Review

BIO Integration

Metabolic Syndrome "Interacts" With COVID-19

Zeling Guo[1,3], Shanping Jiang[4], Zilun Li[5,6,*] and Sifan Chen[1,2,*]

Significance statement

Coronavirus disease 2019 (COVID-19) has rapidly spread worldwide and has exerted a great influence on public health and society, urging scientists to find efficient therapeutics. Metabolic disturbance involving various organs has been found in these patients, including diabetes, fatty liver, acute kidney injury (AKI), etc. In turn, these preexisting metabolic syndromes could exacerbate COVID-19. In this review, we focus on the close interaction between COVID-19 and metabolic syndrome, as well as the potential of repurposing metabolic-related drugs and the importance of treating metabolic diseases in COVID-19 patients.

Abstract

COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged as a global pandemic and poses a great threat to public health and society in general. SARS-CoV-2 invades cells via its spike protein, which initiates endocytosis via its binding to host receptor angiotensin-converting enzyme 2 (ACE2) and membrane fusion after being cleaved by the serine protease, TMPRSS2. The most common clinical manifestations are fever, dry cough, fatigue and abnormalities on chest computed tomography (CT). However, some patients rapidly progress to severe pneumonia and develop acute respiratory distress syndrome (ARDS). Furthermore, SARS-CoV-2 triggers a severe cytokine storm, which may explain the deterioration of pre-existing metabolic disorders. Interestingly, conversely, underlying metabolic-related diseases, including hypertension, diabetes, cardiovascular disease, etc., are associated with progression and poor prognosis of COVID-19. The putative mechanisms are dysregulation of ACE2, impaired immunity especially uncontrolled hyperinflammation, hypercoagulability, etc. In this review, we summarize the cross-talk between COVID-19 and metabolic diseases and propose that in addition to controlling COVID-19, more intensive attention should be paid to the symptomatic treatment and prevention of pre-existing and foreseeable metabolic comorbidities.

Keywords

ACE2, COVID-19, cytokine storm, metabolic syndrome.

[1]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

[2]Medical Research Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

[3]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

[4]Department of Respiratory and Critical Care Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

[5]Division of Vascular Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[6]National-Guangdong Joint Engineering Laboratory for Diagnosis and Treatment of Vascular Diseases, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

*Correspondence: Zilun Li, E-mail: lizilun@mail.sysu.edu.cn; Sifan Chen, E-mail: chensf26@mail.sysu.edu.cn

Received: September 20 2020
Revised: November 7 2020
Accepted: November 18 2020
Published Online: December 22 2020

Available at:
https://bio-integration.org/

Introduction and background

The Coronavirus disease 2019 (COVID-19) pandemic has become an unprecedented global crisis, resulting in 48,534,508 confirmed cases and 1,231,017 deaths by 7 November 2020 as declared by the World Health Organization (WHO). Most humans are generally susceptible to infection while the elderly or those with pre-existing conditions (e.g., diabetes, cardiovascular diseases, and cancers) are more vulnerable to severe COVID-19 [1]. Patients infected with COVID-19 may develop multiple organ failure suggesting that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) not only causes damage to the lungs, but also to the heart, kidney, gastrointestinal duct, kidneys, etc. [2–5]. In addition to the burden placed on healthcare systems, COVID-19 imposes an immense threat to social welfare and the global economy [6]. In our review, we first introduce the background on COVID-19, especially the molecular mechanisms of its hazardous nature. More importantly, we discuss the current and evolving evidence on the interplay between COVID-19 and metabolic syndrome and repurposing metabolic drugs for COVID-19 treatment.

The molecular characteristics of COVID-19

SARS-CoV-2 is a beta coronavirus (CoV) containing a positive-sense, single-stranded RNA [7]. SARS-CoV-2 was found to share several similarities with MERS-CoV and

BIOI 2020, Vol 1, No. 4, 168–177
https://bio-integration.org doi: 10.15212/bioi-2020-0035

SARS-CoV, especially the latter, as they all belong to the same highly pathogenic CoV family. Moreover, SimPlot and phylogenetic analysis has shown that the sequence of SARS-CoV-2 shares 96.2% identity to that of bat CoV RaTG13 [8], 79% to SARS-CoV, and 50% to MERS-CoV, indicating a bat origin [9]. At the molecular level, SARS-CoV-2 uses the same entry receptor angiotensin-converting enzyme 2 (ACE2) with SARS-CoV [10]. However, the notable exception was the crucial virus surface protein, a spike protein. The binding affinity of ACE2 with SARS-CoV-2 was 10–20 times higher than SARS-CoV [11], which is possibly due to an additional S1/S2 cleavage site of the spike protein and may explain the higher transmission efficiency of SARS-CoV-2 [12]. Another difference is the distinct cytokine profiles they induced. In patients with COVID-19, besides T helper 2 cytokines, T helper 1 cytokines were also elevated [13].

The SARS-CoV-2 genome encodes four structural, 16 nonstructural, and a variety of accessory proteins. Four key structural proteins are the spike protein, membrane protein, envelop protein and the nucleocapsid protein, all with different functions. The trimeric spike protein forms a unique spike structure on the virus surface and mediates receptor binding and fusion to the cell. Therefore, antibodies mainly target the spike protein [12]. The membrane protein, the main protease of SARS-CoV-2, plays a vital role in RNA translation and thus in viral replication. The envelop protein plays an essential part in viral assembly and release. Besides, the ion channel activity of envelop protein is potentially needed for the pathogenesis of SARS-CoV-2 [10]. The nucleocapsid protein forms a ribonucleoprotein core with a viral genome and has attracted attention because of its diverse functions in different stages of viral infection including transcription, translation, etc. [14]. Furthermore, the nucleocapsid protein could act as a viral suppressor of RNA interference and possibly contribute to immune evasion of SARS-CoV-2 [15]. Three important nonstructural proteins, nsp3, nsp5, and nsp12 (more often named RdRp) are requisites for viral production [16]. More importantly, RdRp was the target of the promising therapeutic candidate, remdesivir [17].

ACE2 is known to be a functional receptor for SARS-CoV [18]. The expression of ACE2, a type I membrane glycoprotein, has been found in various organs including the lung, heart, kidney, testis, intestinal tract, liver, brain, and pancreas [19–21]. ACE2 was experimentally confirmed to be the cell entry receptor of SARS-CoV-2 using virus infectivity studies, in which SARS-CoV-2 was able to enter HeLa cells expressing ACE2 from humans, Chinese horseshoe bats, civets, and pigs, but not those without ACE2 [8]. The hypothesis was also supported by some structural evidence. The Cryo-EM structure indicated that the ACE2 homodimer can bind to two SARS-CoV-2 S proteins simultaneously [22]. In detail, in the case of SARS-CoV, once the SARS-CoV-2 S1 subunit is bound to the ACE2 N-terminal peptidase domain of the host cell, the S1 subunit dissociates while the metastable pre-fusion S2 subunit transforms to a profoundly stable post-fusion conformation. For receptor occupancy, the epitopes for receptor recognition are instantly hidden or exposed, mediated by the hinge-like conformational transition of the receptor-binding domain of S1. The S protein is cleaved at the S1/S2 and at the S2′ sites to form S1 and S2 by the host-cell protease, which is another prerequisite for SARS-CoV-2 infection, allowing viral membrane fusion. A recent study investigated TMPRSS2 and CatB/L, two alternative proteases hijacked by SARS-CoV. It suggested that SARS-CoV-2 might use TMPRSS2 but not CatB/L as a crucial protease, partly supported by the results that camostat mesylate, a TMPRSS2 inhibitor, significantly blocked SARS-CoV-2 entry while directed expression of TMPRSS2 rescued virus entry from the inhibition of CatB/L [23].

