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Commentary

Metformin in COVID-19: A possible role beyond diabetes

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1. Metformin: Historical re-purposing and pleiotropy

It is a lesser-known fact that metformin was originally introduced as an anti-influenza drug and that glucose-lowering was only one of its side effects [1]. The many pleiotropic effects of metformin and its widespread utility in medicine today have led scientists to call it the aspirin of the 21st century [2].

In the current scenario, when there is no specific agent against COVID-19, and when re-purposing of drugs is the primary weapon, we suggest that metformin be used as one of the drugs to combat the virus.

2. Metformin: Mechanism of action on molecular level

Metformin activates AMP-activated protein kinase (AMPK) in hepatocytes by causing its phosphorylation. This is the main mechanism by which metformin brings about favourable effects on glucose and lipid metabolism [3].

2.1. *Metformin-AMPK-ACE2-SARS-CoV-2*

The juggernaut virus, SARS-CoV-2, that has led to the deaths of over 1.7 lakh people across the world uses angiotensin-converting enzyme 2 (ACE2) as its receptor. It enters the human

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body through interaction between its spike proteins (S1) and the N-terminal region of ACE2 [4,5]. The receptor binding domain (RBD) of the virus binds with the protease domain (PD) of the ACE2 receptor and forms an RBD-PD complex [4].

Acute Respiratory Distress Syndrome (ARDS) is one of the commonest complications developing in patients with COVID-19 [6]. There have been animal studies that have implicated ACE2 in the acute lung injury (ALI) caused due to SARS-CoV [4]. It has been hypothesized that ACE2 causes ALI by bringing about autophagy through the AMPK/mTOR pathway [7]. AMPK has been shown to increase the expression of ACE2 as well as to increase its stability by phosphorylating ACE2 Ser^{680} in human umbilical vein endothelial cells (HUVECs) and human embryonic kidney 293 (HEK293T) cells [8].

Since metformin works through AMPK activation, which leads to phosphorylation of ACE2 [8], we can consider that theoretically this addition of a phosphate group (PO_4^{-3}) would bring about conformational and functional changes in the ACE2 receptor [9]. This could lead to decreased binding with SARS-CoV-2 RBD due to steric hindrance by the addition of a large sized PO_4^{-3} molecule.

Nonetheless, once the virus is inside, there is a downregulation of ACE2 receptors. This in turn leads to an imbalance in the renin-angiotensin-aldosterone system (RAS) promoting the deleterious effects of its pro-inflammatory and pro-fibrotic arm, further giving rise to the lethal cardio-pulmonary complications [10]. By upregulating ACE2, the imbalance in RAS could be averted. Hence, metformin would not only prevent the entry of SARS-CoV-2 as described above, but also prevent the detrimental sequelae by causing activation of ACE2 through AMPK-signalling.

2.2. *Metformin-mTOR-Coronavirus*

The mammalian target of rapamycin (mTOR) signalling plays an important role in the pathogenesis of influenza, besides modulating antibody response for cross-protective immunity against infective influenza viruses. Metformin activates AMPK via liver kinase B1 (LKB1), inhibiting the mTOR pathway. It also indirectly attenuates AKT activation through phosphorylation of insulin receptor substrate 1 (IRS-1) resulting in inhibition of the mTOR signalling cascade [11]. Other biguanide molecules, buformin and phenformin have been associated with better survival outcomes in animal models of influenza [12,13]. Further, the PI3K/AKT/mTOR pathway plays major roles in MERS CoV infection [14]. Since metformin inhibits the same pathway, it would be interesting to decipher its role against SARS-CoV-2.

2.3. *Protein-protein interaction map and network-based drug repurposing*

A study was attempted to narrow the existing molecular-level knowledge gap of SARS-CoV-2 by mapping the interactions between SARS-CoV-2 and human proteins [15]. With the help of affinity purification mass spectrometry (AP-MS), 332 protein–protein interactions (PPIs) could be identified. Further, 66 druggable human proteins/factors targeted by 69 medicines which were either FDA-approved or in clinical trials or pre-clinical molecules were recognized. To our interest, it was found that human proteins regulated by the mTORC1 signalling pathway, specifically LARP1 and FKBP7, interact with important viral proteins, N and Orf8 [15]. Since metformin inhibits mTOR signalling, it could act as an indirect modulator of the protein–protein complex, thus preventing the viral replication and pathogenesis.

2.4. *Viral replication: Lessons learnt from Zika virus*

Zika virus (ZIKV), a single-stranded RNA virus, is a mosquito transmitted flavivirus. A study using HUVECs and human retinal vascular endothelial cells (HRvECs) showed that AMPK restricts the replication of ZIKV in the endothelial cells [16]. Activation of AMPK with the help of two well-known AMPK activators, metformin and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) led to attenuation of ZIKV replication. Activated AMPK further potentiated the expression of certain genes with known antiviral properties such as IFNs, OAS2, ISG15, and MX1 while inhibiting inflammatory mediators like TNF-α and CCL5. It would be useful to explore whether the same is observed for SARS-CoV-2. A recent study has reported that inhibition of glycolysis by non-toxic concentration of 2-DG completely attenuated SARS-CoV-2 replication in Caco-2 cells [17]. All of these indicate towards a possible frontline role of metformin against COVID-19.

2.5. *Insulin resistance and SARS-CoV-2*

A few case reports from China and Italy, along with a Chinese meta-analysis, have shown diabetes to be an important risk factor for severe disease requiring ventilation [18]. Further, a study had shown a direct metabolic link between SARS-CoV and diabetes, postulating that the virus enters the pancreatic islets which express ACE2, leading to acute β-cell damage and transient Type 2 diabetes mellitus (T2DM) [19]. Evidence from an animal study points toward increased ACE2 activity in pancreas of persons with diabetes besides its elevated expression in other tissues such as lung, liver and heart [20]. Hence, optimal control of T2DM, for both chronic and transient cases, might help in the treatment of COVID-19. Although recent discussions point out that oral hypoglycaemic agents such as Sodium-Glucose-Transporter-2 inhibitors (SGLT-2i), Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1RAs), Pioglitazone and even Insulin might actually be harmful for COVID-19 individuals with diabetes [21,22], limited evidence is available on metformin for the same. Considering its pleiotropic effects and a possible role in combating hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV) through increasing insulin sensitivity [23], metformin can be a real game-changer for treating this pandemic.

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