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COMMENT

# Insulin may increase disease severity and mortality of COVID-19 through $Na^+/H^+$ exchanger in patients with type 1 and type 2 diabetes mellitus

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The glucose-lowering treatment of patients with diabetes mellitus (DM) and severe novel coronavirus disease 2019 (COVID-19) still remains a mystery. A recent meta-analysis and a large-scale retrospective cohort study showed that the use of insulin in patients with COVID-19 and type 1 DM or type 2 DM was associated with the frequency of hospital admissions, serious complications, and mortality [1, 2]. The authors have reported that insulin can cause these effects by stimulating the release of cytokines [1]. The role of insulin in the treatment of patients with DM and COVID-19 should be discussed due to the low glucose transporter 1 (GLUT1)/$Na^+/H^+$ exchanger (NHE) ratio in the blood of patients with COVID-19 [3], the close relationship between NHE and cytokine storms [4], and this meta-analysis [1] and similar publications. Insulin is a potent activator of NHE1 in many tissues [5]. Insulin also increases intestinal NHE3 activity [6]. Here, we will mention the NHE-mediated harmful effects of insulin in patients with DM and COVID-19.

Hyperinsulinemia accompanied by insulin resistance stimulates the nuclear factor kappa B signaling pathway by increasing the formation of enhanced glycated end products and increased reactive oxygen species (ROS) and circulating free fatty acids [7]. Thus, proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6, are released [7]. Also, insulin boosts the release of proinflammatory cytokines by active macrophages during severe infections like sepsis [8]. In addition, high insulin levels can trigger pathological inflammation, such as cytokine storms by overriding phosphoinositide 3-kinases' inhibition usually exerted by immune checkpoint proteins [9]. On the other hand, hyperinsulinemia increases the affinity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein and predisposes DM patients to COVID-19 by increasing the inflammatory response [7, 10]. Hyperinsulinemia enhances mortality by raising proinflammatory cytokines [7, 10]. Both type 1 DM and type 2 DM have chronic and permanent immune system deficiencies and are prone to infectious diseases [11]. The mortality rate in Type 2 DM patients using insulin is higher than in Type 1 DM patients [2]. Not only insulin but many comorbid conditions may increase mortality in diabetic patients. In particular, COVID-19 is more severe and fatal in elderly patients, since the immune system of elderly patients is prone to hyperactivation, and angiotensin-converting enzyme (ACE)2 expression decreases with age [11].

NHE is a pump that regulates intracellular pH and signal communication and provides the movement of $Na^+$ inward and $H^+$ outward. Increased angiotensin II levels in COVID-19 patients, the interaction of cholesterol with SARS-CoV-2 [12], and stimulation of cytokine release by the virus lead to NHE overstimulation [4]. Overstimulation of NHE1 found in many tissues can lead to intracellular $Na^+$ and $Ca^{+2}$ overload and reactive oxygen species generation [12], resulting in cytokine storms [4]. In addition, SARS-CoV-2 inhibits intestinal NHE3, unlike in other tissues, by increasing the level of angiotensin II and TNF-α release [4]. The increased luminal $Na^+$ disrupts the microbiota, causing cytokine release and diarrhea [4]. High cytokine release determines the severity of COVID-19.

In patients with type 2 DM, raised renin–angiotensin system (RAS) activation increases NHE activity [13–15]. Increased NHE activity leads to insulin resistance and decreased intracellular pH [12]. Patients with DM are predisposed to SARS-CoV-2 infection, since SARS-CoV-2 infects the cell effortlessly at low intracellular pH. In patients

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with DM and COVID-19, the virus fuses to ACE2, rendering it dysfunctional; as a result, increased angiotensin II overstimulates NHE. In addition, GLUT1 is ubiquitous in many tissues and plays a significant role in glucose regulation in cardiomyocytes [16]. Angiotensin II leads to insulin resistance by reducing the level of GLUT1 in the cell membrane [17]. The reduction of GLUT1 also leads to a decrease in the energy supply of cardiomyocytes. GLUT1 level was low in COVID-19 patients, especially in long COVID-19 patients, but its mechanism has not been fully explained [18]. In patients with COVID-19, the GLUT1 level may be decreased by angiotensin II-mediated suppression or due to NHE1-mediated lysosomal degradation [19, 20].

In diabetic patients with severe COVID-19, insulin can stimulate NHE1, which is already overstimulated. Further increase in NHE1 stimulation may facilitate the trigger of a cytokine storm in the patient. On the other hand, by stimulating intestinal NHE3, insulin overrides the suppressive effects of TNF-α and angiotensin II on NHE3 and protects gut microbiota containment. Thus, insulin may exert a positive impact by preventing the suppression of intestinal NHE3 activity, another mechanism that initiates cytokine storms. However, SARS-CoV-2 primarily causes infection in the lung and heart tissues, and the negative effect of insulin may occur. That is, insulin can exacerbate NHE1 overstimulation by directly stimulating NHE1 and by increasing proinflammatory cytokine release. Decreased GLUT1 in patients with DM and COVID-19 by high angiotensin II can require higher doses of insulin therapy [21–23]. As the insulin dose increases, insulin may become more toxic for patients with DM and COVID-19. Therefore, instead of insulin therapy alone, combined use with agents that inhibit NHE, such as metformin [24], sodium-glucose cotransporter 2 (SGLT2) inhibitors [25], and dipeptidyl peptidase-4 (DPP-4) inhibitors, may be beneficial in patients with type 2 DM and COVID-19. Metformin and DPP-4 inhibitors have been shown to have beneficial effects in the COVID-19 treatment [26–28]. Although the use of SGLT2 inhibitors in COVID-19 is still controversial, there is no clear evidence that they increase mortality and progression in COVID-19 [29]. However, there is also no evidence proving that SGLT2 inhibitors have a beneficial effect on COVID-19 [2]. Considering that they have no harmful effects on COVID-19 patients, they may have a beneficial effect by neutralizing the effects of insulin on NHE.

In conclusion, patients with type 2 DM have an acidic intracellular pH due to RAS activation, and SARS-CoV-2 can easily cause infection at acidic intracellular pH. Type 2 DM patients with COVID-19 need a higher dose of insulin therapy [23]. Insulin therapy may increase the need for mechanical ventilation and the mortality rate in diabetic patients with COVID-19 [23]. Patients with type 1 DM and type 2 DM and severe COVID-19 using insulin may be at increased risk of cytokine storm due to NHE1 overstimulation. Combining insulin with metformin, SGLT2 inhibitors, or DPP-4 inhibitors may be helpful in patients with type 2 DM and COVID-19. In addition, insulin can be combined with an ACE inhibitor in patients with type 1 DM, thus, causing COVID-19 to avoid the stimulating effect of insulin on NHE activity. Finally, the mechanism we propose may be part of a complex scenario that the clinical significance of which needs to be determined better, and detailed studies are required. In diabetic patients with COVID-19, factors affecting mortality and whether insulin affects mortality should be clarified immediately.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** No informed consent.

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