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OPINION REVIEW

Rifampicin for COVID-19

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Abstract

Vaccinations for coronavirus disease-2019 (COVID-19) have begun more than a year before, yet without specific treatments available. Rifampicin, critically important for human medicine (World Health Organization's list of essential medicines), may prove pharmacologically effective for treatment and chemoprophylaxis of healthcare personnel and those at higher risk. It has been known since 1969 that rifampicin has a direct selective antiviral effect on viruses which have their own RNA polymerase (severe acute respiratory syndrome coronavirus 2), like the main mechanism of action of remdesivir. This involves inhibition of late viral protein synthesis, the virion assembly, and the viral polymerase itself. This antiviral effect is dependent on the administration route, with local application resulting in higher drug concentrations at the site of viral replication. This would suggest also trying lung administration of rifampicin by nebulization to increase the drug's concentration at infection sites while minimizing systemic side effects. Recent *in silico* studies with a computer-aided approach, found rifampicin among the most promising existing drugs that could be repurposed for the treatment of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Rifampicin; Antiviral activity; RNA polymerase

Core Tip: Rifampicin may prove pharmacologically effective, supplying a possible and cost-effective solution to the global battle against severe acute respiratory syndrome coronavirus 2, not only for treatment but also for chemoprophylaxis of those at higher risk. It is also possible to administer rifampicin by nebulization. The publications describing the *in vitro* mechanisms and providing proof of clinical efficacy of rifampicin against RNA viruses with their own RNA polymerase have emerged since 1969-1971. Recent *in silico* studies using a computer-aided approach, found rifampicin among the most promising existing drugs that can be repurposed for the treatment of coronavirus disease-2019.

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INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic presents a puzzling challenge without specific treatment yet[1], and while vaccinations have been initiated more than a year before[2], there is still a long way to go before herd immunity can be achieved, even in the developed countries[3]. In the critically ill patients, plasma transfusions from recovered patients have been tried[4] and specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) memory T cells could also treat moderate/severe cases of COVID-19[5]. When and with which pharmacological cocktail to intervene is under rigorous investigation worldwide[6]. Chemoprophylaxis of exposed healthcare personnel[7], along with those at higher risk for severe illness, is also equally exigent, at least until sizable worldwide immunization will be achieved[8]. And even if vaccination campaigns do make progress in the Western world, this process may take much longer in the developing countries. Even then, the possible emergence of SARS-CoV-2 new mutated strains could substantially impact the protection of currently available vaccines or the physical immunity acquired from previous illness from the previous SARS-CoV-2 variants[9] (https://theconversation.com/the-lambda-variant-is-it-more-infectious-and-can-it-escape-vaccines-a-virologist-explains-164156).

Rifampicin, discovered in 1965, was marketed in Italy in 1968, and approved in the United States in 1971. It is on the World Health Organization's (WHO) list of essential medicines, classified by the WHO as critically important for human medicine. Made by the soil bacterium *Amycolatopsis rifamycinica*, rifampicin is widely available as a generic medication with an extremely low cost compared to any other modern antiviral medication. It belongs to the *Rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses[10]. While in the fourth wave of this pandemic, without specific medications available yet, along with the ongoing computational analysis of potential drugs[11], it becomes clearer that - at least for now and beyond active immunization - we still need to rely on one hand on the enhancement of our immune system and on the other hand on the known anti-inflammatory and immunomodulatory effects of some antibacterials and the emerging antiviral effects of old but precious drugs, such as rifampicin. For the first task, which is to strengthen our immunity, adding zinc sulphate increased patients' discharges, decreasing the need for ventilation, intensive care unit admissions, and mortality[12]. Increased intracellular zinc concentrations seem to inhibit RNA-dependent polymerases, helping to support robust immune responses and modulating immune cell activity. For that task, researchers have tried high doses of vitamin C[13]. And last but not least, proper supplementation[14,15] or even adjunctive therapy with vitamin-D[16], to capitalize on its extra-skeletal immunomodulatory properties, may also prove valuable, playing a crucial role in enhancing and coordinating the immune system's response to SARS-CoV-2 infection[17,18]. For that purpose, personalized immunotherapy approaches with agents/monoclonal antibodies that block receptors for interleukin-1/6 have been initiated, aiming to control the macrophage activation syndrome which has been suggested as a major mechanism of lung impairment in COVID-19[19]. Monoclonal antibodies have shown promising results, with prompt administration though being a key issue to exert their benefit[20]. Bamlanivimab, a neutralizing monoclonal antibody against SARS-CoV-2, reduced the incidence of COVID-19[21].

