



The Possible Protective Effect of Metformin in COVID-19 Infection

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Coronavirus 2019 (COVID-19) infections with more than 30 million confirmed cases are increasing rapidly, requiring urgent and safe treatment. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a virus responsible for the infection of COVID-19. Metformin (M) is a biguanide drug used as a first choice for the management of hyperglycemia in type 2 diabetes mellitus (T2DM). Furthermore, it is safe and currently available. It is speculated that metformin can be used for T2DM patients with COVID-19, because in addition to its hypoglycemic effect, this biguanide also shows many beneficial effects, including anti-inflammatory effects and cardiopulmonary protection especially by angiotensin converting enzyme 2 (ACE2) targeting. Therefore, the reasons for the use of metformin in COVID-19 patients were discussed in this study. Metformin has a promising role in treatment of COVID-19 in T2DM and obese women patients.

Keywords: COVID-19; type 2 diabetes mellitus; metformin; angiotensin converting enzyme 2.

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1. INTRODUCTION

COVID-19 has been spread rapidly around the world, with more than 30 million confirmed case and more than 92500 deaths [1]. The number of these cases urgently needs to determine safe and available treatments immediately. SARS-CoV-2, a virus responsible for the infection COVID-19, it contains a spike protein called S protein, which is a binding domain that is similar in the structure to S protein of the virus that causes severe acute respiratory syndrome (SARS), SARS-CoV-1 [2].

ACE2 is very abundant in the lungs, so respiratory symptoms are common in COVID-19 infections, but ACE2 is also found in endothelial cells, so thrombosis, hypertension, pulmonary embolism and renal function have also been observed in COVID-19 patient's damage [3,4].

Metformin is still the first choice for the management of hyperglycemia in type 2 diabetes. Furthermore, it is safe and currently available. It is speculated that metformin can be used for T2DM patients with COVID-19, because in addition to its hypoglycemic effect, this biguanide also shows many beneficial effects, including anti-inflammatory effects and cardiopulmonary protection by ACE2 targeting [5]. Therefore, the reasons for the use of metformin in COVID-19 patients were discussed in this study.

2. THE SUGGESTED METFORMIN CELLULAR MECHANISMS

Firstly, SARS-CoV-2 has 10 times stronger affinity for a receptor of angiotensin converting enzyme 2 (ACE2) than that SARS-CoV-1 and this high affinity could be partly explain the rapid spread of SARS-CoV-2 [6]. The entry of the virus requires binding to ACE2 in intestinal epithelial cells and lung cells. However, paradoxically, when patients are given treatments that enhance ACE2 expression, COVID-19 complications are reduced [7].

The renin-angiotensin-aldosterone system (RAAS), consists from two main arms, the protective arm which is angiotensin converting enzyme 2 (ACE2)–Ang 1-7–Mas that counteract the deleterious effects of the ACE1–Ang II arm by reducing the pulmonary and systemic hypertension and enhance the anti-inflammatory pathway after the injury of tissues [7]. The expression of ACE2 is interestingly decreased in

patients infected with SARS-CoV-1, and this low level of ACE2 is associated with acute respiratory distress syndrome (ARDS) and some cardiovascular disease [8]. Recently, Monteil and his colleagues used the SARS-CoV-2 human organoid model to study the role of human recombinant ACE2 (hrACE2), a positive result was obtained by using this hrACE2 [9].

AMP-activated protein kinase (AMPK) activation by metformin on pulmonary and cardiovascular systems refers to the beneficial effects of the biguanide [10]. AMPK controls the metabolic homeostasis of the whole body, so it acts as an energy scale. The phosphorylation of ACE2 on Ser-680 is carried out by the activation of AMPK by metformin [10,11]. This will lead to post-translational modification of ACE2 that reduce its ubiquitination, thus prolonging the half-life of ACE2, which may show a protective effect on the lung. Hang and his colleagues further confirmed this hypothesis by studying transgenic mice overexpressing ACE2 S680D, and that ACE2 S680D can reduce lung damage in harmful environments [10]. The second concept is that metformin can cause a 3-D conformational change in the extracellular domain of ACE2 through its post-translational modification, thereby reducing the recognition rate of SARS-CoV-2 virus. Yu and his colleagues believe that diabetic patients treated with metformin may have a lower risk of lung injury, so this finding can strengthen the second concept [12].

