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A Review: How Metformin Improves the Prognosis for Coronavirus Disease-19 Patients with Hypertension?

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ABSTRACT

Background: Hypertension is one of the comorbidities for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Hypertension has been shown to increase the severity and mortality of the Coronavirus disease-19 (COVID-19) patients. Metformin has various benefits, such as an anti-inflammatory and antiviral agent, which can be used in several diseases including cardiovascular disease. **Objectives:** We were interested in assessing the potential of metformin in improving the prognosis of COVID-19 patients with hypertension. **Methods:** Our article reviews use a non-systematic review method. **Discussion:** Metformin could reduce blood pressure by activating AMP-activated protein kinase (AMPK) signaling through various mechanisms, such as vascular, neural, renal, hormonal, immunological, and insulin resistance mechanisms. Metformin could phosphorylate the angiotensin-converting enzyme 2 (ACE2) expression through AMPK signaling to prevent binding between SARS-CoV-2 and the ACE2 receptor. The AMPK signaling pathway in metformin has been proven to suppress cytokine storms in severe COVID-19 patients. Several observational studies have been published showing improvement in the prognosis among COVID-19 patients with metformin use. **Conclusion:** Metformin can improve the prognosis of COVID-19 with comorbid hypertension.
Keyword: AMPK signaling, COVID-19, Hypertension, Metformin, Prognosis

ABSTRAK

Latar Belakang: Hipertensi merupakan salah satu penyakit penyerta pada pasien severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Hipertensi terbukti dapat meningkatkan keparahan dan mortalitas pasien penyakit Coronavirus-19 (COVID-19). Metformin memiliki berbagai manfaat, seperti sebagai agen antiinflamasi dan antivirus, yang dapat digunakan pada beberapa penyakit termasuk penyakit kardiovaskular. **Tujuan:** Kami tertarik untuk meninjau potensi metformin dalam meningkatkan prognosis pasien COVID-19 dengan hipertensi. **Metode:** Tinjauan artikel kami menggunakan metode tinjauan non-sistematis. **Diskusi:** Metformin dapat menurunkan tekanan darah dengan mengaktifkan sinyal AMP-activated protein kinase (AMPK) melalui berbagai mekanisme, seperti mekanisme vaskular, neural, renal, hormonal, imunologi, dan resistensi insulin. Metformin dapat memfosforilasi ekspresi angiotensin-converting enzyme 2 (ACE2) melalui sinyal AMPK untuk mencegah pengikatan antara SARS-CoV-2 dan reseptor ACE2. Jalur pensinyalan AMPK dalam metformin telah terbukti menekan badai sitokin pada pasien COVID-19 yang parah. Beberapa studi observasional terbukti menunjukkan adanya perbaikan prognosis pada pasien COVID-19 dengan penggunaan metformin. **Kesimpulan:** Metformin dapat meningkatkan prognosis COVID-19 dengan hipertensi komorbid.
Keyword: COVID-19, Hipertensi, Metformin, Pensinyalan AMPK, Prognosis

1. Introduction

Hypertension has become one of the comorbidities for patients with SARS-CoV-2 infection.[1,2] A meta-analysis showed that hypertension was found to be an independent risk factor in predicting the severity and mortality of COVID-19 patients.[3] Data showed that 30-49% of COVID-19 patients who were hospitalized had hypertension.[4] In this case, COVID-19 patients with hypertension tend to worsen the patient's prognosis.[5,6] Currently, management of COVID-19 patients with hypertension use angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) drugs that can modulate the renin-angiotensin-aldosterone system (RAAS).[7,8] Various studies have been conducted, but only three out of twelve studies have proven that ACE-I/ARB drugs could reduce the severity of COVID-19 patients with hypertension.[9] Interestingly, ACE-I/ARB can potentially aggravate COVID-19 patients by increasing the ACE2 receptor.[10] Garvin et al. showed that ACE-I in COVID-19 patients could induce a cytokine storm by increasing bradykinin.[11] This is a major health problem that needs to be reviewed to find other alternative therapies for improving the prognosis of COVID-19 patients with hypertension.

