BPG on hemoglobin affinity to oxygen [32]

In other words, if COVID-19 patients raise their HbF levels, they may be able to avoid the tissue damage and cardiac arrest caused by hypoxia and desaturation, as shown in the rare but life-threatening instances of joyful hypoxia. Fetal blood transfusions, in which blood is taken from a newborn's umbilical cord and given to the patient, or the drug hydroxyurea, which increases f-cells and HbF by increasing nitric oxide levels, thereby activating soluble guanylyl cyclase, which in turn increases cyclic guanosine monophosphate (c-GMP) and activates the -globin gene expression and subsequent -chain synthesis required for HbF formation, are two viable options. Hydroxyurea is utilized in situations of thrombocytosis and leukocytosis when there is an increased risk of thrombosis since it also prevents the growth of bone marrow granulocytes with a slight immunosuppressive impact [(29)].

Several of viral transmutations may affect immune consequences directed toward the key antigenic zones of receptor binding protein and deletion of segment of the N-terminal domain [(48,49)].

Conclusion

Focusing on hypoxia as the primary cause of severe morbidity in COVID-19 patients is thought to result from an increased stability of the relax (R-state) of hemoglobin at the tissue level due to a decrease in glucose metabolite produced from glycolysis process in RBCs (decrease 2,3-BPG concentration in the blood). This theory proposes raising 2,3-BPG levels, which is to free up more O2 from the R-form of Hb in the tissues.

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Correspondance to Nadia Gh. AbdulKareem
E-mail: nadya_abdulkareem@aliraqia.edu.iq, myd7810@gmail.com
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