The detrimental effects and molecular mechanisms of COVID-19

The most common onset symptoms of COVID-19 are fever, dry cough, and fatigue, while less common symptoms involve the gastrointestinal tract and the central nervous system. Some patients may progress to dyspnea, acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, and even death [3]. The lungs are the primary targets of SARS-CoV-2, and the typical abnormalities of computed tomography (CT) scans are bilateral patchy shadows and ground-glass opacity. The laboratory results are characterized by lymphocytopenia, elevated D-dimer, inflammatory factors, and other related markers suggesting the existence of multiple organ damage [24].

Here, we will discuss the putative mechanisms of how SARS-CoV-2 harms cells, especially the lungs. Furthermore, it may provide inspiration about how COVID-19 potentially exacerbates metabolic diseases.

Attacking host cells via ACE2 binding and entry

One potential mechanism is that SARS-CoV-2 directly uses the ACE2 receptor expressed by pneumocytes for entry to induce lung injury. Histopathologic examination of lung biopsies of COVID-19 patients shows diffuse alveolar damage, reactive type II pneumocyte hyperplasia, and intra-alveolar fibrinous exudates. Furthermore, rich expression of Rp3 nucleoprotein of SARS-CoV-2 has been found in alveolar epithelial cells [25].

A human ACE2 knock-in mouse model was generated to further study the pathogenesis of COVID-19, and high viral loads were detected in lung, trachea, and brain after intranasal infection with SARS-CoV-2 compared with no viral RNAs detected in wild-type mice [26]. Based on this hypothesis, expression of ACE2 on extrapulmonary organs may indicate potential infection and patterns of injury [27]. The expression levels of ACE2 across 31 healthy human tissues was investigated and the results showed ACE2 was expressed highest in the small intestine, testis, kidney, heart, and thyroid glands, and lowest in the blood, spleen, bone marrow, brain, and muscle. Intriguingly, ACE2 was only expressed

at a medium level in the lungs, colon, liver, bladder, and adrenal glands [28]. Clinical, pathological, and experimental evidence of damage in extrapulmonary tissue is consistent with the expression of ACE2 in the kidneys [29, 30], liver [31–33], brain [34], blood vessels [27, 30, 35], etc.

Liver injury is discussed in detail as an example. Elevated markers of liver cell injury in COVID-19 patients [36], microvesicular steatosis, decreased lobular activity, and SARS-CoV-2 RNAs found in liver biopsies implied the possible direct infection of the liver [33]. To explore the role of ACE2 in SARS-CoV-2-induced liver damage *ex vivo*, human liver ductal organoids that preserved human ACE2$^+$ cholangiocytes were established and the results showed that SARS-CoV-2 could infect and replicate abundantly in these special organoids. Furthermore, quantitative reverse transcription-polymerase chain reaction (QRT-PCR) analysis revealed dysregulation of genes related to a tight junction (claudin 1) formation and impaired bile acid transportation caused by virus infection, which may explain the bile acid accumulation and consequent liver injury in COVID-19 [31].

In addition, a positive association between the amount of viral load and disease severity highlighted the potential importance of direct viral toxicity in the pathogenesis of COVID-19 infection [37]. Notably, emerging evidence has demonstrated that complications in metabolic-related organs were potentially caused by SARS-CoV-2. It implies the link between COVID-19 and metabolism. The liver, the main metabolic organ in the body, showed hepatic congestion, mild steatosis, portal fibrosis, lobular cholestasis, and massive necrosis [38]. The small intestine, the primary site of nutrition absorption, was also susceptible to SARS-CoV-2 [39]. Pancreatic injury in COVID-19 patients included increased plasma levels of amylase and lipase, dilated pancreatic ducts [40], and focal pancreatitis [41]. Alterations in glucose, lipid [42], and protein metabolism indicated that SARS-CoV-2 may hijack the host metabolism to fuel its rapid infection and replication [43]. Proteinuria, hematuria, acute kidney injury (AKI) [44], and even kidney failure [45] have been observed. The endothelium is not only the lining of the blood vessels but also an endocrine organ, and the endothelialitis seen in various organs may be attributed to direct viral infection and host inflammatory response [27]. The new-onset myocarditis after SARS-CoV-2 infection implies the involvement of the heart, especially the myocardium, in the clinical course of COVID-19 [46].

The inflammatory factor storm

A cytokine storm, an auto-amplifying cytokine overproduction, is correlated with disease severity and has attracted growing concerns about its role in COVID-19 pathogenesis. Several studies found that most severe patients tended to have elevated pro-inflammatory cytokines including interleukin (IL)-6, IL-2, IL-2R, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1-alpha (MIP1α), and tumor necrosis factor (TNF)-alpha, and the subsequent cytokine storm [3, 47, 48]. Transcriptome sequencing of bronchoalveolar lavage fluid and peripheral blood mononuclear cells of COVID-19 patients drew similar conclusions [49].

A potential mechanism through which SARS-CoV-2 triggered a cytokine storm is summarized as below [50]. SARS-CoV-2 caused apoptosis or necrosis of infected cells, followed by positive feedback between the recruitment of inflammatory cells and the production of pro-inflammatory cytokines or chemokines. The immune system dysregulation manifested a specific pattern. An increased number and activation [51] of macrophages were seen in severe COVID-19 patients and may be the main cytokine producers involved in the pathogenesis of the cytokine storm [52]. The apoptosis of lymphocytes, especially CD4+ and CD8+ T cells, induced by SARS-CoV-2 leads to lymphocytopenia, which further reduces viral clearance and relieves the inhibition of T cells on overreactive innate immune systems [53]. In addition, the number of anti-inflammatory regulatory T cells declines [47]. Based on serum proteomic and metabolomic profiling, it was suggested that in addition to the imbalance of immune cells, impaired platelet degranulation, complement activation, and substantial metabolic decline possibly further exacerbates the cytokine storm and the progression of COVID-19 [54]. It is still an under-investigated phenomenon as to whether cytokines may induce the release of glucocorticoids and other peptides by modulating the neuroendocrine system [55].