Metformin was recognized as the first line in treating type 2 diabetes mellitus (DM).[12] Previous studies mentioned the benefits of using metformin as an antiviral, antibiotic, and anti-inflammatory agent.[13–15] A retrospective study also proved that metformin was beneficial in reducing the mortality rate of COVID-19 patients with type 2 DM.[16] Moreover, metformin could activate AMPK, which acts as an immunomodulator and has an anti-hypertensive effect.[15,17,18] AMPK activation through metformin was found to phosphorylate ACE2, which could reduce the severity of COVID-19 patients.[19] Based on this evidence, metformin has the opportunity to be a candidate for further therapy in improving the prognosis of COVID-19 patients with hypertension.

2. Method

We used a non-systematic review method for this review. A computer-based literature search was performed to identify relevant articles published from 2014 to 2023 in Google Scholar, Pubmed, Science Direct, and Research Gate. The main search terms used medical subject headings (MeSH) to create subgroup terms: *"SARS CoV-2", "COVID-19", "Coronavirus disease 19", "Metformin"*, and *"Hypertension"*.

The inclusion and exclusion criteria were determined before the search. The included studies fulfilled the following inclusion criteria: (1) the study was published during 2014 – 2023; (2) the study had relevant topics and conformity between the research objectives and the journal's conclusions; (3) the study was available in full text. The exclusion criteria included: (1) the study was published less than 2014; (2) the study had irrelevant topics for this review and did not match the research objectives with the research conclusions.

3. Discussion

3.1 Pathogenesis of COVID-19 Patients with Hypertension

The pathophysiology of hypertension is influenced by various factors including genetic and environmental factors.[20] Hypertension is caused by various mechanisms in the body system such as vascular, neural, renal, hormonal, immunological, and insulin resistance mechanisms (Table 1). The vasoconstriction of blood vessels due to a decrease in nitric oxide (NO) or the influence of the sympathetic system can increase blood pressure.[21,22] Activating the sympathetic nervous system to release plasma catecholamines can increase blood pressure through vasoconstriction and heart rate.[22] Hypertension can also occur due to increased sodium reabsorption by the renal system.[23] The process of renal sodium reabsorption through several transporters, such as Na+/Cl cotransporter (NCC), type 3 sodium hydrogen exchanger (NHE3), Na-K-2Cl cotransporter (NKCC2), and Na+/K+-ATPase (NaKATPase).[17]

The RAAS system is a central regulator of blood pressure.[24] Increasing RAAS is correlated with decreased AMPK expression.[25] The mechanism of increasing blood pressure in the RAAS system is through the effect of aldosterone, which can induce sodium and water reabsorption from the kidneys, increase water retention, and induce the sympathetic nervous system as well as release of norepinephrine.[26] Furthermore, the RAAS system can also induce the formation of atherosclerosis, which will increase vascular resistance.[27]

Previous studies showed that the inflammatory process could cause vascular endothelial dysfunction, increasing blood pressure.[28,29] The activation of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and nuclear factor-kappaβ (NF-kβ) plays an essential role in increasing blood pressure.[29] In patients with type 2 DM, blood pressure is elevated because insulin resistance can cause blood vessel vasoconstriction.[30]

The pathogenesis of COVID-19 patients is caused by the interaction between SARS-CoV-2 and ACE2, which can damage endothelial cells (Figure 1), especially in patients with hypertension, and make endothelial cell

damage more widespread.[31] The ACE2 receptor is expressed by epithelial cells of the airways (particularly in type 2 alveolar cells), the gastrointestinal system, the heart, and the kidneys.[32] Expression of ACE2 in SARS-CoV-2 infection will trigger target organ damage due to the inflammatory reaction.[33] Inflammatory reactions induced by cytokine storms play an important role in determining the severity of COVID-19 patients.[34] Various proinflammatory cytokines that play a role in SARS-CoV-2 infection are TNF- α, interleukin-1α (IL-1α), interleukin-1β (IL-1β), and IL-6.[35] Some COVID-19 patients with severe symptoms showed the presence of IL-6 in the patient's plasma.[36] On the other hand, high neutrophil counts were also associated with the severity of SARS-CoV2 infection.[37] These neutrophils can differentiate into neutrophil extracellular traps (NETs), which may lead to lung damage, and increase mortality in COVID-19 patients.[38] Furthermore, adaptive responses also contribute to the severity of COVID-19 by contributing T helper-1 (Th1) and T helper-2 (Th2) cells by producing proinflammatory cytokines, such as IL-17, IL-21, IL-22, and IL-6.[39]

