

# Metformin and Coronavirus Disease 2019: A New Deal for an Old Drug

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## Abstract

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed a remarkable global challenge as a previously unrecognized viral infection with high infectivity. The high prevalence of diabetes makes it one of the most common comorbidities observed in patients with COVID-19 infection. Studies have suggested that diabetes is associated with unfavorable COVID-19-related outcomes. Lower mortality rates have been observed among individuals with good glycemic control than among those with poor glycemic control, and glycemic management may affect the prognoses and outcomes of COVID-19 infection. Several studies have demonstrated that COVID-19 infection contributes to hyperglycemia, metabolic dysfunction, and increased microvascular complications and thrombotic events against the backdrop of aberrant endothelial function. Metformin, the most prescribed oral antidiabetic medication, exhibits multiple beneficial effects beyond its glucose-lowering functions, such as anti-infection, anti-inflammation, immunomodulation, anti-hypertension, preventive effects on chronic obstructive pulmonary disease and heart failure. Hence, metformin may share similar mechanisms of these pleiotropic benefits or contribute to the reduced morbidity/mortality in COVID-19 infection. Therefore, metformin is a feasible candidate drug for repurposing to address the rising number of patients with COVID-19 infection who have diabetes. This review article presents a summary of the multiple potential mechanisms through which metformin produces beneficial therapeutic effects and summarizes real-world data supporting the repurposing of metformin for use in patients with COVID-19 who have type 2 diabetes.

**Key Words:** COVID-19, SARS-CoV-2, Metformin, Type 2 diabetes, Hyperglycemia, Mortality

## Introduction

In late December 2019, a previous unidentified coronavirus, currently named as the 2019 novel coronavirus, emerged from Wuhan, China, and resulted in a formidable outbreak in many cities in China and expanded globally. The disease is officially named as Coronavirus Disease-2019 (COVID-19) by the World Health Organization<sup>1</sup>. The relatively severe outcomes and high mortality rates in patients

infected with COVID-19 can be attributed to various factors such as age; obesity; and chronic diseases including diabetes, hypertension, and cardiovascular disease (CVD). These factors may be associated with imbalances in angiotensin-converting enzyme 2 (ACE2) and cytokine storms induced by glucolipid metabolic disorders<sup>2</sup>. Moreover, ACE2 is the main entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is highly expressed in human pancreatic beta cells, renal

proximal tubules, and the small intestine<sup>3</sup>. Therefore, SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that can complicate the pathophysiology or induce new mechanisms of pre-existing diabetes.

A clinical study by Zhu et al. reported that well-controlled blood glucose was associated with a lower mortality risk and improved outcomes of multiple organ injury in patients with COVID-19<sup>4</sup>. Since the outbreak, drug repurposing studies have explored the potential of different treatments, including antidiabetic medications, for use in the management of COVID-19. Several clinical studies have demonstrated that metformin exerts multiple pleiotropic functions beyond its glucose-lowering actions, such as anti-infection<sup>5,6</sup>, anti-inflammation/immunomodulation<sup>7,8</sup>, anti-hypertension<sup>9</sup>, and preventive effect on heart failure (HF)<sup>10</sup>. Therefore, metformin may share similar mechanisms of these pleiotropic benefits or contribute to the reduced morbidity/mortality (e.g., hypertension/HF) in COVID-19 infection. This article provides an in-depth review of the beneficial effects of metformin through various molecular mechanisms and summarizes clinical evidence that supports repurposing metformin for use in patients with COVID-19 with type 2 diabetes (T2D).

## Excessive inflammation of COVID-19 infection and its association with diabetes

ACE2 is the main entry receptor for SARS-CoV-2 and is highly expressed in various human organs<sup>3</sup>. Hence, SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that complicate the pathophysiology or engender a new mechanism of pre-existing diabetes. Moreover, high expression of ACE2 is closely associated with SARS-CoV-2-related multiorgan failure by initiating or even directly targeting certain organs<sup>11</sup>.

A growing body of research has investigated

the mechanisms through which COVID-19 infection affects beta-cell function; such research has proposed mechanisms such as those involving direct attacks on beta cells, bystander effects on beta cells through the infection of surrounding cells, and systemic effects of COVID-19 that exert direct or indirect impacts on beta cells<sup>12</sup>. Attachment of SARS-CoV-2 to ACE2 causes the virus to penetrate the islet cells, which contributes to the destruction of insulin-producing beta cells, thereby causing insulin deficiency that induces acute diabetes in patients with COVID-19 infection<sup>13</sup>.

Since the onset of the pandemic, several studies have investigated COVID-19-induced pancreatic injury and pancreatitis, revealing elevations in lipase and amylase, which resulted in both endocrine and exocrine cell damage and diabetes<sup>12</sup>. Moreover, proinflammatory cytokines play key roles in the pathogenesis of both diabetes and COVID-19; they drive beta-cell dysfunction, damage, and even demise in diabetes through intrinsic cellular signaling pathways and through the augmentation of the islet cell immune response<sup>12</sup>. Therefore, in predisposed individuals, COVID-19-associated local islet inflammation may lead to increased islet autoimmunity. Accordingly, diabetes is one of the most common comorbidities observed in patients with COVID-19 infection<sup>14</sup>. Several mechanisms underlying increased COVID-19 severity are associated with less efficient innate immune system responses, diabetes-related endothelial dysfunction (ED), and impaired viral clearance in patients with COVID-19 infection with diabetes<sup>15</sup>.