Herein, we discuss the possibility of repurposing rifampicin for COVID-19, and we call for immediate coordinated - international if possible - collaboration[22] in *in vitro* studies, open-label pilot trials, and definitive phase 3 clinical trials.

ANTIVIRAL PROPERTIES OF RIFAMPICIN: MECHANISMS AND FACTS

Careful analysis of the COVID-19 clinical characteristics and computed tomography scans indicates that the pulmonary nontuberculous mycobacterial disease, in which azithromycin and rifampicin are among

first line treatment options, seems to share a striking analogy with SARS-CoV-2 pneumonia[23]. Going back to 1969, a conventional antibacterial of proved pharmacological acceptability in man, rifampicin (or rifampin: https://www.accessdata.fda.gov/drugsatfda_docs/Label/2018/050420s077,050627s020Lbl.pdf), was found to have a direct antiviral effect in some mammalian viruses as poxviruses including the causative agent of smallpox and mainly on viruses which have their own RNA polymerase[24], which is the case for SARS-CoV-2 and the main mechanism of action of remdesivir. Initially developed against Ebola, remdesivir raised hope, as it incorporates into nascent viral RNA chains and results in premature termination of viral replication. Remdesivir showed higher recovery and hospital discharge rates, but no significant reduction in mean time to clinical improvement or mortality[25].

Regarding large DNA viruses, the antiviral activity of rifampicin arises from its binding to the F-ring, highly conserved across mammalian poxviruses, which cannot mutate in response to rifampicin inhibition and thus provide a potential base for the development of broad-spectrum inhibitors against infectious poxviruses species in animals and humans[26]. However, the efficacy of rifampicin against viruses with their own RNA polymerase shares the same mechanism with its antibacterial activity against microbial RNA polymerases. The inhibitory mechanism of rifampicin on the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function[27]. The rifampicin molecule is a condensation product of 3-formyl rifamycin SV and 1-amino 4-methyl piperazine with the antiviral activity existing in the rifamycin part of the molecule. Its antiviral effect is reversible as removal of the drug late in the virus cycle leads to a mature and infectious virus even within 1 h. This would mean that careful monitoring of rifampicin levels may assure effectiveness. The selective antiviral effect of rifampicin involves inhibition of late viral protein synthesis[28], virion assembly[29], and the viral polymerase itself[30].

Table 1 summarizes the studies on the possible antiviral properties of rifampicin against SARS-CoV-2 presenting their main findings.

ADMINISTRATION ROUTE AND POTENTIALS

Studies in volunteers have also shown a dependence of rifampicin's antiviral effect on administration route, with local application resulting in higher concentrations of the drug at the site of viral replication [31]. This would suggest trying lung administration of rifampicin by nebulization[32], increasing the drug's concentration at infection sites while minimizing systemic side effects. This approach, using aerosolized rifampicin-loaded polymeric microspheres, reduced most measures of tuberculosis infection in experimental animals[33]. However, since the major cell entry receptor for SARS-CoV-2 is the metallocarboxyl peptidase angiotensin receptor 2[34], whose expression is very low in the lung, the approach of lung administration may not exhibit the expected systemic antiviral effects of rifampicin and requires further investigation.

An effective intracellular concentration of rifampicin without serious toxicity seems possible and probable, given its pharmacokinetic profile, suitable also for chemoprophylaxis (https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin#section=Drug-Classes). Current studies have evaluated intravenous rifampicin 20 mg/kg for 2 wk followed by high dose oral formulation (35 mg/kg for 6-8 wk) for improved survival from adult tuberculous meningitis[35]. Data concerning intracellular rifampicin concentrations to exhibit effective antiviral activity against influenza virus A[36], African swine fever virus[37], and cytomegalovirus[38] have been already available.