The role of hypertension in the severity of COVID-19 is still unclear. However, some studies suggested the probability of this mechanism (Table 2). COVID-19 patients with previous history of hypertension have been shown to worsen the prognosis of COVID-19. Bai et al illustrated that critical COVID-19 patients were mostly caused by hypertension.[40] COVID-19 patients with hypertension have a higher D-dimer level and persistent viral shedding.[41] Immune system dysregulation is one of the pathways that make the prognosis of COVID-19 poor in hypertension.[42] One study suggested that IL-6 could cause hypertension by increasing blood pressure.[29] Interestingly here, the cytokine IL-6 significantly plays a role in exacerbating the immunological and inflammatory reactions of COVID-19 infection.[43] IL-6 is considered one of the most important pro-inflammatory cytokines involved in the development of cytokine storms and complications such as acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and multi-organ failure (MOF).[44] IL-6 increases the risk of COVID-19 mortality by stimulating the acute phase response, specific immune reactions, and hematopoiesis.[44] A prospective cohort study involving 102 COVID-19 patients from Renmin Hospital, Wuhan, China, compared with 45 healthy controls, described that IL-6 and other pro-inflammatory cytokines were higher in COVID-19 patients than controls.[45]

Individuals with hypertension have deregulation of CD4+ and CD8+ lymphocytes.[46] A descriptive study confirmed that lymphopenia could predict COVID-19 severity, poor clinical outcomes, and death.[47] Similarly, immunosenescent CD8+ T cells failed to be activated during viral infections in hypertensive patients, which may explain the COVID-19 prognosis in hypertensive patients.[46] Harrison et al. showed that antigen-presenting cells, namely macrophages and dendritic cells, were believed to present neo-antigens causing activation of T cells, which produce pro-inflammatory cytokines with successive development of hypertension.[48] In patients with COVID-19, there is an activation of T and B cells with excessive immune response leading to severe complications due to higher release of pro-inflammatory cytokines accompanied by the development of a cytokine storm.[49] Abnormal immune responses to COVID-19 may be a potential mechanism that worsens the prognosis of patients with pre-existing hypertension.[50]

Additionally, COVID-19 patients with underlying comorbidities, including hypertension, are associated with reduced SARS-CoV-2 viral clearance.[51] Trump et al., observed that hypertension might delay SARS-CoV-2 clearance and exacerbate lung inflammation in COVID-19 patients due to the abnormal immune response and airway inflammation in hypertension.[52] Therefore, hypertension by delaying SARS-CoV-2 clearance may worsen the prognosis of COVID-19 patients.

3.2 Potential of Metformin to Decrease Blood Pressure in Hypertensive Patients

Metformin was found to be able to activate AMPK which has the potential as an anti-hypertensive agent (Table 1). AMPK is a serine/threonine protein kinase that plays an important role in various pharmacological activities of metformin, especially in regulating blood pressure.[17] Activation of AMPK by metformin can boost NO production in vascular endothelial cells.[53]

Increasing blood pressure because of sodium retention in some cases of hypertension can be reduced by giving metformin, which can stimulate sodium excretion. In addition, AMPK activation may interfere with renal sodium reabsorption by regulating several sodium transporters, such as NKCC2 and NaKATPase. AMPK expression has the potential to down-regulate blood pressure in hormonal mechanisms. AMPK will induce ACE2 and prevent the occurrence of hypertension due to the RAAS system.[17]