SARS-CoV-2 infection stimulates an exaggerated or hyperactive inflammatory immune response. A study suggested that the plasma levels of cytokines, chemokines, growth factors, and vascular endothelial growth factor—were higher in patients with COVID-19 than in healthy adults<sup>16</sup>. A meta-analysis of 44 articles (50 studies) revealed that compared with other individuals, patients with

severe COVID-19 exhibited elevated neutrophil-to-lymphocyte ratios; increased interleukin (IL)-2, IL-4, IL-10, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels; elevated routine inflammatory-related parameters; and reduced total lymphocytes and lymphocyte subsets<sup>17</sup>. This meta-analysis also indicated significant decreases in CD4 and CD8 T lymphocytes in patients with severe COVID-19<sup>17</sup>. Similarly, another meta-analysis of 23 studies demonstrated that severe COVID-19 was significantly associated with increased levels of proinflammatory cytokines (IL-6, IL-8, IL-10, IL-2R, and TNF- $\alpha$ ) and reduced numbers of T lymphocytes (CD3, CD4, and CD8)<sup>18</sup>. These findings suggest that a patient's inflammatory immune response is correlated with the severity of their COVID-19 progression.

Neutrophil extracellular traps (NETs) are key mediators of tissue damage in inflammatory diseases<sup>19</sup>. A 2020 study reported that the concentration of NETs was elevated in the plasma, tracheal aspirate, and lung tissues of patients with COVID-19 and that the patients' neutrophils exhibited higher NET expression<sup>19</sup>. Notably, the study observed that viable SARS-CoV-2 could directly induce the release of NETs by healthy neutrophils<sup>19</sup>. NETs triggered by SARS-CoV-2 depend on ACE2, serine protease, virus replication, and protein arginine deiminase-4; NETs released by SARS-CoV-2-activated neutrophils promote lung epithelial cell death *in vitro*<sup>19</sup>. These findings reveal that NETs may play a detrimental role in the pathophysiology of COVID-19. Therefore, targeting NETs with existing drugs is suggested to reduce the clinical severity of COVID-19<sup>19</sup>.

Accumulating bodies of evidence indicate that aberrant activation of immune cells may contribute to the severity of COVID-19 symptoms. Aberrant T helper (Th)1 and Th17 may activate innate immune cells by producing proinflammatory cytokines such as IL-17, TNF- $\alpha$ , and interferon- $\gamma$  (IFN- $\gamma$ )<sup>20</sup>. In a single-cell study of bronchoalveolar large fluid,

patients with mild COVID-19 presented with highly expanded clonal CD8<sup>+</sup> T cells, whereas those with severe COVID-19 exhibited a decline in T cells and natural killer (NK) cells and an increase in inflammatory FCN<sup>+</sup> macrophages<sup>21</sup>. These results indicate that weak adaptive immunity may be associated with an inadequate ability to control viral infection. Hence, persistent COVID-19 infections may activate alveolar macrophages or epithelial cells to produce various inflammatory cytokines and chemokines, triggering or recruiting more innate immune cells and thereby amplifying inflammation<sup>20</sup>.

Overall, the aforementioned findings reveal the pivotal role of inflammatory immune responses in COVID-19. Therefore, targeting patients' inflammatory immune responses may attenuate the severity of disease progression.

## Molecular mechanisms underlying metformin action

The molecular mechanisms underlying the effect of metformin have long been a topic of debate, and variable responses to metformin have been studied<sup>22</sup>. In patients with diabetes, metformin can activate the cellular energy sensor AMP-activated protein kinase (AMPK) to reduce hepatic gluconeogenesis and increase hepatic insulin sensitivity.<sup>23</sup> AMPK activation increases glucose utilization by the gut, enhances glucagon-like-1 secretion, and potentially alters the intestinal microbiome<sup>23</sup>. Metformin inhibits the secretion of proinflammatory cytokines irrespective of diabetes status<sup>24</sup>, which may be of primary significance in the treatment of COVID-19. Metformin directly blocks complex I activity of the mitochondrial electron transport chain, resulting in AMPK activation that inhibits the expression of proinflammatory cytokines<sup>20</sup>. Metformin substantially reduces lipopolysaccharide-induced and paraquat poisoning-induced acute lung injury<sup>20</sup>. Moreover, metformin may mediate the expression of cytokines involved in the inhibition of inflammatory storms

in an AMPK-independent manner<sup>20</sup>. Although the exact mechanism underlying SARS-CoV-2-triggered cytokine storms remains poorly understood, severe COVID-19 is implicated in cytokine storms, which lead to considerable morbidity and mortality<sup>20</sup>. Metformin may contribute to the reduction of

mortality risk in patients with diabetes with severe COVID-19 by suppressing cytokine storms<sup>20</sup>. The possible mechanisms through which metformin protects against COVID-19 have been explored in recent studies<sup>25,26</sup> and are summarized in Figure 1.

