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# Methylglyoxal in COVID-19-induced hyperglycemia and new-onset diabetes

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**Abstract. – Elevation in blood glucose is common in COVID-19 patients. There is also a high incidence of new-onset diabetes mellitus (DM) in COVID-19 patients following hospitalization. To date, the underlying cause(s) for the hyperglycemia and new-onset DM post-COVID-19 remain poorly understood. In this narrative review, we suggest that upregulation of the cytotoxic and diffusible glycolytic byproduct methylglyoxal (MGO) arising from increased glycolysis in infected pancreatic islets, macrophages, and peripheral cells/tissues is impairing insulin production, secretion, and signaling. This hypothesis is based on our recent discovery that MGO levels were elevated in the plasma of hospitalized COVID-19 patients without and with DM and even higher in COVID-19 patients that succumb to the disease. In pancreatic islets infected with SARS-CoV-2, elevated MGO will disrupt mitochondrial function, perturb $Ca^{2+}$ homeostasis, and activate the receptors for advanced glycation end-product (RAGE) and nuclear factor kappa B (NF-κB) resulting in impaired insulin production and secretion. In macrophages, excess MG production can diffuse into the vasculature disrupting endothelial function and triggering micro/macro hemorrhage, ischemia, and tissue fibrosis. In skeletal muscle and liver cells, MGO disruption of insulin signaling can blunt glucose absorption. Metformin and N-acetyl cysteine have recently been shown to decrease morbidity and mortality in COVID-19 patients. Here we propose that these agents may be exerting their beneficial effects by chemically reacting with and lowering MGO levels. Knowledge gained from this review should provide novel mechanistic insights for hyperglycemia in COVID-19 patients and strategies to blunt the development of new-onset of DM in post-COVID patients.**

*Key Words:*

*COVID-19, Post-COVID-19 syndrome, New onset of diabetes mellitus, Methylglyoxal, Glyoxalase-1, Vascular adhesion protein-1, Hypoxia-inducible factor 1α.*

## Introduction

### Overview of Coronavirus Disease-19

Coronavirus disease-19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 is a highly contagious virus and infects cells that express the angiotensin-converting enzyme 2 (ACE2) receptor on their cell membranes, such as type I and type II lung alveolar epithelial cells, vascular endothelial cells, peripheral blood mononuclear cells (PBMCs), small intestinal, liver, kidneys, heart, testis, brain, and pancreatic islet cells[1,2]. As of October 1, 2022, more than 600 million individuals have been infected with SARS-CoV-2 and more than 6.5 million confirmed COVID-19-related deaths worldwide[3]. Although, the majority of individuals infected with SARS-CoV-2 remain asymptomatic or develop mild symptoms such as fever, cough, muscle weakness, headache, sore throat, diarrhea, and loss of taste and smell, about 10% of patients develop a severe or critical illness which may rapidly progress to acute respiratory distress syndrome (ARDS) and multiorgan failure requiring intensive care unit (ICU) facilities and mechanical ventilation assistance[4,5]. Unvaccinated individuals, people over the age of 65, obese, and individuals with pre-existing comorbidities such as diabetes mellitus (DM), cardiovascular disease, hypertension, kidney failure, and respiratory disease are at higher risk of morbidity and mortality[6,7]. Many clinical reports[6-8] have indicated that COVID-19 also worsens glycemic control in DM patients. A large body of evidence[9,10] indicates that many COVID-19 patients also have post-COVID-19 syndrome (PCS). PCS is characterized by persistent symptoms beyond 3-4 weeks from the onset of acute COVID-19 and is not attributable to alternative diagnoses. These symptoms include fatigue, dyspnea, myalgia, cognitive disturbanc-



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es, depression, insomnia, and brain fog. The PCS may also affect multiple organ systems, leading to pulmonary dysfunction, myocarditis, chronic kidney disease, and the new onset of DM[9,10].

### SARS-CoV-2-Induced Diabetes Mellitus

The complexity of bidirectional interactions between COVID-19 and diabetes presents a major concern facing healthcare providers. A recent meta-analysis study[11] found individuals with DM, particularly those with poor glycemic control, were 2.5 to 3-fold more likely to develop COVID-19, acute respiratory distress syndrome (ARDS), need mechanical ventilation, and die, compared to non-DM COVID-19 patients. Higher rates of new-onset DM (both type 1 and type 2) have also been reported in many countries during the pandemic[12]. For instance, data obtained from Multicenter Regional Findings in Northwest London[13] found an 80% increase in the rate of newly diagnosed type 1 DM during the pandemic compared to the prior year[13]. Birabaharan et al[14] also reported 3- and 12-fold increases in the rate of new onset of T2DM after mild and moderate/severe COVID-19 compared to the general population in a cohort study (n = 600,055). A retrospective cohort study[15] of 35,865 patients in Germany also found a 28% increase in the incidence of T2DM in individuals with COVID-19 compared to individuals with acute upper respiratory tract infections. Collectively, these findings suggest a potential diabetogenic effect of SARS-CoV-2 infection. Whether the incidence of DM will increase over the next few years remains largely unknown.

### Proposed Mechanisms for New-Onset DM in Post COVID-19 Patients

To date, the reasons why people with diabetes (PWD) are at higher risk for severe adverse outcomes, including ICU admission and death following SARS-CoV-2 infection remain poorly understood[6,16]. It is likely that SARS-CoV-2 infection could be accelerating or worsening the already insufficient insulin secretion, peripheral insulin resistance (PIR), and chronic systemic low-grade inflammation[17,18]. Additionally, studies[12-15] have shown that some non-DM individuals infected with SARS-CoV-2 also develop DM. The latter is likely to arise from multiple mechanisms. First, SARS-CoV-2 directly infects and impairs the function of pancreatic β-cells. Second, systemic inflammation resulting from immune dysregulation that alters the physiological functions of the main target organs of insulin, including skeletal muscle, liver, and adipose tissues, leads to PIR. Third, the binding of SARS-CoV-2 to the ACE-2 receptors and endocytosis of the SARS-CoV-2 cause downregulation of the ACE-2 receptor, which in turn increases blood levels of angiotensin II, leading to impaired peripheral insulin sensitivity and insulin secretion[19,20]. Fourth, drugs often used to blunt the cytokine storm, such as systemic dexamethasone may worsen hyperglycemia by enhancing hepatic gluconeogenesis and increasing PIR[21,22]. However, these mechanisms do not explain why some PWD develop more severe COVID-19 than others, and why some non-DM infected with SARS-CoV-2 develop the new-onset DM. To the best of our knowledge, specific drugs to treat severe COVID-19 patients with and without DM and to prevent the new onset of DM in non-DM individuals remain limited.

In this review, we postulate that the accumulation of the cytotoxic glycolysis byproduct methylglyoxal (MGO) may be contributing to the increased susceptibility of COVID-19 severity and new-onset DM. Accumulation of MGO can arise (1) from increased production and/or reduced degradation. The increase in MGO can arise from increased glycolysis in infected cells to support SARS-CoV-2 replication, (2) from increased glycolysis in recruited immune cells, particularly macrophages to remove SARS-CoV-2 infection, (3) from a reduction in glutathione (GSH), the co-factor that reacts with MGO to form a reversible hemi-thioacetal and (4) a reduction in expression of the primary MG-degrading enzyme glyoxalase-1 (Glo1) under inflammatory conditions. Here, we will describe the formation of MGO in mammalian cells, the primary pathway responsible for MGO detoxification, and the cellular damage induced by elevated MGO. Additionally, we will also describe how elevated MGO can impair pancreatic insulin secretion and PIR, leading to perilous clinical outcomes in COVID-19 patients and the development of a new onset of DM in infected individuals. Finally, we propose that lowering MG could be a therapeutic strategy to blunt the adverse clinical outcomes of COVID-19 and attenuate PCS.