ARDS has been the leading cause of death in patients with COVID-19, and the cytokine storm had been found to play a pivotal role in ARDS. Vigorous proinflammatory cytokines induced inflammatory cells infiltration and apoptosis of pulmonary endothelial cells, which contributed to vascular leakage together with the downregulation of E-cadherin caused by IL-6. Another consequence of the cytokine storm was the apoptosis of airway and alveolar epithelial cells, which results in alveolar edema [56]. Thus, the cytokine storm appears to be the dominating mechanism of ARDS.

Hypoxemia and systemic endothelial injury caused by ARDS may be the mechanisms that lead to the extrapulmonary dysfunction. Of patients on ventilators 89.7% had AKI while only 21.7% of nonventilated patients had AKI. Severe AKI most commonly occurred simultaneously with intubation and mechanical ventilation, which may imply the causal relationship between hypoxemia and AKI [57]. COVID-19 may predispose patients to thrombosis through several mechanisms. Directly, the endothelial injury caused the loss of anticoagulant function of the vascular lumen [58]. Dysregulation of coagulation-related genes and vasoconstriction [53] induced by hypoxia also promoted the vascular occlusion. What is more, multiorgan dysfunction could be found in COVID-19 patients without ARDS, which indicates additional mechanisms independent of ARDS. The autopsy of six COVID-19 patients with renal dysfunction showed high levels of CD68+ macrophages infiltrated into the tubulointerstitium, suggesting that SARS-CoV-2 might induce kidney injury mediated by proinflammatory cytokines released from macrophages. In addition, pro-inflammatory cytokine, especially IL-6, IL-1, and TNF, could contribute to arrhythmia through regulating gap junctions and ion channels of cardiomyocytes. In detail, CX40 and CX43 are two subunits of gap junctions between atrial myocytes. TNF could impair expression and/or distribution of CX40

and CX43, and therefore inhibit the function of gap junctions, which could induce conduction slowing and heterogeneity in the atria, or even atrial fibrillation [59]. Moreover, TNF decreased specific K+ currents and increased L-type Ca2+ currents through downregulating ion channel expression and/or changing channel-gating kinetics. IL-6 and IL-1 could exert similar effects and these alterations may lead to prolongation of the action potential duration, the QT interval, and associated malignant arrhythmias [60].

Metabolic diseases exacerbate COVID-19

The pre-existing metabolic syndrome worsens COVID-19

People with pre-existing metabolic disorders have a higher prevalence of severe COVID-19 and in-hospital death [1]. Growing evidence supports that metabolic diseases potentially aggravates COVID-19, and the mechanisms can be summarized into three key points: dysregulation of ACE2, impaired immunity especially uncontrolled hyperinflammation, and hypercoagulability. Next, we will discuss several representative metabolic diseases, respectively (see **Table 1**).

Diabetes status correlated with higher severity, need for intensive medical care, and mortality [61]. First, dysregulation of ACE2 could affect the susceptibility and progression of COVID-19. Specifically, in a recent study, lung samples of 26 diabetic patients showed significantly increased protein levels of ACE2 in both alveolar and bronchial epithelium [62]. In mouse models with type 2 diabetes, the pancreatic ACE2 expression displayed an early increase and a late decrease, which may reveal the course from compensation to decompensation of β-cell dysfunction [63]. The seemly contradictive effects on ACE2 expression, upregulation [64, 65] or downregulation [66, 67], may result from different species, types of diabetes, studied organs, and stage of diseases chosen in different studies. ACE2 is a double-edged sword for COVID-19 patients as ACE2 could prevent diabetic complications like diabetic nephropathy [68] but potentially facilitate SARS-CoV-2 entry. Therefore, more clinical and laboratory evidence is needed to determine the authentic effects of diabetes on ACE2, and thus on COVID-19. Second, high glucose levels could damage immunity from many aspects. Hyperglycemia inhibited chemotaxis, phagocytosis, and toxic chemicals release to kill pathogens. Enhanced direct glycosylation of antibodies and structure alteration of complement by glucose can attenuate opsonization. Third,

Table 1 The Evidence and Putative Mechanisms of Pre-existing Metabolic Syndrome Worsening COVID-19

Evidence	Putative Mechanisms
Diabetes	
• Higher severity, need for intensive medical care and mortality	• Dysregulation of ACE2 • Decreased chemotaxis, phagocytosis and toxic chemicals release • Attenuated opsonization • High baseline pro-inflammatory state • Destruction of the structure of lungs
Obesity	
• Three-fold higher risk of severe illness and longer hospital stay	• Low-grade, chronic inflammation • Attenuated innate and adaptive immune response • Storage of pre-activated cytokines in adipose tissue • Respiratory dysfunctions • Higher prevalence of pulmonary embolism • Higher risk of comorbidities
Liver injury	
• Common elevated ALT, AST, and bilirubin • 4-6 folds higher risk of progression • Longer viral shedding time	• Altered liver synthetic function • Increased inflammatory cytokines • Increased factor VIII, PAI-1, and decreased protein C
Cardiovascular diseases	
• Two-fold higher risk of mortality • Delayed viral clearance	• Upregulation of ACE2 caused by taking ACEI/ARBs • CD8+ T cells dysregulation • Inflammatory cytokines overproduction
Kidney disease	
• 4.3-fold increased risk of severe COVID-19	• Cardiogenic pulmonary edema and noncardiogenic edema • Increased serum inflammatory cytokines • Dysregulation of acid–base balance • Impaired erythropoietin production of kidney • Increased strength and decreased breakdown of clot

COVID-19: coronavirus disease 2019; ACE2: angiotensin-converting enzyme 2; ALT: alanine aminotransaminase; AST: aspartate aminotransaminase; PAI-1: plasminogen activator inhibitor-1; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers.

a high baseline pro-inflammatory state could exacerbate the cytokine storm in COVID-19 [69]. However, it should be noted that one study found only marginally increased inflammation in the lung in diabetic mice [70]. Fourth, in other animal models of disease, diabetes caused destruction in the structure of lungs, including collapse of the alveoli and greater permeability of the vasculature [71].

Patients with obesity, defined as body mass index (BMI) > 25 kg/m^2, had a three-fold higher risk of severe illness and longer hospital stay [72]. The mechanisms underlying the significant association between obesity and COVID-19 severity are still unknown and there are several hypotheses. Obesity is featured by low-grade, chronic inflammation [73] and attenuated innate and adaptive immune response [74, 75], which therefore worsened the stress. Human adipose tissue may serve as a reservoir for specific pre-activated cytokines and thus prolong viral shedding [76]. Besides, increased small airways resistance, lower respiratory muscle strength, impaired gas exchange, higher prevalence of pulmonary embolism [77], and other respiratory dysfunctions are common in the obese. Also, obesity is associated with a higher risk of comorbidities leading to higher COVID-19 severity, such as cardiovascular disease, diabetes, and kidney disease [78].