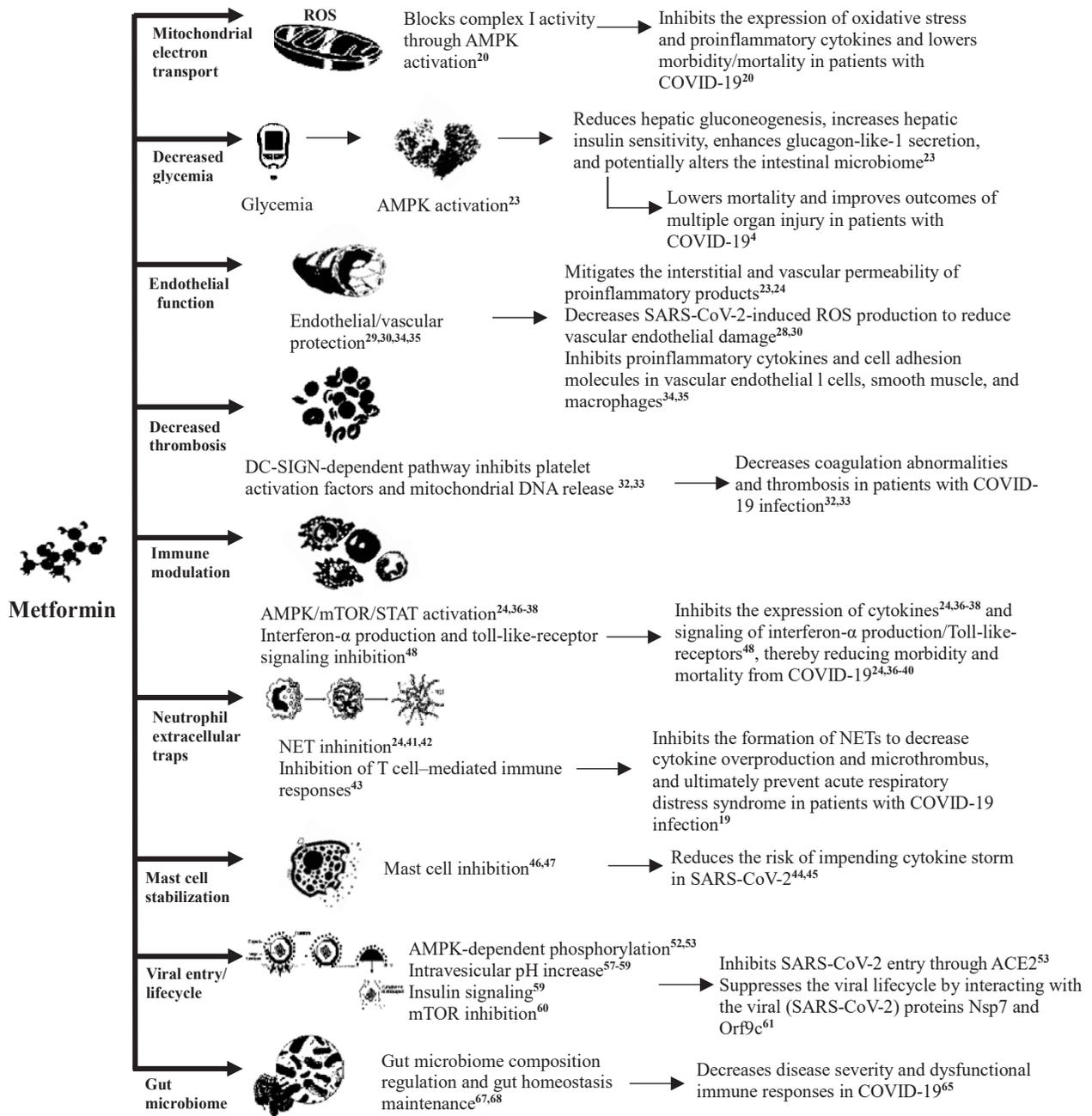


Figure 1. Molecular mechanisms through which metformin attenuates the severity of COVID-19.

Abbreviations: ACE2: angiotensin-converting enzyme 2; AMPK: adenosine monophosphate-activated protein kinase; COVID-19: coronavirus disease 2019; mTOR: mammalian target of rapamycin; NETs: neutrophil extracellular traps; ROS: reactive oxidative stress; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; STAT: signal transducer and activator of transcription.

### 3.1 Anti-inflammatory effects

In diabetes, the activation of receptors of advanced glycation end product (RAGE) by advanced glycation end products triggers the nuclear factor-kappa B (NF- $\kappa$ B)-mediated transcription of inflammatory genes that contribute to chronic ED and vascular complications characterized by vascular hyperpermeability, increased leukocyte adhesion and extravasation, and consequent acquisition of procoagulant status<sup>27</sup>. SARS-CoV-2 infection can increase the levels of inflammatory mediators such as inflammatory cytokines, toxic metabolites, and lipopolysaccharides and modulate NK cell activity and INF- $\gamma$  production, all of which can increase the interstitial and vascular permeability of proinflammatory products<sup>28</sup>. Moreover, SARS-CoV-2 infection is associated with increased reactive oxygen species (ROS) production<sup>28</sup>. ROS production and viral activation of the renin-angiotensin-aldosterone system (RAAS) cause insulin resistance (IR), hyperglycemia, and even vascular endothelial damage, all of which contribute to cardiovascular and all-cause mortality following SARS-CoV-2 infection<sup>28</sup>.