## Methylglyoxal

### Methylglyoxal Formation

The principal pathways of MGO formation and detoxification by the glyoxalase system are summarized in (Figure 1, Panel A). MGO is produced primarily from the spontaneous break-

down (non-enzymatic) of the glycolytic triose intermediates; glyceraldehyde 3- phosphate (G3P) and dihydroxyacetone phosphate (DHAP) during converting glucose into pyruvate (glycolysis). Under normal conditions, it is estimated that 0.1% of the glucotriose flux is converted into MGO. Smaller amounts of MGO are also formed from the breakdown of glucose *via* the sorbitol pathway (polyol pathway) and enzymatic degradation of protein and lipid in the cytoplasm. Physiological levels of MGO on average are between 60-250 nM in plasma and 1-5 μM in cells[23,24]. About 1% of MGO is present as free, while 99% of MGO inside cells is reversibly bound to the arginine, lysine, and cysteine residues of proteins[25-27]. Free and reversibly bound forms of MGO are in equilibrium with each other. Free MGO is also readily exchanged between cellular and extracellular compartments, including juxtaposed cells[23]. At a physiological level, MG plays important roles in regulating cell proliferation, differentiation, and apoptosis. MGO also regulates non-rem sleep and anxiety by activating γ-Aminobutyric acid type A ($GABA_A$) receptors[28,29]. Under normal glycemia, MGO also activates transient receptor potential (TRP) channels expressed in the cell membrane of pancreatic b-cells, leading to depolarization, $Ca^{2+}$ influx, and insulin secretion[30].

### Methylglyoxal Detoxification and Glyoxalase 1 Regulation

MGO levels are usually maintained below 250 nM in plasma and below 5 μM in cells/tissues. Under normal circumstances, more than 99% of MGO is detoxified *via* the glyoxalase system. The glyoxalase system consists of two enzymes, glyoxalase 1 (Glo-1, EC4.4.1.5, the rate-limiting enzyme), and glyoxalase 2 (Glo2, EC3.1.2.6,). Both Glo1 and Glo2 are in the cytoplasm and in the mitochondria[31]. Reduced glutathione (GSH) is a co-factor in MGO degradation. GSH is a tripeptide, γ-L-glutamyl-L-cysteinyl-glycine and is synthesized in two sequential steps. In the first step, glutamate cysteine ligase (GCL, EC 6.3.2.2; known as γ-glytamylcysteine synthetase) links L-glutamate and L-cysteine to form γ-glutamyl-L-cysteine. In the second step, glycine is added to the cysteine γ-glutamyl-L-cysteine *via* glutathione synthetase (GSS; EC 6.3.2.3) to form GSH[31]. In the glyoxalase system, MGO spontaneously reacts with GSH to form GSH-MG hemi-thioacetal. Glo-1 then catalyzes the conversion of GSH-MG hemi-thioacetal into S-d-lactoylglutathione. In the presence of water, Glo2 hydrolyzes S-d-lactoylglutathione into D-lactate and reproduces the intracellular GSH[24,32]. In the liver, D-lactate is metabolized by mitochondrial D-lactate dehydrogenase to pyruvate. D-lactate levels in the blood can also be used as a surrogate indicator of MGO flux[33,34].

It is important to recognize that the level and activity of Glo-1 are regulated both at the transcriptional and post-translational levels. The promoter region of the human *GLO-1* gene has several functionally operative regulatory elements, including an insulin-response element (IRE), a metal-response element (MRE), and an antioxidant response element (ARE). Binding of insulin to IRE, $Zn^{2+}$ to MRE, and an antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) to ARE region of *GLO-1* increase Glo-1 mRNA expression, protein synthesis, activity, and subsequently decrease MGO stress. Conversely, the expression of Glo-1 is downregulated by hypoxia-inducible factor 1α (HIF-1α). Under normoxic conditions, the HIF-1α is degraded by proteasomes, while under hypoxic conditions (ischemia), commonly seen in COVID-19 patients, HIF-1α is translocated to the nucleus, where it forms a heterodimer with HIF-1b. The HIF-1α/HIF-1b heterodimer can bind to the ARE region of *GLO-1* and suppress Glo-1 expression[24,35]. Studies[36,37]also confirmed that Glo-1 activity is regulated by post-translational modifications. For example, phosphorylation on Thr 107 by $Ca^{2+}$/calmodulin-dependent kinase II delta (CaMKIIδ) enhances the Glo-1 activity and blunts the formation of MGO. It is therefore not surprising that CamKIIδ knockout mice showed a significant decrease in Glo-1 activity and have increased levels of MGO levels in various organs, including the liver, kidney, heart, and brain[36]. Moreover, several studies[24,37] confirmed that excessive inflammation (a condition seen in COVID-19 patients) suppresses Go-1 activity. For instance, de Hemptinne et al[37] demonstrated that proinflammatory cytokine TNF-α activates protein kinase A (PKA) which induces phosphorylation of Glo-1 on Thr 106 and subsequently inhibits the Glo-1 activity to detoxify MGO. In the next sections, we will describe two potential sources of MGO formation in COVID-19 patients, upregulation of glycolysis in infected pancreatic islets and in recruited immune cells (Figure 1, Panel B). We will also link elevation of MGO to the pancreatic β-cells dysfunction, impairment of pancreatic microvascular endothelial cells, and PIR, pathophysiological characteristics of DM.