Liver injury with elevated alanine aminotransferase (ALT), aspartate aminotransaminase (AST), and bilirubin was common in patients with COVID-19, ranging from 14% to 53%. Metabolic dysfunction-associated fatty liver disease (MAFLD), one of the most common global health burdens, was associated with 4–6-fold higher risk of severe COVID-19 and longer viral shedding time [79]. These patients often suffered from other metabolic diseases like obesity, diabetes, and hypertension that may exacerbate the disease simultaneously. However, after adjusting for some possible confounding factors, the incidence of severe COVID-19 was still 2-fold higher, suggesting additional mechanisms. As a great number of acute phase reactants, cytokines, and coagulation factors were synthesized and secreted by the liver, the altered liver synthetic function may provide higher inflammatory and coagulable basal levels [41]. Increased chemotactic factor MCP-1, IP10, and pro-inflammatory cytokines TNF-α, IL-6, and IL-1β were commonly observed in MAFLD [80]. MAFLD was also featured by a prothrombotic state, possibly resulting from increased factor VIII, plasminogen activator inhibitor-1 (PAI-1) [81] and decreased protein C [82]. In addition, the procoagulant imbalance might explain the higher risk of cardiovascular events and hepatic fibrosis associated with MAFLD.

Cardiovascular diseases were prevalent among COVID-19 patients, among which hypertension was the most common comorbidity, with a prevalence of 21.1%. After adjustment for confounders, the risk of mortality was 2-fold higher in patients with hypertension than those without [83]. COVID-19 patients with hypertension displayed delayed viral clearance and some hypothesized it was caused by taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and the subsequent upregulation of ACE2 [84]. The immune dysregulation was another putative mechanism that deciphered the relationship between hypertension and COVID-19. CD4+ and CD8+ T cells dysregulation play a vital role in the pathogenesis of hypertension [85]. In particular, the proportion of immunosenescent proinflammatory cytotoxic CD8+ T cells was higher in patients with hypertension. The increased fraction of this phenotype may result in overproduction of cytokines and antiviral capacity retardation. An increase in IL-6, IL-1β, IFN-γ, TNF-α, CXCR3, etc., and a similar profile of cytokines with COVID-19, was observed in both hypertensive animal model and patients [86, 87].

AKI was associated with a 4.3-fold increased risk of severe COVID-19 [44] and kidney–lung crosstalk might play a central role. Cardiogenic pulmonary edema induced by fluid overload and noncardiogenic edema by inflammation-induced epithelial and endothelial apoptosis, has a detrimental effect on the gas exchange function and lung mechanics. In detail, serum cytokines IL-6, IL-8, and TNF were increased in AKI [88]. Dysregulation of the acid–base balance triggered not only pneumocyte dysfunction due to decreased enzymatic activity, but also pulmonary vasoconstriction and bronchoconstriction. Moreover, decreased oxygen-carrying capacity might be caused by impaired erythropoietin production of the kidneys [89]. For patients with chronic kidney disease, hypercoagulability due to increased strength and decreased breakdown of clots may augment the severity of COVID-19 [90].

Clinical treatments of metabolic diseases ameliorate COVID-19

Inference could be drawn that drugs for metabolic dysfunction would improve the symptoms and prognosis of COVID-19 due to their shared pathogenesis. Yet no specific drug for COVID-19 has been established. Repurposing of "old" drugs designed for metabolic disease would be an efficient approach as COVID-19 still being a public health emergency of international concern declared by the WHO. Moreover, the physiological status under COVID-19 may limit the use of certain drugs. Here, we investigated the potential effects and mechanisms of metabolic drugs on COVID-19 (see **Table 2**).

For glucose-lowering drugs, available evidence suggested insulin to be the best choice for glycemic control in diabetes patients with severe COVID-19. Whereas it remains unclear whether it has any direct impact on COVID-19, insulin reduced renal ADAM-17, the enzyme that cleaved and inactivated ACE2, and therefore resulted in ACE2 overexpression [91]. Metformin could reduce pulmonary injury in a lipopolysaccharide (LPS)-induced ARDS mouse model and was associated with reduced mortality from chronic lower respiratory tract disease in a population-based prospective cohort [92, 93]. It could indirectly phosphorylate ACE2 and thereby bring about structural and functional changes of ACE2 via AMP-activated protein kinase (AMPK) activation. These changes could hinder not only the binding of SARS-CoV-2, but also the following ACE2 downregulation [94]. However, the increased risk of lactic acidosis under a hypoxic state limited its use in patients with severe COVID-19. The incretin-based drug, GLP-1RA, might prevent CoVs entry via competitive binding to ACE2 [95] and induced ACE2 upregulation in both diabetic and control rats [96]. Metformin [97] and thiazolidinediones may also be potential

Table 2 Potential Metabolic Drug Repurposing and Putative Mechanisms

Drugs	Putative Mechanisms
Glucose-lowering	
• Insulin	• Reduced renal ADAM-17 and subsequent ACE2 overexpression
• Metformin	• Indirectly phosphorylation ACE2 via AMPK activation • Anti-inflammation
• GLP-1RA	• Prevention of CoVs entry via competitive binding to ACE2 • ACE2 upregulation
• Thiazolidinediones	• Anti-inflammation
Anti-hypertensive	
• ACEIs/ARBs	• ACE2 upregulation, harmful in the infection period but protective in the inflammatory period
Cholesterol-lowering	
• Statins	• Lipid rafts disturbance • Immune modulation • Atherosclerotic plaques stabilization
Anti-obesity	
• Cetilistat	• Reduced viral particle production, viral antigen expression and viral load of SARS-CoV-2
Anti-coagulant	
• Heparin	• Improved prognosis in severe COVID-19 with coagulopathy
• Nafamostat	• Suppression of CoVs entry
Antiplatelet	
• dipyridamole	• Inhibited viral replication via its binding to SARS-CoV-2 membrane protein

ADAM-17: A disintegrin and metalloprotease-17; ACE2: angiotensin-converting enzyme 2; AMPK: AMP-activated protein kinase; CoV: coronavirus; GLP-1RA: glucagon-like-peptide-1 receptor agonists; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; COVID-19: coronavirus disease 2019.

medication in treating COVID-19 due to their anti-inflammatory properties [98].

Hypertension was the most common comorbidity in patients with COVID-19 [99] and ACEIs and ARBs are commonly used as the first-line antihypertensive medications. Results of different studies diverged as some found no difference in mortality between patients who used ACEIs/ARBs and those who did not use them, while others found a lower peak viral load [100], severity, and mortality after taking ACEIs/ARBs [101]. However, the effects of ACEIs/ARBs mediated by ACE2 remains paradoxical theoretically. ACEIs/ARBs increase ACE2 activity, which might facilitate viral entry into cells and result in the progression of COVID-19, although a cohort study of 18,472 patients found the use of ACEIs/ARBs had no association with a COVID-19-positive test, which suggests ACEIs/ARBs would not increase the susceptibility to SARS-CoV-2. On the other hand, more Ang II was converted into Ang (1–7), which was proven to inhibit inflammation. However, whether anti-inflammation is harmful or beneficial in COVID-19 remains elusive [102]. A more comprehensive hypothesis was that ACE2 upregulation could be harmful in the infection period but protective in the inflammation period [103]. What is more, we focused on lung ACE2, which may be a more reliable indicator of SARS-CoV-2 susceptibility compared with soluble ACE2 in the serum and urine. In animal models of H5N1 infection [104], chronic cigarette smoke exposure [105], and ARDS [106], pulmonary ACE2 decreased and were restored after taking losartan, a widely used ARB. As for captopril, the first ACEI on the market, it was found to increase lung ACE2 expression in both LPS and control groups [107]. However, to the best of our knowledge, there are no clinical data on the effects of ACEIs/ARBs on pulmonary ACE2. Furthermore, the conflicting results regarding the ACE2 expression also suggested more complex regulation of ACEIs/ARBs on ACE2 or other possible mechanisms [108]. Further investigation is needed while at present, various guidelines recommend continuation of ACEIs/ARBs during the COVID-19 pandemic [109].