The second possible role of metformin in COVID-19 is through its effect on neutrophils. Neutrophils are the first line of protection against viral infections. Although organized neutrophil recovery is required to fight infection, unorganized neutrophil recovery can be harmful [13]. Metformin is associated with a decrease in neutrophil gelatinase-associated lipocalin (NGAL), which is an acute-phase protein secreted by neutrophils and has been determined to be elevated in diabetic patients [14]. In animal studies, metformin reduces the damage after myocardial infarction by reducing cardiac remodeling and neutrophil activity in myocardial tissue, thus showing important functions [15]. Additionally, hypoxia that induced lung injury in neonatal rats, in which metformin can reduce infiltration of neutrophil and macrophage [16,17].

The third possible mechanism of metformin is through its gender specific action. Among a large number of patients hospitalized for Covid-19 in

the United States, metformin has shown that women have a lower mortality rate than men with T2DM or obesity. The noteworthy protective value in a women attributed to metformin has been shown to diminish TNF α level in females more than that of males [18,19]. TNF α shows a great role in the Covid-19 pathology [19], through activation of macrophage and elevation of cytokine release [20]. Therefore, inhibitors of TNF α reduce the mortality in persons that hospitalized for COVID-19.

Furthermore, researchers can consider other (overlapping) mechanisms for reducing the severity of SARS-CoV-2 infection through metformin can improve the ratio of neutrophils to lymphocytes, reducing blood sugar (via AMPK), stabilizing mast cells, reducing thrombosis, and improving endothelial cells [20,21]. These effects are notable, as IL-6 and TNF α are thought to contribute to Covid-19 pathology [22]. Metformin's effects on these cytokines have been shown to differ by sex, with favorable effects in females over male mice, particularly for TNF α . These findings of a strong sex-specific response to metformin in Covid-19 indicate that reducing TNF α may be the main way for metformin to reduce Covid-19 mortality. Park and colleagues strengthened the impact of metformin on women that have colorectal cancer [23]. The influence of estrogen, progesterone and epigenetic changes on the Y chromosome may be the cause of the specific female effect of metformin [24]. In addition, metformin inhibits mast cell activation through aryl hydrocarbons and IgE, and these effects provide additional support for gender-specific effects. The activation of mast cells has been considered as an initial indicator of the SARS-CoV2 inflammatory response and cytokine storm. For these reasons, metformin has broad prospects in reducing the pathogenesis of COVOD-19 [25]. A recent study by Mackey and his team confirmed that female rats secrete more TNF α than male rats' mast cells. These differences support the anti-inflammatory effects of metformin in women, indicating that it benefits from metformin in COVID-19 [25,26].

Finally, Metformin can improve glucose control, reduce weight, reduce insulin resistance, inhibit mTOR pathway and prevent immune hyperfunction, reduce neutrophils and mitochondrial complex 1, inhibit mitochondrial reactive oxygen species (ROS) signaling and prevent ROS [27–29]. In addition, the basic properties of metformin have a neutralizing

effect, can resist acidic SARS-CoV-2 vesicles (13), and can prevent serious infections [30]. Furthermore, metformin has previously shown antifibrinolytic activity [31] and can prevent inflammatory cytokines such as interleukin-6 or tumor necrosis factor alpha [32,33]. It is assumed that these effects play a role in the immune response to COVID-19, [33], therefore, metformin may improve the prognosis [34].

3. CONCLUSION

Metformin has a promising role in treatment of COVID-19 in T2DM and obese women patients.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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