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Interactions between antihyperglycemic drugs and the renin-angiotensin system: Putative roles in COVID-19. A mini-review

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ABSTRACT

Background: Diabetes mellitus is associated with a more severe course of coronavirus disease 2019 (COVID-19). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes angiotensin-converting enzyme II (ACE2) receptor for host cell entry. We aimed to assess the interactions between antihyperglycemic drugs and the renin-angiotensin system (RAS) and their putative roles in COVID-19.

Methods: A literature search was performed using Pubmed to review the interrelationships between hyperglycemia, RAS and COVID-19, and the effects of antihyperglycemic medications.

Results: The RAS has an essential role in glucose homeostasis and may have a role in COVID-19-induced lung injury. Some antihyperglycemic medications modulate RAS and might hypothetically alleviate the deleterious effect of angiotensin II on lung injury. Furthermore, most antihyperglycemic medications showed anti-inflammatory effects in animal models of lung injury.

Conclusions: Some antihyperglycemic medications might have protective effects against COVID-19-induced lung injury. Early insulin therapy seems very promising in alleviating lung injury.

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1. Main text

Diabetes mellitus is associated with a more severe course of coronavirus disease 2019 (COVID-19) and higher mortality [1]. Data obtained from 21 hospitals in Wuhan, China, showed that 25% of the reported COVID-19 fatalities had a history of diabetes mellitus [1]. A literature search was performed using Pubmed to review the interrelationships between hyperglycemia, renin-angiotensin system (RAS) and COVID-19, and the effects of antihyperglycemic medications. Herein, we discuss the roles of the classic and non-classic renin-angiotensin system (RAS) in lung injury and glucose homeostasis among patients with COVID-19. We also discuss the putative roles of glucose-lowering medications in type 2 diabetic patients with COVID-19 and introduce the current evidence for their use in hospitalized patients.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme II (ACE2) receptor to enter the host cell and the serine protease TMPRSS2 for virus spike protein priming [2]. The binding of SARS-CoV-1 Spike protein to ACE2 activates disintegrin and metalloprotease-17 (ADAM17) and

induces ACE2 shedding via a process tightly coupled with TNF- α production [3]. Down-regulation of ACE2 cell surface expression in lung tissue is associated with a severe clinical outcome in cases of SARS-CoV-1 infection [4]. Considering that SARS-CoV-1 and SARS-CoV-2 share >70% sequence in the Spike protein [5], SARS-CoV-2 is likely to downregulate the ACE2 expression. Recently, Monteil V et al. showed that human recombinant soluble ACE2 significantly blocks SARS-CoV-2 infections, providing a rationale that soluble ACE2 might not only protect from lung injury but also block the SARS-CoV-2 from entering target cells [6].

ACE2 is expressed in the lung, kidney, pancreas and other tissues, and degrades angiotensin II to angiotensin-(1–7) [7]. The ACE2 receptor protects against lung injury by modulating of the RAS and decreasing angiotensin II levels [8]. Moreover, activation of the angiotensin-(1–7)/ACE2 axis inhibits reactive oxygen species production, downregulates proinflammatory cytokine secretion, and has immunomodulatory tissue-protective features [9]. From a physiologic standpoint, while increased baseline ACE2 expression could potentially increase SARS-CoV-2 infectivity, upregulation of ACE2 expression and ACE2 replacement in the acute respiratory distress syndrome phase (ARDS) phase may turn out to be beneficial.

Accumulating evidence supports the protective roles of ACE2 in diabetes. ACE2 might play several roles in glucose homeostasis:

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- 1) ACE2 deficiency leads to altered glucose metabolism; ACE2-knockout mice showed a β -cell defect associated with a decrease in insulin secretion in a manner that is not dependent on angiotensin II but may reflect the collectrin-like action of ACE2 [10]. In mice, ACE2 overexpression in the pancreas significantly improved glucose tolerance, enhanced islet function, and increased β -cell proliferation and insulin content [11].
- 2) Loss of ACE2 increases insulin resistance in the high-calorie diet fed mice, by reduction of GLUT4, and administration of angiotensin-(1–7) improved insulin tolerance, suggesting a significant role of angiotensin-(1–7) in glucose homeostasis [12].
- 3) Hyperglycemia stimulates tissue RAS and vice versa; that is, increased activity of angiotensin II signaling pathways contribute to the development of diabetes and its complications [13,14]. ACE2 is thought to act as a compensatory mechanism for hyperglycemia-induced RAS activation. Loss of ACE2 in mice disrupts the balance of the RAS in a diabetic state and leads to an angiotensin II/AT1 receptor-dependent systolic dysfunction and impaired vascular function [15].
ADAM17 is involved in the shedding of transmembrane ACE2 to release the catalytically active ectodomain into the circulation [16]. ADAM17-mediated ectodomain shedding might compromise the RAS compensatory axis by impairing ACE2 enzymatic activity or its ability to process angiotensin II on the cell surface [16]. In mice, hyperglycemia increases ADAM17 activity and renal ACE2 shedding into the urine [17]. This urinary ACE2 excretion correlated positively with the progression of diabetic renal injury, probably resembling an unopposed angiotensin II effect. In humans, urinary ACE2 levels are significantly higher in insulin-resistant subjects and type 2 diabetes mellitus than in controls with normal glucose tolerance [18]. In addition, urinary ACE2 appears to be positively associated with inflammatory cytokines, resembling increased ACE2 shedding [18].
- 4) The localization of ACE2 expression in the endocrine part of the pancreas suggests that SARS coronavirus enters islets using ACE2 as its receptor and damages islets causing acute diabetes. In fact, Yang J et al. reported that 50% of SARS patients who had no previous history of diabetes or steroid treatment, have been diagnosed with diabetes during hospitalization, and only 10% had diabetes after 3 years of follow-up [19].