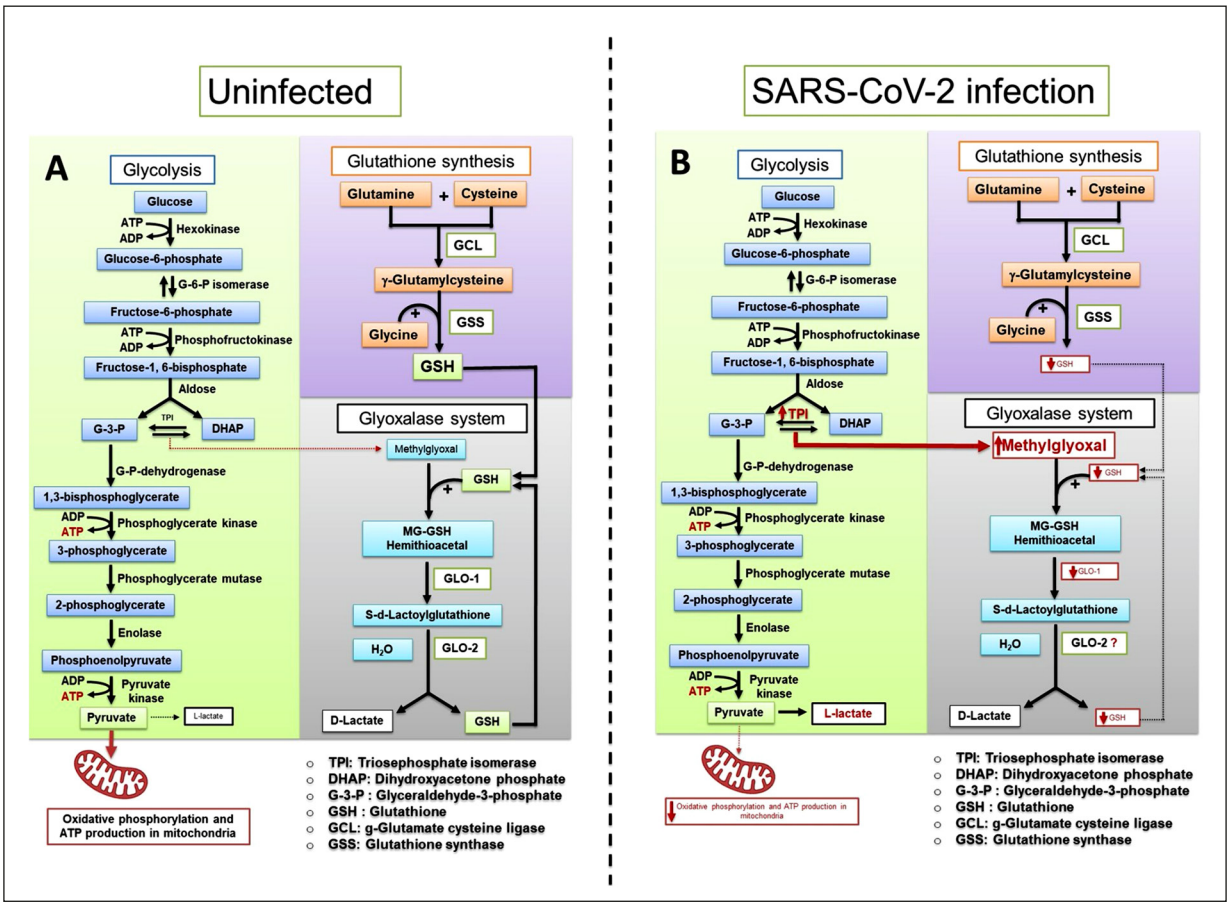


**Figure 1.** Schematic representation of methylglyoxal (MGO) formation *via* glycolysis and the degradation of the MGO-GSH hemi-thioacetal in uninfected **(A)** and SARS-CoV-2 infected cells **(B)**. MGO is formed from the spontaneous fragmentation of the dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3- phosphate (G3P). MGO is detoxified by the dual-enzyme glyoxalase system. In the first step, glyoxalase 1 (Glo1) converts the MGO-GSH hemi-thioacetal formed between MGO and GSH to the thioester S-D-lactoylglutathione. In the second step, glyoxalase 2 (Glo2) catalyzes the hydrolysis of S-D-lactoylglutathione into D-lactate, and glutathione is recycled. In COVID-19 patients, glycolysis is upregulated in the infected cells and recruited immune cells. At the same time, Glo1 and GSH are downregulated, resulting in the accumulation of cytotoxic glycolysis byproduct MGO.

### *Cellular Damage Induced by Methylglyoxal*

MGO, also known as 2-oxopropanal, is the most potent reactive carbonyl species (RCS) identified in mammals. MGO is an uncharged molecule and has a longer half-life (several minutes) than most ROS (msec), allowing it to migrate far from its production site and modify target molecules both inside and outside of cells[26,38]. MGO is a major precursor of advanced glycation end-products (AGEs) and can react with basic amino acid residues proteins, including arginine, lysine, histidine, and sulfhydryl groups (cysteine), leading to the formation of a variety of AGEs, some of which can be crosslinking. The hydroimidazolones (MG-H1, MG-H2, and MG-H3) and argpyrimidine, which are produced non-enzymatically by the interaction of MGO and arginine residue, are the most important MGO-derived AGEs. MGO can also modify membrane phospholipids and nucleotide bases (deoxyguanosine) in DNA, producing well-established covalent adducts and potentially modifying their functions[24,39].

### *Upregulation of Glycolysis in SARS-CoV-2 Infected Cells*

The human pancreas consists of ~95% exocrine tissue that secretes digestive enzymes into the duodenum of the small intestine to digest food. These enzymes include trypsin and chymotrypsin to digest proteins, lipase to digest fats, and amylase to break down carbohydrates. The

remaining tissue (~5%) consists of a cluster of endocrine cells formerly called islets of Langerhans. These islets play an important role in regulating blood glucose levels and metabolism[40-42]. In humans, the islets of Langerhans are typically composed of 60% insulin-releasing β-cells, 30% glucagon-releasing α-cells, and the remainder (10%) made up of δ-cells, γ-cells, and ε-cells release somatostatin, pancreatic polypeptide, and ghrelin, respectively[43]. Recent studies[44,45] have shown that the ACE2 receptor is expressed in pancreatic islet cells and pancreatic microvascular endothelial cells (PaMECs). SARS-CoV-2 can infect both pancreatic β-cells and PaMECs, disrupting their functions through an unknown mechanism.

Like most viruses, SARS-CoV-2 after entry hijacks the host cell metabolism to establish the optimal environment to produce the macromolecules needed for virion replication and survival. These metabolic changes include upregulating glycolysis and attenuating the oxidative phosphorylation in mitochondria, stimulating the uptake of extracellular nutrients such as glucose, glutamine, and fatty acid, and increasing nucleic acids, amino acids, and lipid synthesis[46,47]. At this time, most COVID-19 studies regarding SARS-CoV-2 hijack of host metabolic pathways have focused on the end-products of these pathways. However, little attention has been given to the toxic byproducts of these pathways. Here, the focus will be on the increased production of the cytotoxic glycolysis byproduct MGO. The most crucial metabolic reprogramming that occurs in virally infected cells is a switch from aerobic glycolysis, the so-called "Warburg effect." Upregulation of glycolysis is accompanied by overexpression of glucose transporters and upregulation of glycolytic enzymes, such as alpha-enolase (ENO1), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), phosphoglucomutase 2 (PGM2), hexokinase, lactate dehydrogenase A, and triosephosphate isomerase 1 (TPI-1)[46,47]. While aerobic glycolysis generates a lesser amount of ATP, it produces ATP at a high rate, approximately 100 times faster than oxidative phosphorylation. Aerobic glycolysis is also essential to supply intermediate substances for protein and nucleic acid synthesis needed for viral replication[48,49]. Because the formation of ATP from glycolysis occurs downstream of the formation of MGO (Figure 1), the glycolytic pathway in the pancreatic b-cells and PaMEC infected with SARS-CoV-2 inevitably produces large quantities of MGO during ATP formation.

### *Upregulation of Glycolysis in Activated/Recruited Immune Cells to SARS-CoV-2 Infected Sites*

In addition to SARS-CoV-2 infected cells, recruited immune cells in response to SARS-CoV-2 infection also upregulate metabolic pathways to orchestrate their highly specific series of actions to combat SARS-CoV-2 infection, remove cellular debris, and aid tissue healing. It is well established that the replication of the virus in the infected cells causes the release of pathogen-associated molecular patterns (PAMPs, such as viral genome and protein), and the host cells undergo pyroptosis release of damage-associated molecular patterns (DAMPs, such as ATP and self-DNA). The PAMPs and DAMPs are recognized by specific receptors expressed on adjacent endothelial cells. Activation of these receptors causes the production and secretion of pro-inflammatory cytokines and chemokines, which recruit immune cells, particularly monocytes, macrophages, and T lymphocytes, to the site of infection[50,51]. Upregulation of glycolysis is required in immune cells to produce a large amount of reactive oxygen species (ROS). These ROS play an important role in cell signaling to regulate proinflammatory cytokine secretion and the phagocytic capacity of immune cells such as macrophages and neutrophils to remove viral invasion[52]. In a recent study, Moolamalla et al[46] reported upregulation of many glycolysis pathway genes in PBMCs isolated from COVID-19 patients, including hexokinase 1 (HK1), pyruvate kinase M1/2 (PKM), lactate dehydrogenase A (LDHA), GAPDH, and TPI1. Scholars[52] have also reported an increase in extracellular acidification rate (ECAR, a measure of lactic acid levels) in PBMCs isolated from COVID-19 patients, indicative of increased glycolytic flux. Moreover, Ferraro et al[53] pointed out that polarization of macrophages requires high-speed ATP production through switching macrophages from mitochondrial oxidative phosphorylation to cytosolic glycolysis to produce rapid ATP even in the presence of a sufficient oxygen supply. They also indicated that M1 macrophages upregulate glycolysis by increasing HIF-1α and glycolysis-related proteins in an $O_2$-independent manner. Like infected non-immune cells, MGO formed in immune cells can diffuse into adjacent pancreatic cells and accelerate b-cell exhaustion and failure, and subsequently render PWD more susceptible to the severity of the clinical outcome of COVID-19 and the develop-

ment of new onset of DM (Figure 2). The following sections will discuss the deleterious effects of MGO on the pancreatic b-cells, PaMEC, and insulin signaling pathways.