The anti-inflammatory effect of metformin has been shown to decrease IL-6 through activation of the AMPK pathway.[54] Moreover, metformin can suppress the expression of IL-1β, IL-8, and TNF-α produced by

macrophages.[55] Metformin, which activates AMPK signaling, can also as an antioxidant by reducing reactive oxygen species (ROS) in conditions of oxidative stress.[56] The antioxidant effect of metformin through the activation of antioxidant systems, such as superoxide dismutase (SOD), uncoupling protein 2 (UCP2), and nuclear factor erythroid-2-related factor (NRF2) in reducing ROS.[57] In addition, AMPK activation can inhibit the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH), which is a major source of ROS.[58]

Improving vascular function in insulin resistance due to type 2 DM patients is one of the metformin's mechanisms for decreasing blood pressure.[59] In this situation, vasoconstriction due to insulin resistance can be reduced by giving metformin. Metformin administration improves autonomic nervous system imbalance, which is a neural mechanism in the pathophysiology of hypertension.[60]

Based on the various pharmacological activities of metformin, the activation of AMPK signaling by metformin has the potential to reduce blood pressure in hypertensive patients. A retrospective cohort study proved that the use of metformin could reduce the risk of hypertension in patients with type 2 diabetes.[61] Moreover, a meta-analysis study showed that metformin could reduce systolic blood pressure.[62]

Table 1. Overview of the mechanism of metformin via AMPK pathway and their relationship to decrease blood pressure

Previous Studies	Pathways	Metformin's mechanism of action
Tain et al.[17] *Int. J. Mol. Sci.*	Hormonal mechanism	AMPK would induce ACE2 and reduce blood pressure by inhibiting the RAAS system
Luo et al.[32] *Cell Discov*	Vascular mechanism	Vasodilatation because of increasing nitric oxide in vascular
Ursini et al.[55] *Front. Immunol.*	Immunology mechanism	The anti-inflammatory effect of metformin could decrease the level of IL-1β, IL-8, and TNF-α produced by macrophages
Liu J et al.[59] *Am J Physiol Endocrinol Metab*	Insulin resistance mechanism	Improving vascular function in insulin resistance
Tain et al.[17] *Int. J. Mol. Sci.*	Renal mechanism	AMPK might inhibit renal sodium reabsorption by regulating several sodium transporters, such as NKCC2 and NaKATPase
Franco CCDS et al.[60] *Front Endocrinol (Lausanne)*	Neural mechanism	Metformin improved autonomic nervous system imbalance

AMPK, activating AMP-activated protein kinase; ACE2, angiotensin-converting enzyme 2; RAAS, renin-angiotensin-aldosterone system; IL-1β, interleukin-1β; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α; NKCC2, Na-K-2Cl cotransporter; NaKATPase, Na+/K+-ATPase.

3.3 Potential of Metformin on Improving the Prognosis of COVID-19 Patients with Hypertension

The potential of metformin to improve the prognosis of COVID-19 patients with hypertension because of the cytokine storm process is shown in Figure 1. Activation of AMPK can inhibit the release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, to reduce the effects of the cytokine storm.[18] Metformin, which acts as an immunomodulator, may prevent the formation of proinflammatory cytokines by inhibiting the formation of NETs. The effect of metformin in suppressing cytokine storm also be through an inhibitory mechanism of Th1 and Th17 cell pathogenesis.[15]