ED may be a key mechanism and therapeutic target in mitigating COVID-19 sequelae. Metformin exerts multifaceted protective effects on the vascular endothelium, attenuates ED, and improves endothelium-mediated vascular responses in patients with diabetes through several potential mechanisms, such as the activation of AMPK, silent information regulator 1, and endothelial nitric oxide synthase<sup>29</sup>. Furthermore, metformin can protect the endothelium by inhibiting inflammation, leukocyte adhesion to endothelial cells, endothelial cell senescence, endothelial-to-mesenchymal transition, and endothelial permeability and by preventing endothelial cell demise and apoptosis, in addition to facilitating the differentiation of endothelial progenitor cells<sup>30</sup>. These pharmacological effects of metformin are

exerted through liver kinase B1/AMPK and AMPK-independent targets<sup>30</sup>. In addition, through its antioxidant effects, metformin inhibits ROS production and reduces ROS levels in endothelial cells<sup>30</sup>.

COVID-19-associated coagulopathy and thrombosis are unique, and the pathophysiology of such conditions remains poorly understood<sup>31</sup>. Metformin has been reported to reduce thrombosis at long-term follow-ups, probably through the inhibition of mitochondrial DNA release and platelet-activating factor<sup>32,33</sup>, and might mediate improved cardiovascular outcomes through mechanisms beyond glucose control.

Endoplasmic reticulum (ER) stress plays a key role in the progression of diabetes and development of complications, especially CVD. Metformin therapy was reported to inhibit ER and oxidative stress by activating the AMPK/peroxisome proliferator-activated receptor  $\delta$  pathway in an animal model of diabetes<sup>30</sup>. Moreover, metformin confers vascular protection through the correction of RAGE overexpression caused by signaling dysregulation and NF- $\kappa$ B targeted gene change, thereby attenuating the effects of proinflammatory cytokines such as TNF- $\alpha$ , cyclooxygenase-2, IL-6, and IL-1 $\beta$  and those of cell adhesion molecules in vascular endothelial 1 cells, smooth muscle cells, and macrophages<sup>34,35</sup>. Some clinical studies have shown that metformin decreases risk of inflammatory bowel disease (IBD)<sup>8</sup>, helicobacter pylori<sup>5</sup>, and tuberculosis<sup>6</sup> infection in T2D patients possibly through the aforementioned pivotal role of inflammatory immune responses.

### 3.2 Immunomodulatory effects

Metformin has been suggested to favorably modulate immune responses irrespective of diabetes status by inhibiting cytokines such as IFN- $\gamma$ , TNF- $\alpha$ , IL-17, IL-1 $\beta$ , and IL-6<sup>24,36</sup>. Metformin can activate the AMPK/mammalian target of rapamycin

(mTOR)/signal transducer and activator of transcription pathway, which inhibits the proinflammatory classical activation of macrophages, thereby inhibiting the expression of IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , cytokines that contribute to morbidity and mortality associated with COVID-19<sup>36-38</sup>. Clinical evidence of this effect has been reported by several retrospective studies<sup>39,40</sup>.

Sera from individuals with COVID-19 infection might trigger the release of NETs from neutrophils<sup>41</sup>. Excessive NET formation results in cytokine overproduction, microthrombus, and ultimately acute respiratory distress syndrome in patients with COVID-19 infection<sup>19</sup>. Moreover, metformin reduces the release of NETs from neutrophils<sup>42</sup> and the neutrophil-to-lymphocyte ratio<sup>24,41</sup>. Metformin may also inhibit T-cell-mediated immune responses, including antigen-specific recall responses and Th1 or Th17 cytokine production, to slow the progression of experimental autoimmune encephalomyelitis and other inflammatory diseases<sup>43</sup>. Furthermore, neutrophil infiltration and lymphopenia in pulmonary capillaries are a key feature of severe COVID-19<sup>24,40</sup>. Hence, targeting NETs with metformin could reduce the clinical severity of COVID-19.

SARS-CoV-2 might activate mast cells (MCs), which release early inflammatory chemical compounds such as histamine and protease and may thus constitute an indicator of impending cytokine storms<sup>44,45</sup>. Metformin inhibits the IgE- and aryl hydrocarbon receptor-mediated activation of MCs<sup>46</sup>. MCs were reported to cause a greater increase in TNF- $\alpha$  in female rats than in male rats, which may explain the observational data reflecting differences in metformin-associated mortality reduction between women and men<sup>47</sup>. Interferon- $\alpha$  and Toll-like receptors play key roles in the pathophysiology of SARS-CoV-2<sup>48</sup>. Metformin inhibits interferon- $\alpha$  production and Toll-like receptor sig-

naling, which can attenuate the severity of COVID-19 symptoms<sup>48</sup>.

### 3.3 Viral entry inhibition

Metformin benefits beta cells by reducing IR, increasing islet cell viability, and improving glucose metabolism<sup>49</sup>. Insulin signaling plays a key role in boosting the immune system and protecting against viral infections. The major immune cells, namely T cells, B cells, and macrophages, express insulin receptors<sup>50</sup>. Impaired T-cell function was reported to be associated with poor viral clearance and inadequate vaccine response and to be correlated with impaired insulin signaling<sup>50</sup>. Hence, metformin might inhibit viral infections by reducing IR through the blockade of the insulin signaling pathway and its associated immune responses.