### *Impairment in Insulin Secretion Following SARS-CoV-2 Infection*

The release of insulin from pancreatic b-cells into circulation is stimulated by elevated blood glucose levels to maintain glucose homeostasis. Glucose enters the β-cell through glucose transport-1, GLUT1 (GLUT2 in rodents), and its rapid metabolism yields an increase in the ATP production and ATP/ADP ratio. This increase in the cytosolic ATP/ADP ratio will close ATP-sensitive potassium ($K_{ATP}$) channels. The reduction in $K^+$ conductance will result in depolarization of the β-cell (more than 99% of $K_{ATP}$ channels must be closed so that membrane depolarization occurs). The depolarization activates voltage-gated T-type $Ca^{2+}$ channels (L-type $Ca^{2+}$ channels in rodents) and subsequently increases the influx of $Ca^{2+}$. In turn, $Ca^{2+}$ triggers insulin granule fusion with the plasma membrane to release their cargo contents into the bloodstream by exocytosis[54,55]. Several studies[56,57] are ongoing to understand the mechanistic link between COVID-19 and DM. For instance, Müller et al[56] demonstrated that pancreatic human β-cells express SARS-CoV-2 entry proteins ACE2 and TMPRSS2. In *in vitro*, they also demonstrated that SARS-CoV-2 can infect and replicate in cultured human islets. Additionally, SARS-CoV-2 hinders pancreatic β-cell functions by reducing the number of insulin-secretory granules and compromising glucose-stimulated insulin secretion (GSIS). In the COVID-19 postmortem study[56,57], these investigators also detected SARS-CoV-2 in pancreatic β-cell. These findings are in line with others reported by Wu et al[57] in which pancreatic autopsy samples collect-

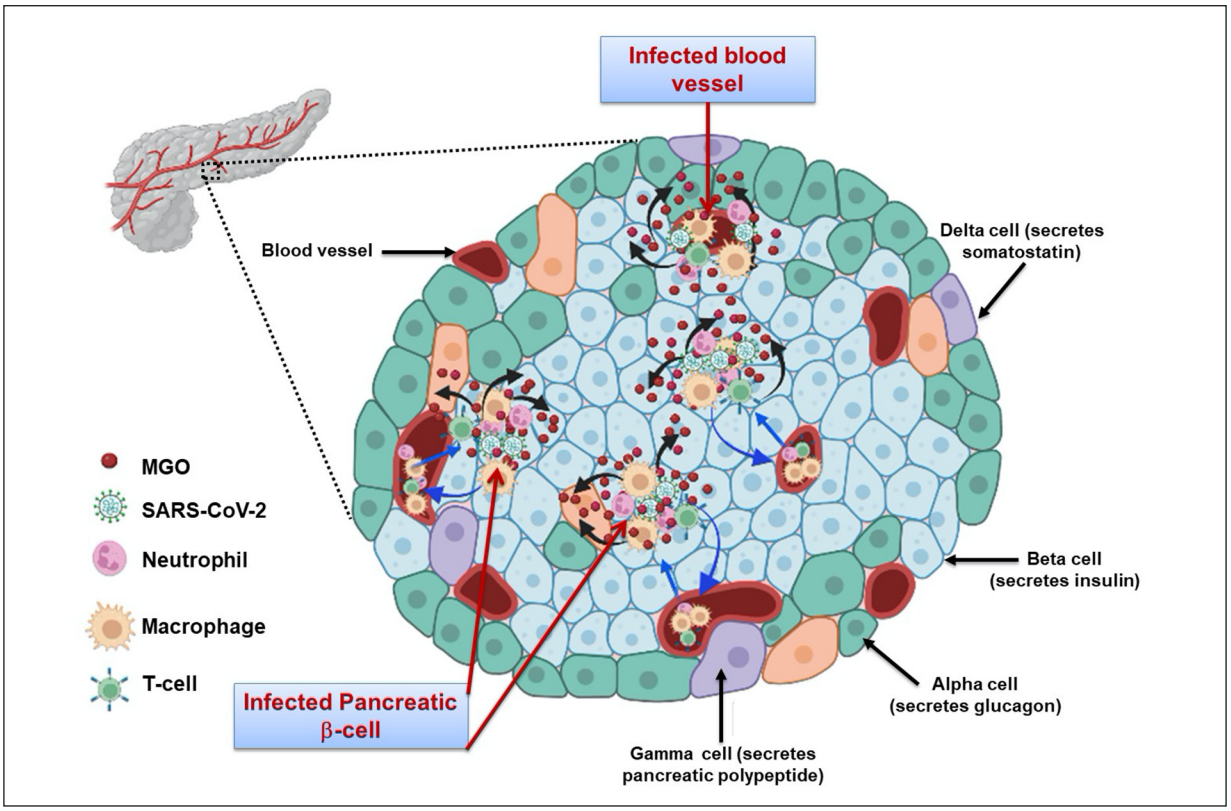


**Figure 2.** Production of MGO in the pancreas after SARS-CoV-2 infection. SARS-CoV-2 after entry into pancreatic b-cells and PaMECs, hijacks host cell metabolism and upregulates glycolysis to establish an optimal environment for virion replication and survival. Glycolysis switching is accompanied by increased levels of the cytotoxic glycolysis byproduct, MGO. The replication of the virus in the infected cells causes the release of PAMPs (viral proteins and genomes) and the host cells undergo pyroptosis release of DAMPs (ATP and self-DNA), which recruit immune cells. Like infected cells, recruited immune cells also upregulate glycolysis and increase MGO production. MGO produced by infected cells can diffuse and enter juxtaposed uninfected cells, leading to pancreatic failure. Figure made using biorender.com.

ed from patients who succumbed to COVID-19 showed SARS-CoV-2 infected pancreatic β-cells. Similarly, in *ex vivo* experiments on isolated human pancreatic islets, they found that SARS-CoV-2 preferentially infected pancreatic b-cells about 10-times more than other pancreatic cell types. They also found a considerable decrease in both insulin production and GSIS, along with an increase in apoptosis of human islets infected with SARS-CoV-2, compared with mock-treated islets[57]. Collectively, these studies suggest that direct infection of pancreatic b-cells by SARS-CoV-2 and disruption of the physiological functions of pancreatic b-cells are underlying causes of hyperglycemia and the new onset of DM. Nevertheless, these studies[56,57] do not provide all the causative factors for the impairment of pancreatic b-cells in patients infected with SARS-CoV-2.

