2-deoxy-d-glucose therapy for preventing inflammatory cascade in COVID19 patients

To the Editor,

Researchers have proved beyond doubt that uncontrolled blood sugars in known diabetic patients or patients without diabetes presenting with increased, uncontrolled sugars due to systemic inflammation status *per se* face adverse outcomes if they have COVID19 disease, due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] It has been demonstrated that when human monocytes in patients with COVID19 infection were exposed to high glucose, there was exaggerated viral replication, upregulation of angiotensin-converting enzyme 2 (ACE2), and an increased cytokine production which compromised T-cell response and its overall function in curtailing underlying infection. This led to further damage to lung parenchymal cells which could explain the exaggerated virulence in diabetic patients and in patients with high blood sugars.[2] This leads to the release of proinflammatory cytokines like TNF-α, IL-1β, and IL-6 thus facilitating cytokine storm. This cytokine storm occurs in certain categories of patients due to the hyperactivation of the innate immune system by SARS-CoV-2 and excessive release of proinflammatory cytokines and chemokines.

Otto Warburg described the Warburg effect or the aerobic glycolysis in the year 1920 in which cancer cells utilize excessive glucose levels in presence of oxygen to produce lactate.[3] Researchers had earlier demonstrated in the previous pandemic that in MERS-CoV disease there was aerobic glycolysis which led to the release of proinflammatory cytokines and worsening of the disease. The same is being postulated in COVID19 disease as well. It was observed that by inhibition of glycolysis by using 2-deoxy-d-glucose, glycolytic enzymes 6-phospho-fructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) which regulated phosphofructokinase-1 (PFK1) and also lactate dehydrogenase A (LDH-A) abolished viral replication and excessive cytokine release.

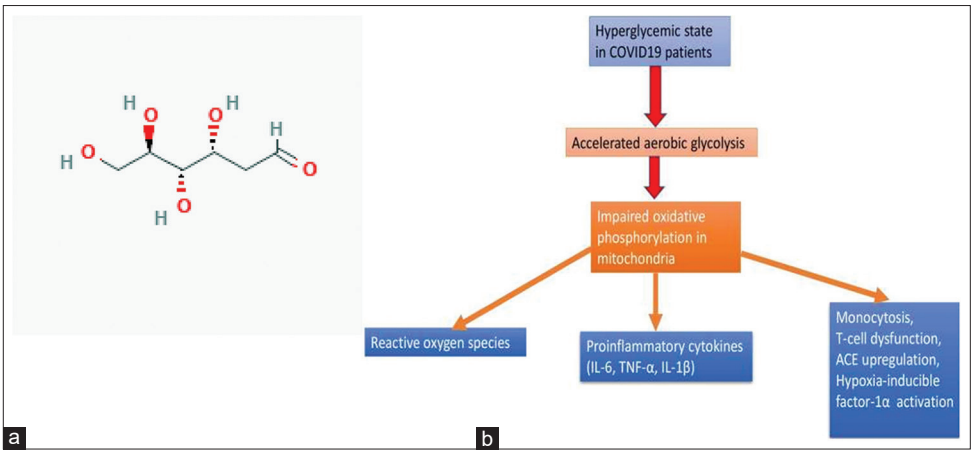

Figure 1: (a) Chemical structure of 2-deoxy-d-glucose. (b) Shows the inflammatory cascade as a result of persistent hyperglycemic state in COVID19 patients. Image source: National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 108223, Deoxyglucose. Retrieved June 05, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Deoxyglucose

Glucose homeostasis is impaired in patients with diabetes mellitus, de novo patients, and also in any patient with systemic inflammatory response syndrome due to any bacterial or viral infection. Aerobic glycolysis causes hyperactivation of M1 macrophages that eventually leads to the recruitment of monocytes, neutrophils, and platelets from circulating blood. This leads to the formation of neutrophil extracellular traps and monocyte-platelet aggregates which is supposedly the reason for thrombosis. As accelerated glycolysis is possibly responsible for excessive viral replication and exaggerated severity of the disease, researchers explored agents which could inhibit glycolysis and thus potentially interfere with viral replication during the early stage of the disease.[4] In underlying viral infection, there is a shift from oxidative phosphorylation to aerobic glycolysis in the host cells which facilitates viral replication. Hypoxia-inducible factor-1α (HIF-1α) has been implicated to be an important regulator of glycolysis. HIF-1α levels are induced in SARS-CoV-2 infected monocytes. HIF-1α stabilization or inhibition has important therapeutic effects like reduced replication, reduced release of inflammatory cytokines, restores T-cell function, and improved lung epithelial cell survival [Figure 1].[5]