IN SILICO STUDIES INDICATE POSSIBLE EFFECTIVENESS OF RIFAMPICIN

The above finding may have just been verified by a recent *in silico* study using a computer-aided drug designing approach: Rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19[39]. Moreover, using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir[40]. Rifabutin, however, belongs to the rifamycins (rifampicin, rifapentine, and rifabutin), but with rifampicin being the most used[41]. *In silico* virtual screening within the United States Food and Drug Administration (FDA)-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, also placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics[42]. Virtual screening of FDA-approved drugs targeting not only the main protease of SARS-CoV-2 but also TNF-α, IL-6, and IL-1β, which are the key molecules involved in the 'cytokine storm' occurring in COVID-19, indicated rifampicin as one of the most promising drugs for the treatment of COVID-19, together with letermovir [43]. These were systematic docking studies, further confirmed by molecular dynamics simulations and molecular calculations; however, such studies are prone to the high probability of artifacts needing experimental verification.

Table 1 Studies on the possible antiviral properties of rifampicin against severe acute respiratory syndrome coronavirus 2

Ref.	Year	Findings
Becker[10]	1976	Rifampicin belongs to the *rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses
[24]	1969	Rifampicin has a direct antiviral effect in mammalian viruses as poxviruses including the causative agent of smallpox and on viruses which have their own RNA polymerase
Campbell *et al*[27]	2001	The inhibition mechanism of rifampicin to the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function
Ben-Ishai *et al*[28], Moss *et al*[29], McAuslan *et al*[30]	1969	Rifampicin inhibits the late viral protein synthesis, the virion assembly, and the viral polymerase itself
Moshkowitz *et al*[31]	1971	Rifampicin's antiviral effect is dependent on the administration route, with local application resulting in higher concentrations at the site of viral replication
Tewes *et al*[32]	2008	Administration of rifampicin by nebulization is possible using aerosolized rifampicin-loaded polymeric microspheres
And *et al*[36]	1980	Intracellular rifampicin concentrations exhibit effective antiviral activity against: Influenza virus A, African swine fever virus and cytomegalovirus
Dardiri *et al*[37]	1971	
Halsted *et al*[38]	1972	

The SARS-CoV-2 RNA-dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs (A-G), and discovered the interactions with rifabutin and rifampicin, among other ligands. Both of them interacted with at least two nsp12 motifs, indicating that they could be both used as inhibitors of SARS-CoV-2 nsp12 protein[44]. Another *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease[45], proposing its use as therapeutic treatment as well as prophylaxis.

Of course, all the above findings require further validation by *in vitro* studies and clinical trials. Table 2 summarizes the *in silico* studies indicating effectiveness of rifampicin against SARS-CoV-2.

DRUG MONITORING AND INTERACTIONS

Experience from coadministration of antitubercular use of rifampicin with antiretroviral therapy may, however, be complicated by drug-to-drug interactions concerning drug metabolism and transport[46], which warrants caution in clinical trials designed to test the efficacy of rifampicin against SARS-CoV-2 in case of co-administration with other drugs that are also metabolized in the liver. A plan is needed to treat COVID-19 in the special group of patients with advanced liver disease[47], as rifampicin is an agonist of the nuclear pregnane nuclear receptor that regulates CYP3A4[48,49], a part of cytochrome P450 enzymes that metabolizes 60% of prescribed drugs. Thus, rifampicin can cause serious drug-to-drug interactions in combination with other medications for COVID-19 treatment. Also, it should be noted that concerning rifampicin, therapeutic drug monitoring is needed when extracorporeal membrane oxygenation is to be used as a life-saving system for critically ill patients with cardiac and/or respiratory failure[50]. The co-administration of plant-derived compounds such as gallic acid and tannic acid, which are effective potentiators resulting in a 4-fold increase in the potency of rifampicin, warrants further study[51]. A known infrequent occurrence, with few cases reported in the literature, of rifampicin-induced pneumonitis mimicking acute respiratory distress syndrome and requiring SARS-CoV-2 testing[52], merits caution. Because of an uncommon immuno-allergic reaction, following intermittent rifampin administration, with disseminated intravascular coagulation including fever, hypotension, abdominal pain, and vomiting within hours of ingestion[53], awareness is warranted for COVID-19 patients suffering from the life-threatening cytokine storm syndrome[54]. Hence, even in the latter case, as in an allergic reaction to rifampicin, apart from targeted anti-cytokine therapy[55], broadly immunosuppressive glucocorticoids would be of value.