ACE2 is the main entry receptor for SARS-CoV-2 and is highly expressed in various organs<sup>3</sup>. Moreover, individuals with diabetes exhibit increased shedding of ACE2 from different tissues, which leads to the redistribution of ACE2 in the body and its accumulation in the lungs, thereby supporting the spread of the virus to different organ systems<sup>51</sup>. Metformin increases ACE2 phosphorylation and expression through AMPK activation<sup>52</sup>. ACE2 receptor phosphorylation may alter the conformation and function of the extracellular domain of ACE2, thereby inhibiting the binding of SARS-CoV-2<sup>53</sup>. Additionally, experimental studies have supported the anti-inflammatory and antifibrotic effects of ACE2<sup>54</sup>. Studies have indicated that SARS-CoV-2 infection downregulates ACE2, which contributes to the overactivation of angiotensin (Ang) II and reduction of Ang 1-7 through RAAS pathway activation. This can lead to a cytokine storm, which results in the excessive synthesis and secretion of proinflammatory cytokines/markers<sup>55</sup>. Through ACE2 upregulation, metformin may avert

the imbalance of RAAS. Therefore, metformin may not only reduce SARS-CoV-2 entry into cells but also attenuate its deleterious effects.

### 3.4 Viral lifecycle interruption

After entering a host cell, SARS-CoV-2 may induce the downregulation of cell-surface ACE2 expression. This in turn results in a RAAS imbalance, which promotes the deleterious proinflammatory and profibrotic effects of SARS-CoV-2 infection, causing lethal pulmonary and cardiac complications<sup>56</sup>. Endosomal pH is crucial for virus survival within the host cell. A low intracellular pH level is conducive to the binding of SARS-CoV-2 to its host cell, multiplication of SARS-CoV-2, and maturation of endosomal virions<sup>57</sup>. Hence, the use of drugs capable of altering endosomal pH may reduce viral maturation, assembly, and survival within the host cell. Another potential mechanism underlying the antiviral action of metformin is the inhibition of the release of SARS-CoV-2 from the endosome. The vacuolar ATPase (V-ATPase) and endosomal Na<sup>+</sup>/H<sup>+</sup> exchangers (eNHEs) are crucial regulators of endosomal pH. Several studies have reported that metformin can regulate the endocytic cycle by altering endosomal pH through targeting the V-ATPase and eNHEs to reduce viral replication<sup>57-59</sup>. Metformin directly and indirectly inhibits mTOR activity through protein kinase B inhibition or AMPK activation, thereby contributing to the suppression of virus–host protein interactions<sup>60</sup>. Furthermore, metformin indirectly alters the mTOR pathway and suppresses the viral lifecycle by interacting with viral (SARS-CoV-2) Nsp7 and Orf9c proteins<sup>61</sup>. Therefore, growing bodies of evidence suggest that mTOR inhibitors can serve as potential therapeutic treatments for COVID-19<sup>62</sup>. Overall, these data support the repurposing of metformin for use as an adjuvant therapy for patients with COVID-19 infec-

tion, irrespective of whether their conditions are acute or chronic or whether they are in the recovery phase.

### 3.5 Gut microbiome regulation

ACE2 expressed in gastrointestinal tissue regulates gut homeostasis and innate immune function<sup>63</sup>. Dysbiosis of the gut microbiome is associated with various disorders and diseases such as T2D, CVD, and IBD<sup>64</sup>. Gut microbiome composition contributes to disease severity and immune response dysfunction in patients with COVID-19 infection<sup>65</sup>. Clinical evidence demonstrates that COVID-19 infection can contribute to microbial dysbiosis, which might be a potential mechanism underlying the immune dysregulation and overt inflammation associated with the disease<sup>64,66</sup>. Pollak investigated the antidiabetic and immunomodulatory effects of metformin on the gut microbiome<sup>67</sup>. Another mechanism potentially underlying metformin's benefits in the treatment of COVID-19 is its ability to alter the composition of gut microbes and the functional aspects of the gut microbiome, as indicated by its association with reductions in fasting blood sugar and glycated hemoglobin concentrations<sup>68</sup>.

In summary, metformin, in addition to exhibiting a powerful glucose-lowering effect, exhibits considerable therapeutic potential against SARS-CoV-2 in the gut because of its anti-inflammatory, immunomodulatory, and ACE2 stabilization effects and its effects on the regulation of gut microbiome composition that allow for maintenance of gut homeostasis.