As lipids are important components of viruses and are involved in the viral life cycle including viral fusion, replication, and exocytosis [110], we investigated the effect of a typical cholesterol-lowering drug, statin on COVID-19. Statins could exert beneficial effects through lipid rafts disturbance, immune modulation, and atherosclerotic plaques stabilization on SARS-CoV-2 or other virus infections [111]. Although a meta-analysis published in 2011 concluded that statins failed to reduce the risk of infections [112], more studies about using lipid-lowering drugs to fight against COVID-19 are needed. Cetilistat, a pancreatic lipase inhibitor, is a novel anti-obesity drug that inhibits fat digestion and absorption. It was comparable to remdesivir in reducing the viral particle production, viral antigen expression and viral load of SARS-CoV-2 *in vitro* [113].

Antithrombotic drugs mainly include anticoagulant and antiplatelet drugs. Heparin, a commonly used anticoagulant agent, seemed to improve the prognosis in severe COVID-19 patients with coagulopathy [114]. Another anticoagulant drug nafamostat which is used to treat pancreatitis and disseminated intravascular coagulation (DIC), was identified to potently suppress the entry of CoVs including SARS-CoV-2 [115, 116]. The antiplatelet drug dipyridamole promoted host coagulation and immune system recovery in severe COVID-19 patients. It could also inhibit viral replication via its binding to SARS-CoV-2 membrane protein *in vitro* [117].

Off-label use of metabolic drugs, may not only reduce time and cost but also provide a novel strategy for further drug design and exploitation. However, more research is needed on the path from bench to bedside.

Summary: the crosstalk between metabolic diseases and COVID-19

In conclusion, growing evidence indicates the remarkable interplay between current COVID-19 and metabolic diseases (**Figure 1**). Research on the pathogenesis of SARS-CoV-2 is helping to discover their shared pathways, including dysregulation of ACE2, impaired immunity especially

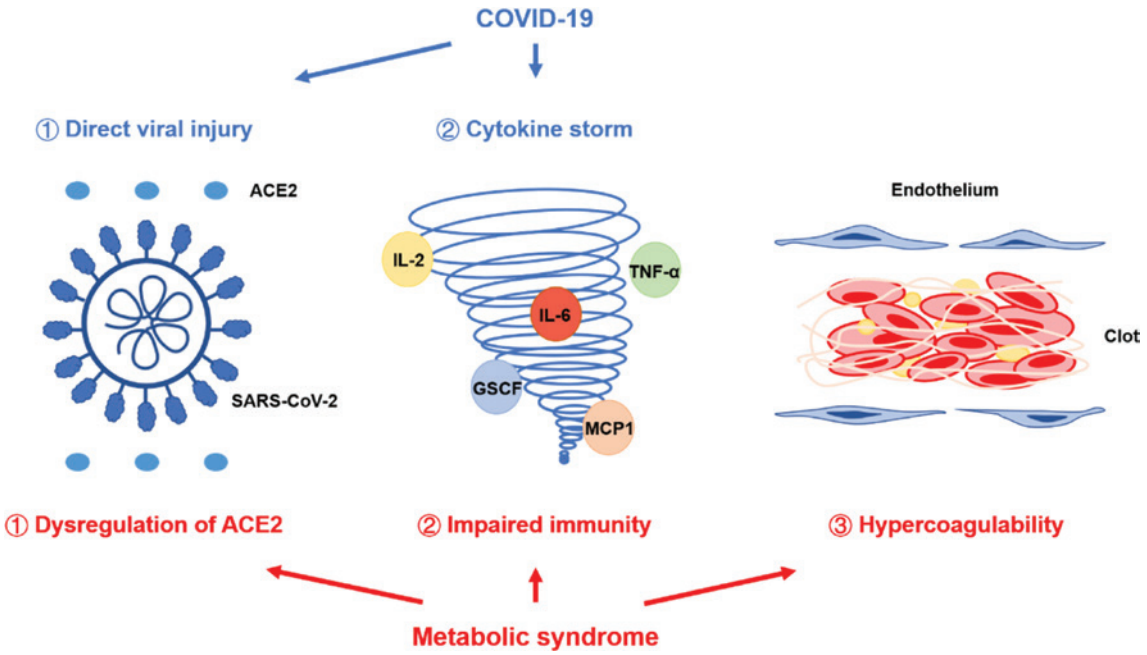

Figure 1 The interactions between COVID-19 and metabolic syndrome.

uncontrolled hyperinflammation, hypercoagulability, etc. These shared pathways potentially explain how metabolic diseases may exacerbate COVID-19, and vice versa. However, as most studies are observational, it is insufficient to infer the causal relationships. Accordingly, several metabolic drugs appear to improve the susceptibility, severity, and prognosis of COVID-19 patients. To date, no specific medicine is recommended to prevent or treat COVID-19 and the interdisciplinary integration of virology and medicine would guide the development of drugs repurposing and novel anti-viral strategies [118]. Prevention and treatment of COVID-19 as well as metabolic disorders is the key to reducing mortality rate and improving the prognosis of patients with COVID-19.

Conflict of interest

The authors declare that they have no competing interests.

References

[1] Zhou F, Yu T, Du R, Fan G, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62. [PMID: 32171076 DOI: 10.1016/s0140-6736(20)30566-3].

[2] Wang D, Hu B, Hu C, Zhu F, Liu X, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9. [PMID: 32031570 DOI: 10.1001/jama.2020.1585].

[3] Huang C, Wang Y, Li X, Ren L, Zhao J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. [PMID: 31986264 DOI: 10.1016/s0140-6736(20)30183-5].

[4] Chen N, Zhou M, Dong X, Qu J, Gong F, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13. [PMID: 32007143 DOI: 10.1016/s0140-6736(20)30211-7].

[5] Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. Circulation 2020;142:68-78. [PMID: 32293910 DOI: 10.1161/circulationaha.120.047549].

[6] Kickbusch I, Leung GM, Bhutta ZA, Matsoso MP, Ihekweazu C, et al. Covid-19: how a virus is turning the world upside down. BMJ 2020;369:m1336. [PMID: 32245802 DOI: 10.1136/bmj.m1336].