It can be hypothesized that SARS-CoV-2-mediated down-regulation of ACE2 expression in the pancreas and peripheral tissues may decrease insulin secretion, increase insulin resistance and, induce hyperglycemia-induced RAS activation. On the other hand, ACE2 expression in the pancreas might facilitate SARS-CoV-2 invasion and direct β -cell damage.

ADAM17 activation by SARS-CoV-2 might also increase the risk of hyperglycemia. In mice, accumulating evidence suggests that increased ADAM17 activity results in increased insulin resistance

and hyperglycemia [20]. ADAM17 plays a potential role in inflammation, as it can cleave and thereby activate a variety of cytokines and cytokine receptors including tumor necrosis factor α (TNF α) and the interleukin-6 receptor (IL-6R) [21]. Increased inflammation might also contribute to the development of islet β -cell failure [22]. Accumulating evidence suggests that patients with severe COVID-19 and ARDS might have a cytokine storm syndrome, including high levels of IL-6 and TNF α [23]. Meanwhile, RAS activation can propagate acute lung injury [24].

Hyperglycemia is commonly observed during acute and critical illness. Early administration of insulin in acute illness is associated with better outcomes and lower mortality rates [25].

Insulin therapy in diabetic patients with COVID-19 disease that warrant hospital care, might be associated with better outcomes, and here are the explanations:

- 1) Insulin exerts immunomodulatory effects independent of glycemic control. Several studies suggest a potential benefit of insulin therapy in different animal models of acute lung injury and ARDS. Insulin inhibits synthesis of pro-inflammatory factors including TNF α and IL-6 and attenuates oxidative stress seen in acute lung injury [26,27].
- 2) Treating hyperglycemia with insulin might restore ACE2 and ADAM17 expression and the RAS balance, as was shown in mice. In the Akita mouse model of type 1 diabetes, insulin treatment normalized hyperglycemia, decreased urinary ACE2 excretion, restored renal ACE2 and ADAM17 expression to physiological levels, and normalized the rate of shedding [28]. A recent study has demonstrated a marked serum and pulmonary alterations in the ACE activity of non-obese diabetic (NOD) mice. In the lung of NOD mice, ACE activity was increased, and the ACE2/ACE activity ratio was decreased, as compared to control mice. Interestingly, insulin significantly increased ACE2/ACE activity ratio in the mice lung, and restored ACE and ACE2, and ACE2/ACE ratio activities in serum samples [29]. Therefore, it can be hypothesized that by restoring ACE2 expression to physiological levels on the cell surface and decreasing angiotensin II levels, insulin therapy might prevent the rapid propagation toward cytokine storm and lung injury in COVID-19.
- 3) Early insulin therapy reduces the risk of developing diabetic ketoacidosis or hyperglycemic hyperosmolar states, taking into account that some diabetic patients with COVID-19 may deteriorate rapidly to acute lung injury and ARDS.

Other antihyperglycemic medications (Table 1) might have a protective role in COVID-19-induced lung injury:

- 1) Metformin, by inhibiting mitochondrial complex I, could be useful in reducing oxidative stress and lung injury [30]. However, metformin should be withheld in hospitalized and

Table 1
The effects of antihyperglycemic drugs on ACE2 expression and the current evidence from preclinical models of lung injury.

Antihyperglycemic drug	Effect on ACE2 expression in animal studies	Preclinical evidence of anti-inflammatory effect in models of lung injury
Insulin	Restored renal ACE2 expression. Increased ACE2 activity in the lung.	Yes
Metformin	No data	Yes
PPAR- γ agonists	Pioglitazone increased ACE2 expression in insulin sensitive tissues Rosiglitazone did not affect renal ACE2 expression	Yes
DPP4 inhibitor	No data	Yes
GLP-1 agonists	Liraglutide increased ACE2 expression in the lungs	Yes
SGLT2 inhibitors	No data	No data
Sulfonylurea	No data	Yes

Abbreviations: ACE2, angiotensin-converting enzyme 2; DPP4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 agonists, glucagon-like peptide 1 agonists; PPAR- γ , peroxisome proliferator-activated receptor- γ ; SGLT2 inhibitors, sodium glucose co-transporter 2 inhibitors.

critically ill patients because of the increased risk of lactic acidosis [31].