It has previously[19,20,56,57] been determined that the relationship between COVID-19 and DM is multifactorial, arising not from direct pancreatic b-cells damage induced by COVID-19 and from other pathways including the impaired immune system, cytokine storm, oxidative stress, increased angiotensin II levels, and increasing IRS. We posit that other factors may also be contributing to the loss of pancreatic b-cell functions. Several studies[58,59] have shown that MGO can alter insulin secretion. Under hyperglycemia, a condition frequently seen in COVID-19 patients, MGO was shown to suppress insulin secretion in pancreatic islets isolated from adult rats[60]. Similarly, Jinshuang et al[58] demonstrated that incubating mouse insulinoma cell line (MIN6) or rat insulinoma cell line (ISN-1) with MGO suppressed insulin secretion in a dose-dependent manner by increasing ROS production. They found high levels of ROS stimulated the c-Jun N-terminal kinase (JNK) and the P38 mitogen-activated protein kinase (MAPK), both of which provoked mitochondrial dysfunction and a decrease in ATP production. Interestingly, N-acetyl cysteine, a GSH precursor, significantly attenuated the deleterious effects of MGO on the pancreatic b-cells[58]. It is important to note that pancreatic b-cells have an exceptionally high glycolytic capacity, which might potentially further increase with SARS-CoV-2 infection. Thus, the intracellular production of MGO inside infected pancreatic β-cells is likely to be high. Moreover, compared to other organs such as the liver, pancreatic b-cells have low intrinsic levels of antioxidant activities such as superoxide dismutase, catalase, and glutathione peroxidase[62]. Since SARS-CoV-2 is associated with a reduction in GSH levels[63], generated MGO will likely accumulate. Additional studies to investigate the impacts of MGO on insulin secretion in COVID-19 patients could aid in understanding the bidirectional interactions between COVID-19 and DM and improve the management of the post-acute sequelae of COVID-19.

### A Role for MGO in Pancreatic Endothelial Cell Dysfunction

The thin monolayer of endothelial cells lining the inner surface of the microvasculature has a tremendous physiological function. Healthy endothelial cells act as a barrier between the blood vessel and surrounding tissues to regulate the exchange of solutes and prevent hemorrhage, capillary leakage, and edema. Endothelial cells also synthesize and secrete a slew of regulatory substances into the environment, including vasodilators like nitric oxide (NO) and prostacyclin, as well as vasoconstrictors like thromboxane A (TXA), endothelin 1 (ET-1) and vascular endothelial growth factor (VEGF) to regulate vascular tone, blood flow, coagulation, angiogenesis, and immune cell trafficking[64-66]. Several studies[67-69] have shown that microvascular endothelial dysfunction (ED) is a central feature of COVID-19 pathogenesis, and the severity of COVID-19 is positively correlated with the degree of ED. ED is characterized by a disruption in the balance between vasodilation and vasoconstriction, decreased endothelial NO bioavailability, oxidative stress, inflammation, and altered endothelial barrier permeability. Studies[68-70] suggest that ED precedes the development of cardiovascular diseases and complications associated with COVID-19 disease progression. Pancreatic islets have a dense microvascular network and receive 5- to 10-times higher blood flow than exocrine pancreatic cells[71]. Furthermore, pancreatic islet endothelial cells have 10 times more fenestrations than exocrine pancreatic tissues, allowing for trans-endothelial transport of secreted hormones and allowing pancreatic islets to respond quickly to fluctuations in blood glucose and adjust insulin secretion as needed[72,73]. Recent studies[44,45] have shown that SARS-CoV-2 can infect and disrupt PaMECs. However, the precise mechanisms responsible for SARS-CoV-2-induced pancreatic ED remains poorly characterized. MGO is the most potent endothelial toxin identified to date. The deleterious effects of MGO on vascular endothelial functions have been extensively investi-

gated in animal and human studies. For example, we and others showed that increased MGO and MGO-derived AGEs levels are underlying causes of ED associated with end-organ complications of DM and they have also been linked to the pathogenesis of ED associated with other conditions, including cardiovascular disease, obesity, aging, neurogenerative disease, and human immunodeficiency virus (HIV) infection[27,74-77]. Additionally, chronic administration of MGO to rats induced diabetes-like ED characterized by decreased acetylcholine-induced NO-mediated vasorelaxation[78]. Moreover, overexpression of Glo-1 in the vasculature of diabetic animals decreased MGO level and MG-derived GE formation in microvascular endothelial cells and prevented microvascular leakage and the loss of responsiveness of arterioles to ADP-mediated vasodilatation[79]. It is important to note that, compared to smooth muscle cells, endothelial cells have a relatively low number of mitochondria and rely largely on glycolysis for ATP production. Glucose can cross the cell membranes of endothelial cells by facilitated diffusion (a passive process) mediated by insulin-independent GLUT-1[80,81]. Accordingly, an increase in blood glucose levels, a condition commonly seen in COVID-19 patients[82], will increase the influx and accumulation of glucose into endothelial cells, leading to an increase in the production of MGO as a glycolysis byproduct, particularly in the endothelial cells infected with SARS-CoV-2[56]. At the molecular level, MGO can disrupt several functions of vascular endothelial cells by several mechanisms, including enhancing ROS formation, vascular hyperpermeability, reducing the synthesis and NO bioavailability, and stimulating cytokine production and apoptosis processes by activating receptors for advanced glycation end-product (RAGE)[83-85].

### MGO Triggers ROS Production

Increased production of ROS, including hydrogen peroxide ($OH^{\bullet}$), superoxide anions ($O^{\bullet}_2$), and peroxynitrite ($ONOO^-$) is responsible for microvascular endothelial cell dysfunction in DM and other metabolic disorders[86]. The mitochondria are considered a vital organelle found in all types of human cells except mature erythrocytes. Mitochondria are essential for the production of ATP used for regulating intracellular $Ca^{2+}$ homeostasis, steroid synthesis, autophagy, and apoptosis. Interestingly, recent studies[87,88] indicate that the SARS-CoV-2 structural and non-structural proteins can interact with mitochondria and impair their metabolisms, characterized by upregulation of mitochondrial cytokine/inflammatory signaling genes and downregulation of genes that are involved in mitochondrial respiration and autophagy. The impairment of mitochondrial metabolic pathways was found to be associated with excessive production of ROS and COVID-19 disease severity[87-90]. Unfortunately, the precise signaling pathway that mediates the harmful effects of SARS-CoV-2 on the mitochondria remains elusive, and more studies are needed to discover novel mechanisms that may lead to the development of novel therapeutic targets.

In the past few decades, accumulating evidence[78,91,92] indicates that supraphysiological levels of MGO can potentiate ROS formation such as OH, $O^{\bullet-}_2$, and $ONOO^-$ and oxidative stress in microvascular endothelial cells. In the endothelial cell, MGO triggers oxidative stress *via* activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a membrane-bound enzymatic complex that reduces $O_2$ to $O^{\bullet}_2$, and complex III of mitochondria[92]. MGO also significantly suppresses the activities of several antioxidant enzymes, including glutathione peroxidase, glutathione reductase, catalase, and superoxide dismutase (SOD), and depletes GSH, causing impairment of MGO degradation and the establishment of a vicious cycle[93,94]. In addition to increasing mitochondrial ROS production, MGO also disrupts mitochondrial functions by increasing mitochondrial membrane permeability, which involves MG-induced apoptosis[95].

### Methylglyoxal Induces Vascular Hyperpermeability

Tight junction (TJ) proteins such as junctional adhesion molecules, occludin, and claudin-5 family members play a key role in the integrity of endothelial cells, regulating vascular permeability and leukocyte extravasation into sites of inflammation and angiogenesis. The TJ protein claudin-5 is the most important and widely expressed in all vascular beds. The low expression of claudin-5 was found to correlate with several pathological settings associated with ED, as it occurs in DM and other central nervous system disorders[96]. A recent study[97] reported that SARS-CoV-2 significantly diminished the expression and caused discontinuity of claudin-5. The reduction in claudin-5 was correlated with capillary barrier dysfunction, vascular leakage, excessive thrombosis, and fibrosis in the endothelium of COVID-19 lung autopsy samples[97].