SAFETY AND ADVANTAGES OF RIFAMPICIN

Rifampicin is not the only antibiotic that could be repurposed for COVID-19. Quinupristin, for example, is an antibiotic in clinical use for two decades now with minor side effects and has also proven *in silico*

Table 2 *In silico* studies indicating rifampicin's possible effectiveness against coronavirus disease-2019

Ref.	Year	Findings
Mishra *et al*[39]	2020	Using a computer-aided drug designing approach, rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19
Parvez *et al*[40]	2020	Using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir
Forrest *et al*[41]	2010	Rifabutin belongs to the rifamycins (rifampicin, rifapentine and rifabutin); rifampicin is the most used
Pokhrel *et al*[42]	2020	In silico virtual screen within the United States Food and Drug Administration-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics
Pathak *et al*[43]	2021	A similar approach, by targeting the main protease of SARS-CoV-2 but also TNF-α, IL-6, IL-1β, revealed rifampicin as one of the most promising drugs
Elkarhat *et al*[44]	2020	The SARS-CoV-2 RNA dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs, and discovered the interactions with rifabutin and rifampicin, concluding that both could function as inhibitors of the SARS-CoV-2 nsp12 protein
Soni *et al* [45]	2020	An *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease, proposing its use as therapeutic treatment as well as prophylaxis

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

potentially effective against SARS-CoV-2[42]. However, the knowledge and clinical experience as well as the safety profile of rifampicin even in neonates, infants[56], and pregnant woman[57] make a compelling case where alternative therapeutic options are limited. Last, but not least in this instance, the particularly low cost and the potential for worldwide availability of rifampicin as a generic medication may prove a worthy solution, for early intervention protocols against SARS-CoV-2.

RIFAMPICIN IN COVID-19 IN CLINICAL PRACTICE

A recent case report described the favorable outcome under treatment with chloroquine and rifampin of an unusual association of COVID-19, pulmonary tuberculosis, and human immunodeficiency virus infection[58], attributed either to rifampicin inhibiting the formation of mRNA of SARS-CoV-2 and/or the possible synergistic effect of chloroquine and rifampin, despite that anti-tubercular drugs such as rifampicin are powerful enzyme inducers that can reduce the effectiveness of chloroquine. Up to now, there are no clinical studies available on the treatment of COVID-19 patients with rifampicin. Anecdotally, experienced pediatricians have also successfully treated neonates and infants[59] found positive for SARS-CoV-2 with rifampicin, clearly aiming for their protection with their parents suffering overt COVID-19 with an eventful clinical course.

CONCLUSION

Timely administration, though, is important for all current regimens on trial: It must not be too late when treatment starts. Specifically, rifampicin interferes with the viral replication, and thus, early administration after diagnosis of COVID-19 could make a significant difference to its presumed effectiveness against SARS-CoV-2 infection. Similarly, for rifampicin's use for postexposure prophylaxis to people exposed to index cases of invasive meningococcal infection, pre-exposure together with post-exposure prophylaxis could also be a potential strategy, at least for unvaccinated people[60]. The WHO proposed a similar approach for people at elevated risk for infection, before or after exposure, during the influenza pandemic.