[7] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583:459-46. [PMID: 32353859 DOI: 10.1038/s41586-020-2286-9].

[8] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3. [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7].

[9] Lu R, Zhao X, Li J, Niu P, Yang B, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74. [PMID: 32007145 DOI: 10.1016/s0140-6736(20)30251-8].

[10] Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med 2020;28:174-84. [PMID: 32275259].

[11] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3. [PMID: 32075877 DOI: 10.1126/science.abb2507].

[12] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181:281-92.e6. [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058].

[13] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020;111:102452. [PMID: 32291137 DOI: 10.1016/j.jaut.2020.102452].

[14] Calligari P, Bobone S, Ricci G, Bocedi A. Molecular investigation of SARS-CoV-2 proteins and their interactions with antiviral drugs. Viruses 2020;12:445. [PMID: 32295237 DOI: 10.3390/v12040445].

[15] Mu J, Xu J, Zhang L, Shu T, Wu D, et al. SARS-CoV-2-encoded nucleocapsid protein acts as a viral suppressor of RNA interference in cells. Sci China Life Sci 2020;63:1-4. [PMID: 32291557 DOI: 10.1007/s11427-020-1692-1].

[16] Atri D, Siddiqi HK, Lang J, Nauffal V, Morrow DA, et al. COVID-19 for the cardiologist: a current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies. JACC Basic Transl Sci 2020;5:518-36. [PMID: 32292848 DOI: 10.1016/j.jacbts.2020.04.002].

[17] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929-36. [PMID: 32004427 DOI: 10.1056/NEJMoa2001191].

[18] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4. [PMID: 14647384 DOI: 10.1038/nature02145].

[19] Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000;87:E1-9. [PMID: 10969042 DOI: 10.1161/01.res.87.5.e1].

[20] Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: putative mechanisms of liver involvement in COVID-19. Liver Int 2020;40:2038-40. [PMID: 32352224 DOI: 10.1111/liv.14500].

[21] Qi J, Zhou Y, Hua J, Zhang L, Bian J, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to COVID-19 infection. bioRxiv 2020:2020.04.16.045690. [DOI: 10.1101/2020.04.16.045690].

[22] Yan R, Zhang Y, Li Y, Xia L, Guo Y, et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444-8. [PMID: 32132184 DOI: 10.1126/science.abb2762].

[23] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8. [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052].

[24] Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol 2020;92:568-76. [PMID: 32134116 DOI: 10.1002/jmv.25748].

[25] Zhang H, Zhou P, Wei Y, Yue H, Wang Y, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med 2020;172:629-32. [PMID: 32163542 DOI: 10.7326/m20-0533].

[26] Sun SH, Chen Q, Gu HJ, Yang G, Wang YX, et al. A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host Microbe 2020;28:124-133.e4. [PMID: 32485164 DOI: 10.1016/j.chom.2020.05.020].

[27] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-8. [PMID: 32325026 DOI: 10.1016/s0140-6736(20)30937-5].

[28] Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene *ACE2* in a wide variety of human tissues. Infect Dis Poverty 2020;9:45. [PMID: 32345362 DOI: 10.1186/s40249-020-00662-x].

[29] Diao B, Wang C, Wang R, Feng Z, Tan Y, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv 2020:2020.03.04.20031120. [DOI: 10.1101/2020.03.04.20031120].

[30] Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 2020;181:905-13.e7. [PMID: 32333836 DOI: 10.1016/j.cell.2020.04.004].

[31] Zhao B, Ni C, Gao R, Wang Y, Yang L, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver organoids. bioRxiv 2020:2020.03.16.990317. [DOI: 10.1101/2020.03.16.990317].

[32] Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2. [PMID: 32085846 DOI: 10.1016/s2213-2600(20)30076-x].

[33] Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med 2020;173:268-77. [PMID: 32374815 DOI: 10.7326/m20-2003].

[34] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995-8. [PMID: 32167747 DOI: 10.1021/acschemneuro.0c00122].

[35] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020 ;383:120-8. [PMID: 32437596 DOI: 10.1056/NEJMoa2015432].

[36] Fan Z, Chen L, Li J, Tian C, Zhang Y, et al. Clinical features of COVID-19 related liver damage. medRxiv 2020:2020.02.26.20026971. [DOI: 10.1101/2020.02.26.20026971].

[37] Zhu H, Rhee JW, Cheng P, Waliany S, Chang A, et al. Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. Curr Cardiol Rep 2020;22:32. [PMID: 32318865 DOI: 10.1007/s11886-020-01292-3].

[38] Kukla M, Skonieczna-Żydecka K, Kotfis K, Maciejewska D, Łoniewski I, et al. COVID-19, MERS and SARS with concomitant liver injury – systematic review of the existing literature. J Clin Med 2020;9:1420. [PMID: 32403255 DOI: 10.3390/jcm9051420].

[39] Lamers MM, Beumer J, van der Vaart J, Knoops K, Puschhof J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369:50-4. [PMID: 32358202 DOI: 10.1126/science.abc1669].

[40] Liu F, Long X, Zhang B, Zhang W, Chen X, et al. ACE2 Expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol 2020;18:2128-30.e2. [PMID: 32334082 DOI: 10.1016/j.cgh.2020.04.040].

[41] Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 2020;173:350-61. [PMID: 32422076 DOI: 10.7326/m20-2566].

[42] Wei C, Wan L, Zhang Y, Fan C, Yan Q, et al. Cholesterol metabolism – impact for SARS-CoV-2 infection prognosis, entry, and antiviral therapies. medRxiv 2020:2020.04.16.20068528. [DOI: 10.1101/2020.04.16.20068528].

[43] Thomas T, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, et al. COVID-19 infection results in alterations of the kynurenine pathway and fatty acid metabolism that correlate with IL-6 levels and renal status. medRxiv 2020:2020.05.14.20102491. [DOI: 10.1101/2020.05.14.20102491].

[44] Li Z, Wu M, Yao J, Guo J, Liao X, et al. Caution on kidney dysfunctions of COVID-19 patients. medRxiv 2020:2020.02.08.20021212. [DOI: 10.1101/2020.02.08.20021212].

[45] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, et al. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J Clin Med 2020;9:1417. [PMID: 32403217 DOI: 10.3390/jcm9051417].

[46] Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet 2020;395:1516. [PMID: 32334650 DOI: 10.1016/s0140-6736(20)30912-0].

[47] Qin C, Zhou L, Hu Z, Zhang S, Yang S, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71:762-8. [PMID: 32161940 DOI: 10.1093/cid/ciaa248].

[48] Shi Y, Tan M, Chen X, Liu Y, Huang J, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. medRxiv 2020:2020.03.12.20034736. [DOI: 10.1101/2020.03.12.20034736].

[49] Xiong Y, Liu Y, Cao L, Wang D, Guo M, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 2020;9:761-70. [PMID: 32228226 DOI: 10.1080/22221751.2020.1747363].