In parallel, others found that incubating human umbilical vein endothelial cells (HUVEC) with moderate and severe COVID-19 plasma for six hours resulted in a significant reduction in claudin-5 expression by an unknown mechanism[98]. In animal models, we found elevation of MGO levels in diabetic animals and humanized animals infected with HIV compromised microvascular endothelial integrity, caused microvascular leakage, and reduced the density of perfused capillaries (local ischemia), and fibrosis. Interestingly, increasing expression of Glo-1 attenuated the increased MGO levels and blunted microvascular leakage, local ischemia, and fibrosis seen in diabetic and HIV-infected animals[76,77]. In an *in vitro* study[79], we also found incubation of human brain microvascular endothelial cells (HBMEC) with MGO decreased expression of claudin-5 and occludin in a dose-dependent manner. Others also showed that incubated HBMEC with MGO increased occludin glycation formation (i.e., MGO-occludin adducts) and augmented HBMEC permeability[99]. Mechanistically, the former study[100] confirmed that MGO can disrupt the integrity of endothelial cells by modifying TJ protein structure and suppressing the expression of TJ protein *via* activating the NF-kB pathway. Recently, it has been shown that SARS-CoV-2 upregulates the NF-kB pathway[101] and because NF-kB antagonizes the Nrf2 pathway[102], activation of NF-kB pathway in COVID-19 patients not only decreases Glo-1 expression and increases the accumulation of MGO but also decreases TJ proteins expression[103]. Taken together, excessive MGO formation could account in part for the reduction of TJ protein expression, and disruption of the integrity of endothelial cells in the COVID-19 state.

### Methylglyoxal Reduces NO Synthesis and Bioavailability

Endothelial NO is the key molecule that induces vasodilatation to ensure enough blood supply to organs. The nitric oxide synthase (eNOS) catalyzes the formation of NO from L-arginine and oxygen ($O_2$). Endothelial NO also regulates the proliferation of vascular smooth muscle cells, platelet aggregation, and leukocyte adhesion. Therefore, a decline in endothelial NO bioavailability will lead to ED accompanied by low $O_2$ supply (hypoxia), as is the case with severe/acute COVID-19[66,104,105]. It is well established that MGO directly interferes with endothelial NO functions. In an *in vitro* study[106], incubation of rat aortic endothelial cells (RAECs) and HUVEC with MGO reduced the production of NO and caused ED. These effects of MGO-induced NO reduction and ED were significantly attenuated by N-acetyl cysteine-GSH precursor and aminoguanidine-MGO scavengers. In agreement with this, we showed bathing arterioles of anesthetized control rats with MGO significantly reduced the ability of the endothelial eNOS-activating ligand adenosine diphosphate (ADP) to vasodilate arterioles, akin to that seen in DM. As we mentioned previously, endothelial cells have a relatively lower Glo-1 content compared to juxtaposed smooth muscle cells. We found overexpression of Glo-1 in the microvasculature in diabetic rats restored endothelial NO to near that in control rats[79].

### MGO Activates Receptors for Advance Glycated End-Product (RAGE)

MGO is well known to react with proteins to form MGO-derived AGEs[107]. In addition to altering protein structure and function, MG-derived AGEs serve as ligands for the membrane-bound receptors for AGE (RAGE), an immunoglobulin superfamily receptor, which triggers inflammation, oxidative stress, and apoptosis. RAGEs are expressed in many cell types, including lung epithelial cells, vascular endothelial cells, immune cells such as monocytes/macrophages, dendritic cells, neutrophils, T cells and B cells, neurons, and pancreas[108-110]. Since RAGE expression was found to be up-regulated in a number of conditions seen with poor clinical outcomes in COVID-19 patients, including DM, aging, obesity, and cardiovascular disease, several review articles suggested that the activation of RAGEs by AGEs may alter gene expression, leading to increased synthesis and release of proinflammatory mediator substances and oxidative stress that could increase the risk of COVID-19 severity and mortality[111,112]. In the vascular endothelial cells, binding of MG-derived AGE to RAGE activates the NF-kB pathway and results in overexpression of various genes involved in inflammation, including cytokines, proinflammatory adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E- selectin, and endothelin-1. In addition, activation of RAGE by MGO-derived AGE causes depletion of intracellular GSH and triggers oxidative stress and apoptosis[113]. Mechanistically, Chen et al[114] indicated that AGE-RAGE interaction increases ROS formation in endothelial progenitor cells (EPCs) through the

Rac1-dependent nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway and induces apoptosis through activation of the JNK signaling pathway, which is downstream of ROS. Furthermore, activation of RAGEs induces the translocation of NF-κB to the nucleus and inhibits the expression of Glo-1[115-117], which may further enhance the formation of MGO and set up a positive feedback loop. As far as we know, there is no study specifically tackling the key role of the interaction of MGO-derived AGE with RAGE in COVID-19 severity.

### A Role for Methylglyoxal in Peripheral Insulin Resistance

Insulin exerts its anabolic responses to nutrient availability by binding to and activating its transmembrane receptor, which belongs to the family of receptor tyrosine kinases (RTK). Insulin receptor (IR) is a hetero-tetrameric complex made up of two α subunits and two β subunits that are linked by disulfide bonds[118]. The binding of insulin to the extracellular α subunits induces conformational changes, that result in activation of the intracellular kinase catalytic domain of the β subunit, and subsequently autophosphorylation of the receptor. Autophosphorylation of IR activates multiple downstream signaling cascades *via* phosphorylating several substrates, including a family of insulin receptor substrates (IRS1/2/3/4), which lead to the final cellular responses to insulin. Although IR is expressed in many mammalian cells, the primary role of insulin in glucose homeostasis is mediated by insulin's effects on skeletal muscle, white adipocytes, and liver. In skeletal muscle, insulin promotes glucose uptake by translocating glucose transporter 4 (GLUT4) from the cytosol to the membrane and regulating a variety of enzymes involved in the glycolysis and glycogenesis pathways. The major functions of insulin in adipose tissues are to increase glucose uptake, stimulate lipogenesis, and inhibit lipolysis. In the liver, insulin stimulates glycogen synthesis and suppresses both glycogenolysis and gluconeogenesis[118,119]. When these target organs fail to respond to insulin, glucose uptake from circulation is blunted and PIR occurs, leading to hyperglycemia. The high circulating glucose triggers insulin secretion from the pancreatic b-cells. High blood insulin levels (or "hyperinsulinemia") are a common phenomenon in people with metabolic syndrome, including individuals with abdominal obesity, prediabetes, and T2DM[119,120].

It is important to note that chronic hyperinsulinemia also promotes resistance of peripheral tissues to insulin by inhibiting insulin receptor signaling cascades, which in turn leads to a vicious circle of PIR and hyperinsulinemia that culminates in eventual pancreatic b-cell failure[121]. Recent reports[122,123] indicate that COVID-19 increases the risk of PIR and hyperglycemia in both non-diabetic and DM patients, which consequently can worsen COVID-19, increase mortality risk, and contribute to the new-onset of DM. To date, the exact molecular mechanisms underlying PIR in COVID-19 patients remains poorly characterized but is likely to be multifactorial, involving immune system dysregulation, excess inflammation, oxidative stress, microvascular endothelial impairment, increased glucose production, and pancreatic b-cell dysfunction[16,122,123]. In addition to DM, studies[124,125] have also linked elevated MGO to a variety of insulin resistance states, including obesity and dyslipidemia severity, conditions that are risk factors for COVID-19 severity[126]. In the following sections, we will describe the key mechanisms by which MGO induces PIR, a major pathogenic factor of DM, namely by altering the insulin signaling pathway and modifying insulin molecules.