## Real-world data in patients with diabetes with COVID-19 infection

Some clinical studies have shown that metformin reduces risk of chronic obstructive pulmonary disease<sup>7</sup>, hypertension<sup>9</sup>, and HF<sup>10</sup> in patient with

T2D, which may contribute to the reduced morbidity/mortality in COVID-19 infection. A growing number of studies have investigated the use of metformin in patients with COVID-19 infection with diabetes<sup>4,69-79</sup>. A retrospective study indicated that well-controlled diabetes (receiving metformin in 39%) had a significant reduction in all-cause mortality, compared to the poorly-controlled diabetes (receiving metformin in 26%) after a 1:1 propensity matching (adjusted hazard ratio [HR], 0.13;  $p < 0.001$ )<sup>4</sup>. A retrospective study suggested that metformin users had a trend of decreased in-hospital mortality compared to the non-users (9.3 vs. 19.5%;  $p = 0.19$ )<sup>69</sup>. An observational study showed that metformin users had a lower rate of mortality, compared to the non-users (odds ratio [OR], 0.59)<sup>70</sup>. Moreover, a trend of lower rate of mortality was also observed in metformin users compared to non-users, even after the full adjustment (OR, 0.80;  $p = 0.45$ )<sup>70</sup>. Similarly, a retrospective study compared the outcome of metformin users and non-users in hospitalized COVID-19 patients with diabetes suggesting that in-hospital mortality was significantly lower in those receiving metformin (2.9% vs. 12.3%;  $p = 0.01$ )<sup>71</sup>; however, this finding might have been driven by selection bias, as patients with severe respiratory problems cannot be treated with metformin<sup>28</sup>. A retrospective study reported that metformin was associated with decreased 30-day mortality among nursing home residents with COVID-19 infection, which may be attributed to its inhibition of the mTOR pathway<sup>72</sup>. Similar results were observed among older minority patients with COVID-19 infection, among whom metformin significantly reduced the rates of hospitalization (relative hazard [RH], 0.71), mortality (RH, 0.34), and severe COVID-19 infection (RH, 0.32)<sup>73</sup>. Notably, metformin use prior to COVID-19 diagnosis was reported to be significantly associated with reduced mortality among patients with COVID-19 infection

with diabetes (OR, 0.33;  $p = 0.0210$ ), whereas prior insulin use did not affect mortality<sup>74</sup>. In addition, the beneficial effects of metformin persisted even after adjustment for other COVID-19 risk factors such as age, sex, race, obesity, hypertension, chronic kidney disease (CKD), and HF<sup>74</sup>.

Several meta-analyses have assessed the use of metformin in the treatment of patients with COVID-19 infection with diabetes<sup>75-77</sup>. Retrospective studies have indicated that metformin was associated with a reduced mortality rate among patients with T2D who were hospitalized for COVID-19<sup>75</sup>. Furthermore, a meta-analysis reported that the mortality rate of patients treated with metformin was 25% lower ( $p < 0.00001$ ) than that of patients not treated with metformin<sup>75</sup>. A meta-analysis of 32 observational studies revealed that metformin reduces the risk of SARS-CoV-2-related mortality (OR, 0.56;  $< 0.001$ ; 22 studies) but not disease severity (OR, 0.85;  $p = 0.077$ ; 15 studies)<sup>76</sup>. Moreover, in the subgroup analysis, metformin reduced the risk of mortality (OR, 0.69;  $p = 0.002$ ) and severity (OR, 0.83;  $p = 0.023$ ) in patients aged 70 years or older<sup>76</sup>. Similarly, a meta-analysis of 5 retrospective cohort studies revealed that metformin is associated with a significant (46%) reduction in mortality ( $p = 0.02$ ) among patients with COVID-19 infection<sup>77</sup>.

Overall, the aforementioned results indicate that metformin may exhibit protective effects beyond its glucose-lowering functions through several mechanisms and may thereby reduce mortality in patients with COVID-19 infection. Nevertheless, additional studies are necessary to explore how metformin can confer these benefits, to provide a thorough risk-benefit assessment, and to determine whether the indications of metformin use should be broadened considering the ongoing COVID-19 pandemic. A summary of the real-world data assessing metformin use in patients with diabetes with COVID-19 infection is presented in Table 1.

Table 1. A summary of real-world data assessing metformin use in patients with COVID-19 infection and diabetes