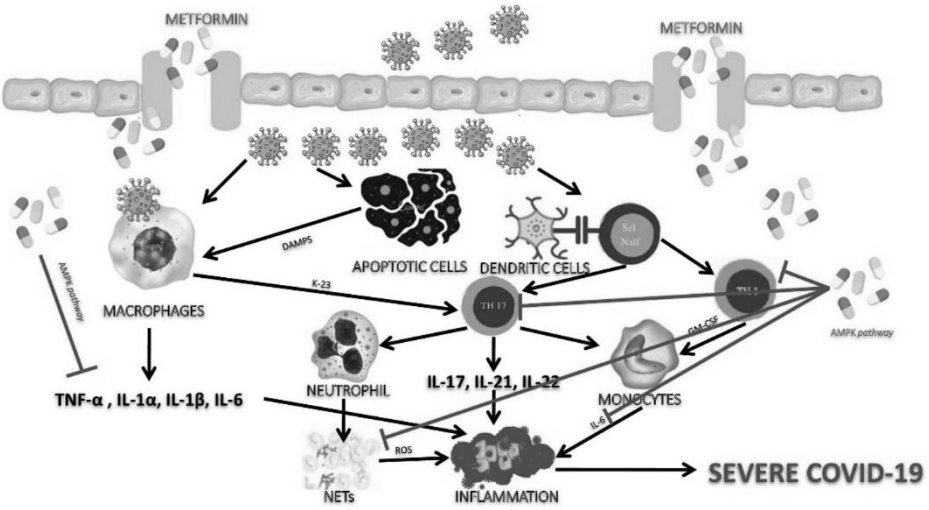

Figure 1. The role of metformin in preventing the severity of COVID-19 patients due to the cytokine storm process. *IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-17, interleukin-17; IL-21, interleukin-21; IL-22, interleukin-22; AMPK, AMP-activated protein kinase; DAMPS, Damage-associated molecular pattern molecules; ROS, reactive oxygen species; GM-CSF, Granulocyte-macrophage colony-stimulating factor; NETs, Neutrophil extracellular traps.*

Some studies showed that metformin could reduce the mortality rate in COVID-19 patients (Table 2). Two systematic reviews and meta-analyses showed that metformin was significantly associated with lower COVID-19 mortality.[63,64] Moreover, some cohort retrospective studies showed that metformin also decreased the mortality of COVID-19 patients.[65–67] A study suggested that metformin could improve acute lung injury by suppressing the inflammatory effect through the activation of AMPK signaling.[18] Based on these results, metformin has a beneficial effect on improving the prognosis for COVID-19.

Table 2. The Potential of Metformin on Improving the Prognosis for COVID-19 Patients

Author	Methods	Finding
Li, Y, et al. (2021)[64]	19 studies with 2,903,435 patients were used for the meta-analysis of the association between metformin use and risk of mortality	Metformin was associated with 34% lower COVID-19 mortality [odds ratio (OR), 0.66; 95% confidence interval (CI), 0.56–0.78; I^2 = 67.9%] and 27% lower hospitalization rate (pooled OR, 0.73; 95% CI, 0.53–1.00; I^2 = 16.8%)
Lukito, AA, et al. (2020)[63]	A systematic review and meta-analysis: nine studies with 10,233 subjects were included in the qualitative and quantitative synthesis	Meta-analysis showed that metformin was associated with lower mortality in the pooled non-adjusted model (OR 0.45 [0.25, 0.81], p = 0.008; $I^{2:}$ 63.9%, p = 0.026) and pooled adjusted model (OR 0.64 [0.43, 0.97], p = 0.035; I^2: 52.1%, p = 0.064).
Lalau, J-D, et al. (2020)[67]	Cohort retrospective: 2449 patients with diabetes hospitalized for COVID-19 were recruited to compare the major outcomes (tracheal intubation and/or death within 7 days of admission) between metformin users and patients without metformin	The mortality rate was lower in metformin users on day 7 (8.2 vs 16.1%, $p < 0.0001$) and on day 28 (16.0 vs 28.6%, $p < 0.0001$)
Luo, P, et al. (2020)[65]	Cohort retrospective: 283 patients with confirmed COVID-19 (104 in the metformin and 179 in the no-metformin group) were included in	The mortality of 2.9% (3/104) in the metformin group was markedly decreased compared with the mortality of 12.3% (22/179) in the no-metformin group (p =

	this study	0.01)
Bramante, CT, et al. (2021)[66]	Cohort retrospective: 6256 of the 15.380 patients with confirmed COVID-19 were used to analyze hospital mortality from COVID-19 with and without metformin	Metformin was associated with decreased mortality in women by Cox proportional hazards (HR 0·785, 95% CI 0·650–0·951) and propensity matching (OR 0·759, 95% CI 0·601–0·960, *p*=0·021)

Hypertension tends to worsen COVID-19 infection, but metformin can prevent it through several pathways including interrupting the viral life cycle, improving immune dysregulation, and increasing viral clearance (Table 3). Metformin has the effect of an antiviral agent. This antiviral agent is played by AMPK signaling which can inhibit intracellular viral replication.[19] Recent studies showed that metformin reduced significantly SARS-CoV-2 viral load[68] and improved sustained virologic clearance.[69,70]