### Methylglyoxal Impairs the Insulin Signaling Pathway

Studies[59,127] have shown that MGO directly interferes with insulin signaling. For example, Guo et al[59] demonstrated, by using the euglycemic hyperinsulinemic glucose clamp (EHGC) technique, that treating animal rats with four-week MGO in the drinking water significantly increased insulin resistance. Co-administration of MGO with N-acetyl cysteine, an MGO scavenger, prevented MGO-induced insulin resistance. Riboulet-Chavey et al[127] showed that short-term exposure of L6 muscle cells (30 min) to MGO decreases insulin-stimulated glucose uptake in a dose-dependent manner independent of ROS formation. They also confirmed that MGO binds to IRS-1 protein and inhibits insulin-stimulated IRS-1 phosphorylation over time. This is likely due to MGO interacting with Lys and Arg residues present on the extracellular α subunits of IR and altering its ability to bind insulin[128].

### Insulin Modification by Methylglyoxal

In addition to the deleterious effects of MGO on the IR/insulin signaling pathway, a study[124] has shown that MGO can also alter the struc-

ture and function of insulin by binding to the N-terminus and internal arginine residue in the B-chain of insulin. Human insulin consists of two polypeptide chains known as chain A (21 amino acids) and chain B (30 amino acids) that are linked together by disulfide bridges[129]. Jia et al[124] demonstrated that MGO can bind to insulin and that MG-insulin adduct decreases glucose uptake in comparison with native insulin. Interestingly, these posttranslational modifications of insulin by MGO become more resistant to degradation by the liver cell lines. It is interesting to point out that the promoter region of the Glo-1 gene contains IRE. The binding of native insulin stimulates Glo-1 mRNA expression and protein synthesis and subsequently accelerates the detoxification of MGO. To the best of our knowledge, there is no published literature showing the effect of MGO-modified insulin on Glo1 expression. If this modification prevents transcription of Glo-1, it may generate a feedback loop between MGO and MGO-insulin adduct and exaggerate PIR in COVID-19 patients and other conditions such as DM, obesity, and age-related diseases. Further research in this area may lead to new mechanisms and therapeutic targets for new-onset DM in post-COVID patients.

### Other Factors that Trigger the Accumulation of Methylglyoxal

Several other factors may also enhance the accumulation of MGO in patients infected with SARS-CoV-2, including oxidative stress, downregulation of Glo-1, activation of the HIF-1 pathway, and overexpression of vascular adhesion protein-1[19,53].

### Oxidative Stress and Downregulation of Glo-1

Glo-1 is the rate-limiting enzyme in the glyoxalase system for MGO-GSH degradation as described earlier. Recently, we found a significant reduction in the plasma levels of Glo-1 and GSH in ICU COVID-19 patients who succumbed, and the Glo-1 and GSH levels were negatively correlated to the MGO levels[130]. Scholars[46] have also reported downregulation of Glo-1 in ACE2 transduced A549 and Calu3 cells infected with SARS-CoV-2. To date, the molecular cause(s) for the reduction of plasma levels of Glo-1 in COVID-19 patients who died remains poorly defined. What we know from the literature is that under non-oxidative stress conditions, binding of Nrf2 to the ARE region of GLO-1 increases Glo-1 mRNA expression and Glo-1 synthesis, and subsequently prevents MGO stress[24,35]. Conversely, we also know that the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) antagonizes the binding of Nrf2 to ARE and inhibits Glo-1 expression. Since COVID-19 increases ROS production (oxidative stress), which is associated with depletion of GSH and activates NF-kB[101], the oxidative stress and increased NF-kB activation could account in part for the reduction of plasma Glo-1 levels and consequently the accumulation of MGO in the COVID-19 state.

### Upregulation of HIF-1α

Under hypoxic conditions (ischemia), as occur in acute COVID-19, HIF-1α binds to the hypoxia response element (HRE) and activates the expression of glycolytic genes[24]. Additionally, during infection, HIF-1α is stabilized in polarized M1 macrophages *via* upregulation of the AKT/mTOR/HIF-1α pathway[131]. Tian et al[132] demonstrated stabilization of HIF-1α, and its transcriptionally regulated genes were upregulated in COVID-19 patients. Since HIF-1α stimulates glycolysis, the major source of MGO, and binding HIF-1α to the ARE of human Glo-1 suppresses Glo-1 expression as, MGO will inadvertently be accumulated in COVID-19 patients. In another study, Ilegems et al[133] demonstrated that HIF-1α protein is expressed in pancreatic β cells of diabetic animal models and is responsible for the aberrant high basal release of insulin, a characteristic of PIR. Treatment of diabetic animals with the HIF-1α inhibitor PX-478 prevented pancreatic β cell dysfunction, maintained elevated plasma insulin concentrations, and improved glucose-induced insulin stimulation index. To the best of our knowledge, there is no published study addressing the link between HIF-1α upregulation and COVID-19-induced hyperglycemia and new-onset DM in post-COVID patients.

### Upregulation of Vascular Adhesion Protein-1

The ectoenzyme, vascular adhesion protein-1 (VAP-1, *AOC3*, EC 1.4.3.21) is highly expressed in endothelium and smooth muscle cells (SMCs) of the vasculature and in adipose tissues. VAP-1 on the vascular endothelial cells plays a crucial role in regulating the adhesion and migration of immune cells into the injured tissues. Studies[79,134,135] in animals and humans demonstrated increased plasma levels and activity of VAP-1 and its soluble form, serum semicarbazide-sensi-

tive amine oxidase (SSAO), and correlated their increases to acute and chronic inflammatory diseases such as severe systemic infections, atherosclerosis, stroke, neurodegenerative disease, congestive heart failure, chronic kidney disease, and DM. Studies[134,135] have also shown that VAP-1 and its soluble form SSAO catalyze the oxidative deamination of aminoacetone, produced by the mitochondrial metabolism of threonine and glycine, to produce $H_2O_2$ and MGO. Recently, we also found significant increases in the activity of SSAO in plasma collected from ICU COVID-19 patients, especially those with DM[130]. Others also found the serum levels of VAP-1 were significantly higher in COVID-19 patients with mild and severe disease[136]. Although the specific mechanisms responsible for increased expression of VAP-1 in COVID-19 patients are not well understood, we found the increase in SSAO activity in the plasma of ICU COVID-19 that died was positively correlated with MGO levels[130]. It is important to mention that the VAP-1 gene (AOC3) is transcriptionally regulated by NF-κB transcription factor[137]. Since activation of NF-κB is upregulated in COVID-19 patients[138] and elevated levels of MGO are a potent activator of the NF-κB pathway[139], the increased NF-κB activity could also account for a part of the increased expression of VAP-1/SSAO plasma. We also found that increasing expression of Glo-1 in animal models of DM and HIV-infection to detoxify MGO significantly lowered VAP-1 levels[77,79]. Others have shown that treating control rats with intravenous aminoacetone for 15 days increased MGO in aortic SMCs[140]. Taken together, MGO is likely to have a feed-forward loop to produce more MGO *via* increasing expression of VAP-1/SSAO. Therefore, using agents that lower MGO in COVID-19 patients is most likely to attenuate VAP-1 expression, excess inflammation, oxidative stress, and potentially blunt diverse clinical adverse outcomes of COVID-19, including new-onset DM.