Authors	Study population	Methods	Outcomes (hazard ratio (HR) [95% confidence interval]; p value)
Zhu et al <sup>4</sup>	952 patients with coronavirus disease 2019 (COVID-19) and pre-existing type 2 diabetes (T2D)	Retrospective longitudinal study assessing the association between plasma glucose levels and clinic outcomes in COVID-19 patients with T2D	Well-controlled diabetes (receiving metformin in 39%) had a significant reduction in all-cause mortality, compared to the poorly-controlled diabetes (receiving metformin in 26%) after a 1:1 propensity matching [adjusted HR 0.13; $p < 0.001$ ]
Chen et al <sup>69</sup>	904 patients with COVID-19 (136 with diabetes, mostly T2D)	Retrospective cohort study, assessing outcome of hospital mortality in metformin users compared to the non-users	A trend of decreased in-hospital mortality was observed in metformin users, compared to the non-users (9.3 vs. 19.5%; $p = 0.19$ )
Cariou et al <sup>70</sup>	1317 patients with diabetes hospitalized for COVID-19 (mostly T2D (88.5%))	Observational study, assessing rate of mortality in metformin users compared to the non-users	Metformin use associated with lower rate of mortality (OR 0.59). A trend of lower rate of mortality in metformin use, even after the full adjustment (odds ratio [OR] 0.80; $p = 0.45$ ).
Luo et al <sup>71</sup>	283 patients with T2D hospitalized with COVID-19	Retrospective cohort study. Compared the outcome of metformin use and no metformin use in hospitalized COVID-19 patients with diabetes	Hospital mortality, metformin vs. no-metformin: (2.9% vs. 12.3%, $p = 0.01$ ) No difference in length of stay (21.0 days for metformin vs. 19.5 days for no metformin, $p = 0.74$ ) No associations with other T2D medications Four-fold decrease in-hospital mortality in metformin users vs. the non-users, in a multi-variate analysis [OR 4.36 (1.22-15.59); $p = 0.02$ ]
Lally et al <sup>72</sup>	775 nursing home residents infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Retrospective cohort study. Main outcome was for 30-day mortality as measured from the date of SARS-CoV-2 positivity; secondary outcome was hospital-free survival at 30 days from the date of SARS-CoV-2 positivity	Relative to no diabetes medications, metformin was significantly associated with decreased 30-day mortality from COVID-19 diagnosis [adjusted HR 0.48 (0.28-0.84)]. No association with insulin [adjusted HR 0.99 (0.60-1.64)] or other diabetes medications [adjusted HR 0.71 (0.38-1.32)].
Ghany et al <sup>73</sup>	1139 COVID-19 positive patients of whom 392 were metformin users	Retrospective cohort study. Main outcome was hospitalization; secondary outcomes were mortality and acute respiratory distress syndrome (ARDS)	Metformin users had a higher comorbidity score vs. non-users ( $p < 0.01$ ). Hospitalization in metformin users: adjusted relative hazard [RH] 0.71 (0.52-0.86). Mortality in metformin users: RH 0.34 (0.19-0.59) ARDS in metformin users: RH 0.32 (0.22-0.45).
Crouse et al <sup>74</sup>	25,326 patients tested for COVID-19 between 2/25/20 and 6/22/20	Retrospective electronic health records study assessing mortality in COVID-19	Metformin treatment prior to diagnosis of COVID-19 was independently associated with a significant reduction in mortality in patients with diabetes and COVID-19 [OR 0.33 (0.13- 0.84); $p = 0.0210$ ].
Oscanoa et al <sup>76</sup>	A total of 32 observational studies with a total of 44306 patients with diabetes and COVID-19	Meta-analysis, assessing the association between metformin use and risk of severity and mortality in SARS-CoV-2 infection	Metformin was associated with a reduced risk of SARS-CoV-2 mortality [OR 0.56 (0.46-0.68); $p < 0.001$ ; 22 studies] but not with disease severity [OR 0.85 (0.71-1.02); $p = 0.077$ ; 15 studies]. Metformin reduced the risk of mortality [OR 0.69 (0.55-0.88); $p = 0.002$ ] and severity [OR 0.83 (0.70-0.97); $p = 0.023$ ] in patients aged 70 and above.
Hariyanto et al <sup>77</sup>	A total of 5 studies with a total of 6937 patients with diabetes and COVID-19	Meta-analysis, assessing benefits of metformin in reducing the mortality rate from COVID-19 infections	Metformin was associated with reduction in mortality rate from COVID-19 infections [risk ratio [RR] 0.54 (0.32-0.90); $p = 0.02$ ]
Cheng et al <sup>78</sup>	1213 patients with COVID-19 and pre-existing T2D admitted in hospitals	Retrospective cohort study, assessing the safety and efficacy of metformin on T2D patients with COVID-19	Metformin users compared to non-users had significantly higher lactic acidosis [adjusted HR 4.66 (1.45-14.99); $p = 0.010$ ] and acidosis [adjusted HR 2.45 (1.08-5.54); $p = 0.032$ ] by Time-Varying Cox Model. No difference between the durations of hospitalization in the metformin and the non-metformin users (21 days vs 21 days; $p = 0.687$ )
Gao et al <sup>79</sup>	110 hospitalized patients with COVID-19 with diabetes	Retrospective cohort study, assessing the effect of metformin on disease severity	Metformin users compared to non-users had significantly higher life-threatening complications (28.6% vs. 7.4%; $p = 0.004$ ). Metformin was associated with a higher risk of disease progression during hospitalization [adjusted OR 3.964 (1.034-15.194); $p = 0.045$ ].

## Adverse effects and possible contraindications of metformin in COVID-19 patients

Although most studies have confirmed the beneficial effects of metformin in COVID-19 patients, some studies have reported that metformin treatment can increase risk of lactic acidosis and disease severity in COVID-19 patients using metformin<sup>78,79</sup>. A retrospective cohort study of 1213 hospitalized patients with pre-existing diabetes with COVID-19 infection revealed that metformin was significantly associated with a higher incidence of acidosis (particularly among patients with severe COVID-19) but not with mortality, which was significantly correlated with high metformin dosage, compromised kidney function, and severe COVID-19<sup>78</sup>. A retrospective case-control study enrolled 110 hospitalized patients with COVID-19 with diabetes prescribed either metformin or non-metformin hypoglycemic treatment<sup>79</sup>. Strikingly, the percentage of patients who experienced life-threatening complications was significantly higher in the metformin group (28.6% vs. 7.4%;  $p = 0.004$ ). Moreover, antidiabetic therapy with metformin was associated with a higher risk of disease progression in patients with COVID-19 with diabetes during hospitalization (adjusted OR, 3.964;  $p = 0.045$ )<sup>79</sup>. This advocates that metformin treatment is not an appropriate choice in patients with severe respiratory distress, renal impairment, or HF<sup>80</sup>, and highlights the importance of paying attention to pre-existing conditions and comorbidities in drug selection. Moreover, contraindications to metformin must be addressed before administration.

