Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis

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ABSTRACT

It has been reported that frequent occurrence of COVID-19 infection in these patients is associated with low cytosolic pH. During virus infection, serum lactate dehydrogenase (LDH) level excessively rises. LDH is a cytosolic enzyme and the serum level increases as the cell break down. When anaerobic conditions develop, lactate formation increases from pyruvate. Cell pH is regulated by very complex mechanisms. When lactate increases in the extracellular area, this symporter carries lactate and H^+ ion into the cell, and the intracellular pH quickly becomes acidic. Paradoxically, Na^+/H^+ exchanger activation takes place. While H^+ ion is thrown out of the cell, Na^+ and Ca^{+2} enter the cell. When Na^+ and Ca^{+2} increase in the cell, the cells swell and die. Dapagliflozin is a sodium-glucose cotransporter-2 inhibitor. Dapagliflozin has been reported to reduce lactate levels by various mechanisms. Also, it reduces oxygen consumption in tissues and causes the use of glucose in the aerobic pathway, thereby reducing lactate production. A lactate decrease in the environment reduces the activation of lactate/H^+ symporter. Thus, the H ion pumping into the cell by this symporter is reduced and the cytosolic pH is maintained. Dapagliflozin also directly inhibits NHE. Thus, Na^+ and Ca^{+2} flow to the cell are inhibited. Dapagliflozin provides the continuation of the structure and functions of the cells. Dapagliflozin can prevent the severe course of COVID-19 infection by preventing the lowering of cytosolic pH and reducing the viral load.

Dear Sir,

The novel coronavirus disease 2019 (COVID-19) infection is common in patients with diabetes, hypertension, and heart failure [1]. It has been reported that frequent occurrence of COVID-19 infection in these patients is associated with low cytosolic pH [1]. It shows angiotensin-converting enzyme 2 (ACE2) activity in an acidic environment [2]. Hydroxychloroquine, used in the treatment of COVID-19, increases the cytosolic pH and alters the glycoprotein structure of ACE2 and prevents virus binding the cells [1–3]. During virus infection, serum lactate dehydrogenase (LDH) level excessively rises. LDH is a cytosolic enzyme and the serum level increases as the cell break down. ACE2 is in the lung, kidney, brain, pancreas, testicles, and vessels [1,4]. A recent study claimed that COVID-19 infects erythrocytes and causes immune hemolysis [3]. Presumably, the virus can be transported through the blood or vascular endothelium and penetrate all tissues containing ACE2 in its structure. The virus may cause the LDH to enter the bloodstream by disrupting the organs and cells. LDH is a two-way enzyme. It causes lactate formation from pyruvate and pyruvate from lactate. In aerobic conditions, lactate converts into pyruvate with lactate dehydrogenase enzyme and enters the TCA cycle. Since tissue oxygenation is disturbed, the hypoxic environment is formed [5,6]. When anaerobic conditions develop, lactate formation increases from pyruvate. The virus can create such a high anaerobic environment by disrupting tissue oxygenation. [5,6]. Energy production in the hypoxic environment is achieved through anaerobic glycolysis and 2 lactate and 2 H^+ ions are obtained. H^+ ion also forms during the hydrolysis of ADP to AMP. A vicious cycle continues and lactate production continues to increment as the hypoxic and acidic environment increases [6]. Besides, elevated lactate levels increase the release of proinflammatory cytokines and oxidative stress.

Cell pH is regulated by very complex mechanisms. Na^+/H^+ exchanger (NHE) and lactate/H^+ symporter (also called

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