[50] Muniyappa R GS. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020;318:E736-41. [DOI: 10.1152/ajpendo.00124.2020].

[51] Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020;142:429-36. [PMID: 32418446 DOI: 10.1161/circulationaha.120.048360].

[52] Liao M, Liu Y, Yuan J, Wen Y, Xu G, et al. The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. medRxiv 2020:2020.02.23.20026690. [DOI: 10.1101/2020.02.23.20026690].

[53] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, et al. High risk of thrombosis in patients with severe SARSCoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089-98. [PMID: 32367170 DOI: 10.1007/s00134-020-06062-x].

[54] Shen B, Yi X, Sun Y, Bi X, Du J, et al. Proteomic and metabolomic characterization of COVID-19 patient sera. medRxiv 2020:2020.04.07.20054585. [DOI: 10.1101/2020.04.07.20054585].

[55] Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 2020;20:269-70. [PMID: 32273594 DOI: 10.1038/s41577-020-0308-3].

[56] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J Infect 2020;80:607-13. [PMID: 32283152 DOI: 10.1016/j.jinf.2020.03.037].

[57] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209-18. [PMID: 32416116 DOI: 10.1016/j.kint.2020.05.006].

[58] Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. Crit Care Med 2020;48:1358-64. [PMID: 32467443 DOI: 10.1097/ccm.0000000000004458].

[59] Sawaya SE, Rajawat YS, Rami TG, Szalai G, Price RL, et al. Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. Am J Physiol Heart Circ Physiol 2007;292:H1561-7. [PMID: 17122196 DOI: 10.1152/ajpheart.00285.2006].

[60] Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol 2019;19:63-4. [PMID: 30552387 DOI: 10.1038/s41577-018-0098-z].

[61] Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31:1068-77.e3. [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021].

[62] Wijnant SR, Jacobs M, Van Eeckhoutte HP, Lapauw B, Joos GF, et al. Expression of ACE2, the SARS-CoV-2 receptor, in lung tissue of patients with type 2 diabetes. Diabetes 2020;69:2691-9. [PMID: 33024003 DOI: 10.2337/db20-0669].

[63] Bindom SM, Hans CP, Xia H, Boulares AH, Lazartigues E. Angiotensin I-converting enzyme type 2 (*ACE2*) gene therapy improves glycemic control in diabetic mice. Diabetes 2010;59:2540-8. [PMID: 20660625 DOI: 10.2337/db09-0782].

[64] Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, et al. ACE and ACE2 activity in diabetic mice. Diabetes 2006;55:2132-9. [PMID: 16804085 DOI: 10.2337/db06-0033].

[65] Rao S, Lau A, So H-C. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: a Mendelian randomization analysis highlights tentative relevance of diabetes-related traits. medRxiv 2020:2020.03.04.20031237. [DOI: 10.1101/2020.03.04.20031237].

[66] Tikellis C, Johnston CI, Forbes JM, Burns WC, Burrell LM, et al. Characterization of renal angiotensin-converting enzyme 2 in diabetic nephropathy. Hypertension 2003;41:392-7. [PMID: 12623933 DOI: 10.1161/01.Hyp.0000060689.38912.Cb].

[67] Reich HN, Oudit GY, Penninger JM, Scholey JW, Herzenberg AM. Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease. Kidney Int 2008;74:1610-6. [PMID: 19034303 DOI: 10.1038/ki.2008.497].

[68] Jiang F, Yang J, Zhang Y, Dong M, Wang S, et al. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. Nat Rev Cardiol 2014;11:413-26. [PMID: 24776703 DOI: 10.1038/nrcardio.2014.59].

[69] Means C. Mechanisms of increased morbidity and mortality of SARS-CoV-2 infection in individuals with diabetes: what this means for an effective management strategy. Metabolism 2020;108:154254. [PMID: 32360397 DOI: 10.1016/j.metabol.2020.154254].

[70] Zechner D, Spitzner M, Müller-Graff T, Vollmar B. Diabetes increases pancreatitis induced systemic inflammation but has little effect on inflammation and cell death in the lung. Int J Exp Pathol 2014;95:411-7. [PMID: 25401425 DOI: 10.1111/iep.12103].

[71] Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur Respir J 1997;10:1850-8. [PMID: 9272930 DOI: 10.1183/09031936.97.10081850].

[72] Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care 2020;43:e72-4. [PMID: 32409499 DOI: 10.2337/dc20-0682].

[73] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415-45. [PMID: 21219177 DOI: 10.1146/annurev-immunol-031210-101322].

[74] Boutens L, Stienstra R. Adipose tissue macrophages: going off track during obesity. Diabetologia 2016;59:879-94. [PMID: 26940592 DOI: 10.1007/s00125-016-3904-9].

[75] Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, et al. Obesity expands a distinct population of T cells in adipose tissue and increases vulnerability to infection. Cell Rep 2019;27:514-24.e5. [PMID: 30970254 DOI: 10.1016/j.celrep.2019.03.030].

[76] Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation and cytokine amplification in COVID-19. Obesity (Silver Spring) 2020;28:1191-4. [PMID: 32314868 DOI: 10.1002/oby.22843].

[77] Movahed MR, Khoubyari R, Hashemzadeh M, Hashemzadeh M. Obesity is strongly and independently associated with a higher prevalence of pulmonary embolism. Respir Investig 2019;57:376-9. [PMID: 30770232 DOI: 10.1016/j.resinv.2019.01.003].

[78] Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol 2020;16:341-2. [PMID: 32327737 DOI: 10.1038/s41574-020-0364-6].

[79] Sharma P, Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. Diabetes Metab Syndr 2020;14:825-7. [PMID: 32540736 DOI: 10.1016/j.dsx.2020.06.013].

[80] Narayanan S, Surette FA, Hahn YS. The immune landscape in nonalcoholic steatohepatitis. Immune Netw 2016;16:147-58. [PMID: 27340383 DOI: 10.4110/in.2016.16.3.147].

[81] Verrijken A, Francque S, Mertens I, Prawitt J, Caron S, et al. Prothrombotic factors in histologically proven nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2014;59:121-9. [PMID: 24375485 DOI: 10.1002/hep.26510].

[82] Tripodi A, Fracanzani AL, Primignani M, Chantarangkul V, Clerici M, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. J Hepatol 2014;61:148-54. [PMID: 24657400 DOI: 10.1016/j.jhep.2014.03.013].

[83] Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J 2020;41:2058-66. [PMID: 32498076 DOI: 10.1093/eurheartj/ehaa433].

[84] Chen X, Hu W, Ling J, Mo P, Zhang Y, et al. Hypertension and diabetes delay the viral clearance in COVID-19 patients. medRxiv 2020:2020.03.22.20040774. [DOI: 10.1101/2020.03.22.20040774].

[85] Perrotta M, Lori A, Carnevale L, Fardella S, Cifelli G, et al. Deoxycorticosterone acetate-salt hypertension activates placental growth factor in the spleen to couple sympathetic drive and immune system activation. Cardiovasc Res 2018;114:456-67. [PMID: 29324984 DOI: 10.1093/cvr/cvy001].