## Practical recommendations for metformin use in the management of COVID-19

Although metformin can reduce morbidity and mortality for patients with COVID-19 infec-

tion with diabetes based on the data from previous preclinical and clinical studies and the most recent information available from current publications, few published recommendations exist for metformin treatment during the COVID-19 pandemic<sup>81</sup>. Based on Drucker's recommendations, metformin should be used with caution in unstable hospitalized patients and should be discontinued in patients with concomitant sepsis or severe impairment of hepatic and renal function<sup>81</sup>. The practical recommendations by Bornstein et al. suggested that dehydration and lactic acidosis will probably occur if patients are dehydrated, therefore, patients should stop taking metformin and follow sick days<sup>82</sup>. Furthermore, renal function should be carefully monitored during illness because of the high risk of CKD or acute kidney injury<sup>82,83</sup>. Similarly, Korytkowski et al. recommended that hospitalized patients with COVID-19 can experience sudden and rapid deteriorations in clinical status which contraindicates continued use of metformin in these patients when hospitalized<sup>84</sup>. Moreover, metformin is contraindicated for patients with respiratory problems and hypoxia, hemodynamic instability, and unstable renal or hepatic function<sup>83,84</sup>. Therefore, physicians should be conservative in their prescription of metformin, with the above considerations in mind, because there is little evidence providing superiority in the efficacy and safety of metformin in diabetic patients with severe COVID-19 infection.

## Conclusions

COVID-19 is a previously unrecognized viral infection with high infectivity that has triggered a global crisis. Although effective vaccines are at the forefront of the fight against COVID-19, the potential efficacy of drugs routinely used for other pathological conditions in the treatment of COVID-19 must not be overlooked. In the context of SARS-CoV-2 infection, metformin offers protection not only metabolically but also through the mitigation of com-

plications related to exaggerated immune responses and thrombotic events. The plausible mechanisms underlying metformin's effect in reducing COVID-19-related morbidity and mortality, its minimal side effects and low cost, and the devastating nature of the global COVID-19 pandemic must be considered when assessing metformin as a potential COVID-19 treatment. Despite the potential benefits of using metformin in the treatment of COVID-19 infection, the continual monitoring of patients for acidosis and renal function deterioration is recommended, especially for patients with severe COVID-19, and decisions to administer metformin under certain conditions should be made judiciously after thorough examination. Furthermore, some concerns related to metformin treatment in patients infected with SARS-CoV-2—such as its clinically beneficial or detrimental effects on patients with COVID-19 infection who have diabetes, its safety or unsafety in patients who have not previously taken metformin, and its effect on patients with other comorbidities, particularly in relation to the risk of adverse cardiopulmonary outcomes—require further investigation. With new biotechnologies combined with advanced molecular genomics and proteomics, a more thorough understanding of COVID-19—including its etiology, possible therapeutic targets for intervention, candidate drugs for its treatment, drug–drug interactions, and underlying molecular mechanisms of the disease and its treatment—will be attained. Nevertheless, bridging the translational gap between research and clinical advancement into patient care remains challenging and warrants more collaborative research between clinicians and academic researchers.

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# 二甲雙胍類與新型冠狀病毒感染症：老藥的新契機

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## 摘 要

由嚴重急性呼吸道症候群冠狀病毒2型 (severe respiratory syndrome coronavirus 2) 所引起的2019年新型冠狀病毒感染症 (coronavirus disease 2019, COVID-19)，是一種前所未有並具高度傳染力的病毒性疾病，已為全球帶來嚴峻的挑戰。高盛行率的糖尿病已成為 COVID-19 感染的其中一種最常見的共病症。許多研究指出糖尿病與 COVID-19 感染結果是具有相關性的。血糖管理的好壞會影響到 COVID-19 感染的預後與結果，相對於控制不佳的血糖而言，良好的血糖控制會有比較低的死亡率。許多研究顯示 COVID-19 感染會導致高血糖、代謝功能異常、增加小血管之併發症與內皮細胞功能異常的環境之下增加血栓事件的發生。二甲雙胍類是最常使用的降血糖藥物，它除了具有降低血糖的功能之外，許多研究顯示它還具有其它多樣性效應，譬如說：抗感染、抗發炎、免疫調節、降血壓、預防慢性阻塞性肺疾病和心臟衰竭等。因此，二甲雙胍類可以藉由這些多樣性效應的類似機轉或有助於減少在 COVID-19 感染後引發的發病率和死亡率。由此觀點，二甲雙胍類可以考慮重新使用來應付日益增加感染 COVID-19 之糖尿病人的一個可行性之選擇用藥。本篇綜論旨在整理二甲雙胍類的多重潛在性的機轉，透過這些分子機轉呈現可能有益於 COVID-19 感染的治療效果，並且概括真實世界資料以支持重新思考使用二甲雙胍類在第二型糖尿病人併有 COVID-19 感染的益處。