Table 3. Evidence that metformin does improve the prognosis for COVID-19 patients with hypertension

Pathways	Role of Hypertension on the Severity of COVID-19	Benefits of Using Metformin
Viral lifecycle	Hypertension increased D-dimer levels and persistent viral shedding.[41]	Inhibiting mTOR reducing-viral protein complexes central to viral replication.[19]
Immune dysregulation	▪ Exacerbate COVID-19 cytokine storm conditions due to elevated IL-6.[43] ▪ Deregulation of CD4+ and CD8+ lymphocytes.[46]	▪ Decreased IL-6, TNF-α, and possibly boosts IL-10 as well.[13] ▪ Increasing metformin-mediated glycolytic activity can recover antigen-specific and non-specific cytokine production due to the disturbance of the link between metabolism and immune function in CD8+.[71] ▪ Metformin reduced CD4 T Cell exhaustion in HIV-Infected.[72] ▪ Metformin could educate CD8+ T cells that restrict *Mycobacterium tuberculosis* replication.[73]
Viral clearance	Hypertension reduced SARS-CoV-2 viral clearance.[51,52]	Metformin has been shown to increase sustained virologic clearance[69,70] and decrease viral load.[68]

mTOR, mechanistic target of rapamycin; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

3.4 Safety of Metformin

Metformin is one of the most widely used antihyperglycemic drugs, which is well tolerated and usually does not cause hypoglycemia in diabetic or non-diabetic patients.[74] For these reasons, metformin is a safe therapy for patients with COVID-19. The safety of metformin is also shown in elderly patients. A previous study showed that metformin could reduce the mortality rate of elderly patients with COVID-19.[75] Several

observational cohort studies showed the association between mortality rate from COVID-19 patients and metformin used.[65–67,76] Mortality is common in the elderly with underlying conditions.[77–79] Given the association between mitochondrial function, ion channels including Ca2+ release-activated Ca2+ channels (CRAC), and inflammatory aging, the ability of metformin to target mitochondrial electron transport and prevent ROS/CRAC-mediated IL-6 release may explain the benefits of metformin in suppressing cytokine storm as well as thrombotic processes are the main cause of COVID-19 morbidity and mortality in the elderly.[80]

The potential of metformin to improve the prognosis of COVID-19 patients with hypertension has several advantages. Metformin can phosphorylate ACE2 through the activation of the AMPK pathway, so it can reduce the penetration of SARS-CoV-2 into body cells and reduce the severity of COVID-19 patients.[19] This evidence showed that metformin has no potential to aggravate COVID-19 patients. The most common safety concern is the possibility of lactic acidosis, but this adverse side effect of metformin is rare.[74] Additionally, while metformin does cross the placenta, it appears to be safe and has been used off-label in pregnancy. A randomized control trial found that metformin was associated with a reduced risk of hypertensive disorders of pregnancy in women with obesity or diabetes mellitus.[81]

3.5 Effectiveness of Metformin

A meta-regression study revealed that hypertensive patients in the elderly independently could reduce the prognosis of COVID-19.[82] Evidence showed that the majority of elderly hypertensive patients had isolated systolic hypertension.[83] Interestingly, a meta-analysis showed that metformin could significantly reduce systolic blood pressure without lowering diastolic blood pressure.[62] This is an excess of metformin when given to elderly hypertensive patients.

Metformin has more benefits in patients with obesity. There was a significant relationship between central obesity and hypertension because blood pressure increased following excess body weight.[84] Obesity is a risk factor that can worsen the prognosis of COVID-19 due to inflammatory cytokines associated with obesity in SARS-CoV-2 infection.[85] Sattar et al. proposed that excessive fat deposition and obesity may be potential risk factors in the development of severe COVID-19 due to immune deregulation.[86] Both obesity and hypertension are interrelated in the development of COVID-19 severity due to impairment of immune response, pro-inflammatory status, and coagulation/prothrombotic disturbances that trigger more severe complications in hypertensive COVID-19 patients with obesity.[87] Activation of adipose TNF-α signaling pathway plays an important role in obesity-related hypertension.[88] Based on this pathogenesis, metformin can suppress TNF-α, which plays an important role in obesity-associated hypertension.[13]