[86] Youn JC, Yu HT, Lim BJ, Koh MJ, Lee J, et al. Immunosenescent CD8+ T cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension 2013;62:126-33. [PMID: 23716586 DOI: 10.1161/hypertensionaha.113.00689].

[87] Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. Nat Rev Immunol 2019;19:517-32. [PMID: 30992524 DOI: 10.1038/s41577-019-0160-5].

[88] Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. Nat Rev Nephrol 2016;12:48-60. [PMID: 26434402 DOI: 10.1038/nrneph.2015.158].

[89] Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. Pediatr Nephrol 2013;28:2239-48. [PMID: 23334385 DOI: 10.1007/s00467-012-2386-3].

[90] Nunns GR, Moore EE, Chapman MP, Moore HB, Stettler GR, et al. The hypercoagulability paradox of chronic kidney disease: the role of fibrinogen. Am J Surg 2017;214:1215-8. [PMID: 28951066 DOI: 10.1016/j.amjsurg.2017.08.039].

[91] Salem ES, Grobe N, Elased KM. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. Am J Physiol Renal Physiol 2014;306:F629-39. [PMID: 24452639 DOI: 10.1152/ajprenal.00516.2013].

[92] Mendy A, Gopal R, Alcorn JF, Forno E. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin. Respirology 2019;24:646-51. [PMID: 30761687 DOI: 10.1111/resp.13486].

[93] Katulanda P, Dissanayake HA, Ranathunga I, Ratnasamy V, Wijewickrama PSA, et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia 2020;63:1440-52. [PMID: 32405783 DOI: 10.1007/s00125-020-05164-x].

[94] Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes. Diabetes Res Clin Pract 2020;164:108183. [PMID: 32360697 DOI: 10.1016/j.diabres.2020.108183].

[95] Feng Y, Wang L, Ma X, Yang X, Don O, et al. Effect of hCMSCs and liraglutide combination in ALI through cAMP/PKAc/β-catenin signaling pathway. Stem Cell Res Ther 2020;11:2. [PMID: 31900217 DOI: 10.1186/s13287-019-1492-6].

[96] Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, Santisteban P, González-Matías LC, et al. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015;156:3559-69. [PMID: 26196539 DOI: 10.1210/en.2014-1685].

[97] Cuschieri S, Grech S. COVID-19 and diabetes: the why, the what and the how. J Diabetes Complications 2020;34:107637. [PMID: 32456846 DOI: 10.1016/j.jdiacomp.2020.107637].

[98] Ciavarella C, Motta I, Valente S, Pasquinelli G. Pharmacological (or Synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease. Molecules 2020;25:2076. [PMID: 32365556 DOI: 10.3390/molecules25092076].

[99] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20. [PMID: 32109013 DOI: 10.1056/NEJMoa2002032].

[100] Meng J, Xiao G, Zhang J, He X, Ou M, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757-60. [PMID: 32228222 DOI: 10.1080/22221751.2020.1746200].

[101] Zhang P, Zhu L, Cai J, Lei F, Qin JJ, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized With COVID-19. Circ Res 2020;126:1671-81. [PMID: 32302265 DOI: 10.1161/circresaha.120.317134].

[102] Aronson JK, Ferner RE. Drugs and the renin-angiotensin system in covid-19. BMJ 2020;369:m1313. [PMID: 32241880 DOI: 10.1136/bmj.m1313].

[103] Kuba K, Imai Y, Rao S, Gao H, Guo F, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-9. [PMID: 16007097 DOI: 10.1038/nm1267].

[104] Yan Y, Liu Q, Li N, Du J, Li X, et al. Angiotensin II receptor blocker as a novel therapy in acute lung injury induced by avian influenza A H5N1 virus infection in mouse. Sci China Life Sci 2015;58:208-11. [PMID: 25655897 DOI: 10.1007/s11427-015-4814-7].

[105] Han SX, He GM, Wang T, Chen L, Ning YY, et al. Losartan attenuates chronic cigarette smoke exposure-induced pulmonary arterial hypertension in rats: possible involvement of angiotensin-converting enzyme-2. Toxicol Appl Pharmacol 2010;245:100-7. [PMID: 20178811 DOI: 10.1016/j.taap.2010.02.009].

[106] Wösten-van Asperen RM, Lutter R, Specht PA, Moll GN, van Woensel JB, et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1–7) or an angiotensin II receptor antagonist. J Pathol 2011;225:618-27. [PMID: 22009550 DOI: 10.1002/path.2987].

[107] Li Y, Zeng Z, Li Y, Huang W, Zhou M, et al. Angiotensin-converting enzyme inhibition attenuates lipopolysaccharide-induced lung injury by regulating the balance between angiotensin-converting enzyme and angiotensin-converting enzyme 2 and inhibiting mitogen-activated protein kinase activation. Shock 2015;43:395-404. [PMID: 25768373 DOI: 10.1097/shk.0000000000000302].

[108] Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-9. [PMID: 32227760 DOI: 10.1056/NEJMsr2005760].

[109] Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II Receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1020-6. [PMID: 32369097 DOI: 10.1001/jamacardio.2020.1855].

[110] Lorizate M, Kräusslich HG. Role of lipids in virus replication. Cold Spring Harb Perspect Biol 2011;3:a004820. [PMID: 21628428 DOI: 10.1101/cshperspect.a004820].

[111] Abu-Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, et al. The role of lipid metabolism in COVID-19 virus infection and as a drug target. Int J Mol Sci 2020;21:3544. [PMID: 32429572 DOI: 10.3390/ijms21103544].

[112] van den Hoek HL, Bos WJ, de Boer A, van de Garde EM. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. BMJ 2011;343:d7281. [PMID: 22127443 DOI: 10.1136/bmj.d7281].

[113] Yuan S, Chan JFW, Chik KKH, Chan CCY, Tsang JOL, et al. Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system. Pharmacol Res 2020;159:104960. [PMID: 32473310 DOI: 10.1016/j.phrs.2020.104960].

[114] Tang N, Bai H, Chen X, Gong J, Li D, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9. [PMID: 32220112 DOI: 10.1111/jth.14817].

[115] Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, et al. Identification of nafamostat as a potent inhibitor of middle east respiratory syndrome coronavirus S protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. Antimicrob Agents Chemother 2016;60:6532-9. [PMID: 27550352 DOI: 10.1128/aac.01043-16].

[116] Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, et al. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother 2020;64:e00754-20. [PMID: 32312781 DOI: 10.1128/aac.00754-20].

[117] Liu X, Li Z, Liu S, Sun J, Chen Z, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 2020;10:1205-15. [PMID: 32318327 DOI: 10.1016/j.apsb.2020.04.008].

[118] Er Saw P, Jiang SJBI. The significance of interdisciplinary integration in academic research and application. BIO Integration 2020;1:2-5. [DOI: 10.15212/bioi-2020-0005].