### Targeting Methylglyoxal

Safe and effective pharmacological intervention to lower MGO is not available in the clinical setting. However, several therapeutic approaches to mitigate MGO have been developed and tested over a few decades. These therapeutic approaches include (1) MGO scavengers such as aminoguanidine, alagebrium, and pyridoxamine; (2) MGO synthesis inhibitors such as metformin and benfotiamine; and (3) Glyoxalase 1 inducer, *via* activation of the Nrf2, such as phenethyl isothiocyanate and sulforaphane isolated from cruciferous vegetables and a combination of trans-resveratrol (tRES)-hesperetin (HESP). More information can be found in the following review[24]. It is paramount to emphasize that COVID-19 is associated with high oxidative stress, and excessive inflammation responses (cytokine storm). Therefore, using agents that boost Glo-1 expression through activation of the Nrf2 pathway, such as the combination of trans-tRES-HESP, might be ineffective chronically because of the overwhelming production of ROS and pro-inflammatory mediators in COVID-19 patients will potentially antagonize and diminish their Glo-1 expression activity. Our lab constructed an adeno-associated virus, AAV2/9, containing glyoxalase-1 driven by the promoter of the inflammation-induced protein, endothelin-1 (AAV2/9-Endo-Glo1). Using diabetic animals and humanized animals infected with HIV models, we found AAV2/9-Endo-Glo1 exhibited significant tropism for microvascular cells. Administering a single dose of AAV2/9-Endo-Glo-I after the onset of DM increased the expression of Glo-1 in the microvasculature, and blunted MGO-derived AGEs and VAP-1 upregulation. AAV2/9-Endo-Glo1 also preserved microvascular endothelial cell functions, inhibited microvascular leakage, inflammation, and fibrosis, and mitigated negative downstream effects of DM in the heart[76,77]. In this review, we propose the two clinically approved drugs may be useful in lowering MGO in COVID-19. Metformin and N-acetylcysteine, Federal and Drug Administration (FDA) approved for the treatment of T2DM[141], and hepatotoxic doses of acetaminophen, respectively[142].

### Metformin

Metformin is the first drug of choice to control blood glucose levels after the initial diagnosis of T2DM. Studies[143,144] have also shown that metformin can reduce plasma levels of MGO and MGO-derived AGE and increase the activity of Glo-1. In a recent meta-analysis of 19 studies, Yin et al[145] found that T2DM patients on metformin with COVID-19 had significant reductions in hospitalization by 27 days and a 34% reduction in mortality rates compared to T2DM patients that were not on metformin. Several mechanisms have been proposed to explain how metformin reduced morbidity and mortality in T2DM-COVID-19 patients, including controlling blood glucose levels, blocking SARS-CoV-2 virus entry into target cells, preventing cytokine storm, improving

endothelial functions, and preventing vascular damage[145,146]. Nevertheless, the exact mechanism by which metformin protects against adverse clinical outcomes in T2DM-COVID-19 patients remains unclear. Here we propose that metformin could reduce hospitalization and mortality rates by lowering MGO levels in COVID-19 patients.

### *N-Acetyl Cysteine*

N-acetyl cysteine is a potent antioxidant and anti-inflammatory agent. Recently, Horowitz et al[147] showed that administration of GSH and N-acetylcysteine (GSH precursors) reduced the cytokine storm syndrome and respiratory distress syndrome seen in COVID-19 patients with pneumonia. Similar findings were observed in the two-central cohort study of 82 patients. Treatment of COVID-19 patients with oral N-acetyl cysteine resulted in a significant reduction in mechanical ventilation support, morbidity, and mortality compared to the control group[148]. We recently reported reduced plasma GSH levels in ICU COVID-19 patients and the reduction in GSH levels negatively correlated with increased MGO levels[130]. Taken together, it is likely that N-acetylcysteine administration would blunt COVID-19 complications by offering the glutathione needed for the degradation of MG by the glyoxalase system.

## Conclusions

In this narrative review, we propose that elevated MGO, through a variety of mechanisms including oxidative stress, inflammation, RAGE activation, endothelial dysfunctions, insulin secretion impairment, and PIR (as summarized in Figure 3), may contribute to hyperglycemia in COVID-19 patients and new-onset DM in post-COVID patients. We also propose using a combination of metformin and N-acetyl cysteine as adjuvant therapy to lower MGO may provide a synergistic effect to blunt hyperglycemia in COVID-19 patients and the development of new onset of DM following SARS-CoV-2 infection.

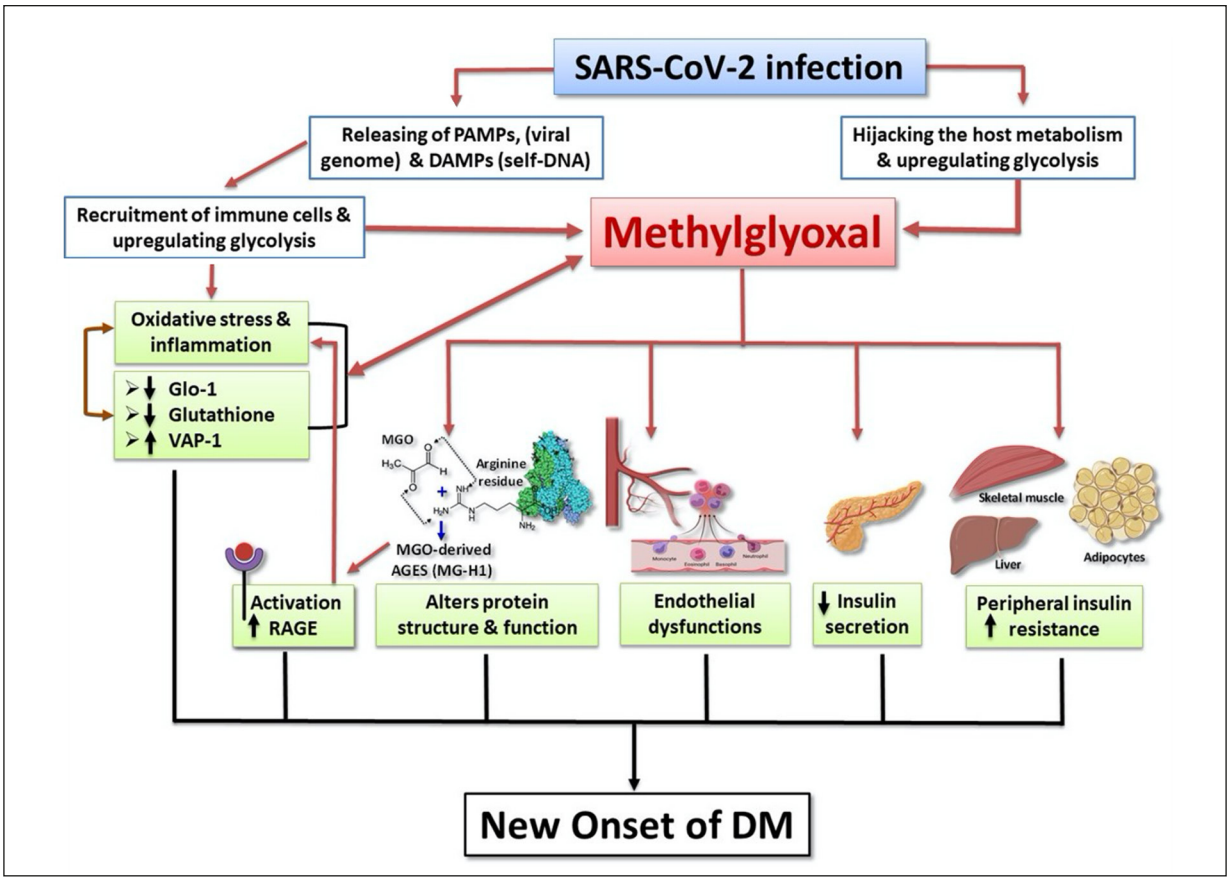


**Figure 3.** Proposed mechanisms for inducing pancreatic b-cell dysfunction, impairment of PaMECs cells, and PIR, making people with diabetes (PWD) more vulnerable to the development of a new onset of DM. Figure made using biorender.com.

### Conflict of Interest
The author declares no competing interests.

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### Ethical Approval
Not applicable.

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