Another effectiveness of metformin is its anti-glycemic effect, which has become a patent medicine for type 2 DM.[12] In a study conducted on a sample of COVID-19 patients with diabetes, the use of metformin was significantly associated with a lower risk of total death (OR 0.70; 95% CI 0.66-0.75), in-hospital mortality (OR 0.68; 95% CI 0.63-0.73), hospitalization for COVID-19 (OR 0.86; 95% CI 0.81-0.91), and ICU admission (OR 0.81; 95% CI 0.69-0.94) compared with patients who did not use metformin.[89] A retrospective cohort analysis from the United States including people with type 2 DM or obesity (2333 metformin users) reported that metformin was associated with significantly less mortality in women, by Cox proportional hazards and propensity matching.[66] The mechanism of metformin to improve the prognosis of COVID-19 in diabetes patients is still unclear. Life-threatening complications and deaths in COVID-19 are associated with an excessive inflammatory response, namely cytokine storm, as well as the incidence of disseminated intravascular coagulation.[90,91] Metformin has anti-inflammatory and antithrombotic effects that may play a role in the immune response to COVID-19. Furthermore, metformin inhibits TNF-α–dependent NF-κB inflammatory signaling, which causes a decrease in the secretion of inflammatory cytokines, such as the chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, IL-1β, and IL-6.[13] We can conclude that metformin administration is very beneficial if the patient has comorbidities such as type 2 DM.

We also examined the effectiveness of the metformin dose used in COVID-19 patients. Previous clinical trial of metformin, researchers used a sample of 421 adults during different waves of SARS-CoV-2 variants to evaluate whether using metformin at a dose of 750 mg twice daily would provide benefit over placebo, including in patients already taking metformin up to 1000 mg metformin for conditions, such as diabetes, prediabetes, weight loss, polycystic ovary syndrome, or non-alcoholic fatty liver disease.[92] Higher doses of metformin may not enhance anti-inflammatory actions, as suggested in recent research on macular

degeneration.[93] No recent study recommended a dose of metformin for COVID-19 patients with hypertension, so further research is needed.

4. Conclusion

Morbidity and severity of COVID-19 patients with hypertension cause the urgency of hypertension therapy in COVID-19 patients at this time. Using ACE-I/ARB anti-hypertensive drugs has the potential to increase ACE 2 expression and will worsen the prognosis of COVID-19 patients. The effect of bradykinin on ACEI use in COVID-19 patients has the potential to trigger a cytokine storm.

Metformin has various pharmacological activities through the activation of AMPK signaling. AMPK activation on metformin can reduce blood pressure through various pathophysiological pathways of hypertension, from vascular, neural, renal, hormonal, immunological, and insulin resistance mechanisms. Moreover, metformin, which activates AMPK signaling, has the potential to improve the prognosis of COVID-19 patients by inhibiting cytokine storms. The use of metformin was found to be able to phosphorylate ACE2 expression through AMPK signaling. In this case, metformin can prevent binding between SARS-CoV-2 and the ACE2 receptor, leading to a better prognosis for COVID-19 patients.

We analyzed the evidence of metformin in improving the prognosis of COVID-19 with hypertension through three pathways including viral lifecycle, immune dysregulation, and viral clearance. Several observational studies showed the beneficial effect of metformin on improving COVID-19 patients. Administration of metformin has an acceptable safety profile in patients with obesity, diabetes, the elderly, and pregnant patients. Further research on the effectiveness of using metformin as anti-hypertensive therapy for COVID-19 patients and in vivo research can be carried out immediately so that clinical trials can immediately be carried out which in turn can be used by the public in the future to improve the prognosis of COVID-19 with hypertension.

Conflict of Interest Declaration

The authors declare that there are no conflicts of interest.

Author Contributions

M.M. and V.E.A.L. designed and drafted the study. M.M. acquired and analyzed data for the study. S.B. as a supervisor and revised the draft critically for important intellectual content. All authors contributed to the final manuscript.

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