- 2) Peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists attenuated lipopolysaccharide (LPS)-induced lung injury in murine models [32]. Of note, in type 2 diabetic mice, the insulin sensitizer rosiglitazone normalized hyperglycemia, attenuated renal injury and decreased urinary ACE2 excretion and renal ADAM17 protein expression, but, unlike insulin, did not affect renal ACE2 expression [33]. On the other hand, pioglitazone upregulated ACE2 protein expression in liver, adipose tissue, and skeletal muscle in rats with high-fat diet-induced nonalcoholic steatohepatitis [34]. An elevated ACE2 expression in insulin-sensitive tissues can attenuate the angiotensin II-induced insulin resistance. Pioglitazone effect on ACE2 expression in the lung is unknown. However, taking into consideration the risk of fluid retention, it is advisable to withhold PPAR- γ agonists in acutely ill patients.
- 3) Dipeptidyl peptidase 4 (DPP4) inhibitors attenuated LPS-induced lung injury in mice models and may have some anti-inflammatory and antiproliferative effects on cultured human lung microvascular endothelial cells in vitro [35]. Nevertheless, the available evidence does not support clinically meaningful alterations in immune response after administration of DPP4 inhibitors to human subjects [36]. Previous study findings have shown that DPP4 serves as the functional receptor for the Middle East respiratory syndrome coronavirus (MERS-CoV) [37]. However, unlike MERS-CoV, the SARS-CoV-2 does not utilize DPP4 for cell entry, and DPP4 inhibition per se seems not to exert direct antiviral effects. A prospective phase IV clinical trial will assess the effect of DPP4 inhibitor, linagliptin, in glucose control and reducing the severity of the COVID-19 infection ([Clinicaltrials.gov](https://clinicaltrials.gov/NCT04341935) NCT04341935) [38].
- 4) Glucagon-like peptide 1 (GLP-1) agonists attenuated LPS-induced lung injury in murine models [39]. Interestingly, the GLP-1 agonist, liraglutide, provoked an increase in ACE2 expression in the lungs of both diabetic and control rats, and in the circulating angiotensin-(1-7) in diabetic animals [40]. Based on these findings, it might be proposed that GLP-1 agonist therapy might exert protective effects against SARS-CoV-2 induced lung injury.
- 5) There is some emerging evidence suggesting anti-inflammatory effect of sodium glucose co-transporter 2 inhibitors (SGLT2) inhibitors [41]. However, recently published treatment recommendations advise to withhold these agents during COVID-19 illness due to the increased risk of dehydration and development of diabetic ketoacidosis (DKA) [42]. Anyhow, a prospective phase III clinical study (DARE-19) is ongoing to assess the potential effect of dapagliflozin in reducing the risk of serious complications and organ failure in hospitalized patients with COVID-19 illness ([Clinicaltrials.gov](https://clinicaltrials.gov/NCT04350593) NCT04350593) [43].
- 6) The sulfonylurea, glibenclamide can alleviate acute lung injury by inhibiting the nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome signaling pathway [44]. Glibenclamide down-regulates proinflammatory cytokines and reactive oxygen species and suppresses migration of inflammatory cells [45]. However, the use of sulfonylureas in the inpatient setting is discouraged because of the potential risk of hypoglycemia [46].

In summary, the current evidence reveals considerable interrelationships between hyperglycemia and coronavirus-induced lung injury. Insulin therapy seems very promising in alleviating lung injury. Given the wide clinical spectrum of COVID-19 and the fact that patients needing hospital care may deteriorate rapidly, it is reasonable to consider the early introduction of insulin upon

admission to the hospital. The suggested target glucose range is 140–180 mg/dL (7.8–10.0 mmol/L) in most cases [47]. Although considerable evidence supports the use of incretin-based therapies in critically ill patients with hyperglycemia, more prospective studies comparing these agents with insulin are required to establish their efficacy and safety [48,49]. Other antihyperglycemic agents lack safety data concerning their use in hospitalized patients with moderate or severe COVID-19 pneumonia. Future studies should be carried out to elucidate the interface between diabetes and COVID-19 and unveil glycemic and extra-glycemic effects of glucose-lowering medications in this disease.

Author contributions

A.N had the idea for this paper. A.N. & N.S. collected the data. A.N. drafted the manuscript. Both authors read and approved the final submitted paper after revision.

Declaration of competing interest

The authors have no conflicts of interest.

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