2-deoxy-d-glucose is a glucose molecule in wherein the 2-hydroxyl group is replaced by hydrogen as a result of which it cannot undergo further glycolysis [Figure 1a]. When administered systemically, it competitively inhibits the production of glucose-6-phosphate from glucose at the phosphorglucoisomerase level i.e., at step 2 of glycolysis.[6] It was observed that by inhibition of glycolysis by using 2-deoxy-d-glucose, glycolytic enzymes 6-phospho-fructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) which regulated phosphofructokinase-1 (PFK1) and also lactate dehydrogenase A (LDH-A) abolished viral replication and excessive cytokine release.

The beneficial effects of 2-deoxy-d-glucose are owing to its anti-glycolytic properties, anti-inflammatory, immune-enhancing properties which can have beneficial effects when used in the acute phase of illness. The immunomodulation properties of 2-deoxy-d-glucose is due to its ability to restore CD/CD8 ratio, enhancing natural killer cells properties, and IFN λ levels.[7] When used in cancer patients, rapid metabolism and short half-life were the problems encountered with the use of 2-deoxy-d-glucose. Safety and efficacy in cardiac, renal, and hepatic ailments has not been validated yet. Fatigue, sweating, dizziness, nausea, symptoms of hypoglycemia are the problems of using 2-deoxy-d-glucose. To address these issues, researchers developed analogues and prodrugs of 2-deoxy-d-glucose. They are 2-halogen substituted d-glucose, fluoro-hexose compounds, and acetates of 2-deoxy monosaccharides as prodrugs. However, these compounds have been used in cancer patients and not in COVID19 patients.[8]

To conclude, providing 2-deoxy-d-glucose as a substrate for inhibiting glycolysis which is a key step in disease progression could have several beneficial effects in patients with COVID19 disease. However, this adjunct therapy needs to validated by conduction well-designed, adequately powered studies. Although the adjunct although appears safe, there is no clarity regarding the dose, timing, and duration of 2-deoxy-d-glucose therapy in COVID19 patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 04-Jun-2021, **Revised:** 05-Jun-2021,
Accepted: 05-Jun-2021, **Published:** 02-Sep-2021

References

1. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: From pathophysiology to clinical management. Nat Rev Endocrinol 2021;17:11-30.
2. Ardestani A, Azizi Z. Targeting glucose metabolism for treatment of COVID-19. Signal Transduct Target Ther 2021;6:112.
3. Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. Biochem Soc Trans 2016;44:1499-505.
4. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, *et al*. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020:e3319. doi: 10.1002/dmrr. 3319.
5. Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, *et al*. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. Cell Metab 2020;32:437-46.e5.
6. Berber E, Sumbria D, Rouse BT. Could targeting immunometabolism be a way to control the burden of COVID-19 infection? Microbes Infect 2021;23:104780.
7. Farooque A, Afrin F, Adhikari JS, Dwarakanath BS. Polarization of macrophages towards M1 phenotype by a combination of 2-deoxy-d-glucose and radiation: Implications for tumor therapy. Immunobiology 2016;221:269-81.
8. Pajak B, Siwiak E, Sołtyka M, Priebe A, Zielinski R, Fokt I, *et al*. 2-deoxy-d-glucose and its analogs: From diagnostic to therapeutic agents. Int J Mol Sci 2019;21:234.

Access this article online	
Website: www.saudija.org	**Quick Response Code**
DOI: 10.4103/sja.sja_419_21	

How to cite this article: Nair A. 2-deoxy-d-glucose therapy for preventing inflammatory cascade in COVID19 patients. Saudi J Anaesth 2021;15;467-9.