Call for studies

Facing this unprecedented global emergency and given the experience, safety, and knowledge behind rifampicin, we call for international collaboration proposing *in vitro* studies, open-label pilot trials, and definite phase 3 clinical trials for testing treatment and chemoprophylaxis efficacy of rifampicin against COVID-19. With all the above compelling evidence, rifampicin merits evaluation against COVID-19.

FOOTNOTES

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MINIREVIEWS

Too hard to die: Exercise training mediates specific and immediate SARS-CoV-2 protection

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Abstract

Several mechanisms may explain how exercise training mechanistically confers protection against coronavirus disease 2019 (COVID-19). Here we propose two new perspectives through which cardiorespiratory fitness may protect against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Physical exercise-activated adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling induces endothelial nitric oxide (NO) synthase (eNOS), increases NO bio-availability, and inhibits palmitoylation, leading to specific and immediate SARS-CoV-2 protection. AMPK signaling also induces angiotensin 1-7 release and enhances eNOS activation thus further mediating cardio- and reno-protection. Irisin, a myokine released from skeletal muscles during aerobic exercise, also participates in the AMPK/Akt-eNOS/NO pathway, protects mitochondrial functions in endothelial cells, and antagonizes renin angiotensin system proinflammatory action leading to reductions in genes associated with severe COVID-19 outcomes. Collectively, all the above findings point to the fact that increased AMPK and irisin activity through exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection. Maintaining regular physical activity levels is a safe and affordable lifestyle strategy against the current and future pandemics and may also mitigate against obesity and cardiometabolic disease syndemics. Move more because a moving target is harder to kill.

Key Words: Adenosine monophosphate-activated protein kinase; Irisin; Physical exercise; Nitric oxide; Endothelial nitric oxide synthase; Severe acute respiratory syndrome coronavirus-2

Core Tip: Increased nitric oxide bio-availability through exercise training-induced activation of the master regulator of metabolism, the energy-sensing cellular enzyme adenosine monophosphate-activated protein kinase and irisin, the fat browning exercise hormone, released from skeletal muscles during aerobic exercise may mediate specific, immediate, and delayed severe acute respiratory syndrome coronavirus-2 protection. Move more because a moving target is harder to kill.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19), has to date (December 2021) infected over 270 million people worldwide and the death tally approaches 5.5 million[1]. Evolutionary evidence supports the survival of the fittest through natural selection for pathogen resistance, with effects mediated through younger age, lifestyle choices and importantly, genetics[2]. Epidemiological data support a lower COVID-19 incidence and severity in children and adolescents[3], individuals with high cardiorespiratory fitness (CRF) and muscle strength[4] as well as certain protective erythropoietin (EPO) augmenting genetic variants[3]. At the other end of the spectrum, inactivity, obesity, insulin resistance, diabetes, and hypertension, are associated with worse SARS-CoV-2 infection course and disproportionate COVID-19 mortality risk[5,6]. Public policies should promote increased physical activity and endeavor to increase the overall physical fitness in society by all available means. This is especially imperative for the population groups associated with worse SARS-CoV-2 prognosis[7]. The scope of this minireview is to focus on the mechanistical perspectives of two novel pathways, namely adenosine monophosphate (AMP)-activated protein kinase (AMPK) and irisin, through which exercise training may mitigate against SARS-CoV-2 infection and improve COVID-19 prognosis.

We conducted a PubMed literature search for publications in the English language since the start of the pandemic until September 2021, using the keywords: "AMPK"; "Irisin"; "physical exercise"; "renin angiotensin system (RAS)"; "angiotensin-converting enzyme 2 (ACE2)"; "nitric oxide (NO)"; "endothelial nitric oxide (NO) synthase (eNOS)"; "beta common receptor (βcR)"; "SARS-CoV-2"; and "COVID-19". We noticed a veritable dearth of publications, especially when the keywords "eNOS", "Irisin", "AMPK" were used in different combinations together with "physical exercise" and "SARS-CoV-2 or COVID-19" which prompted us to focus on AMPK/eNOS and Irisin. Those pathways are known for their cardiometabolic, and vascular protective properties and suggest concrete mechanisms that offer immediate and delayed SARS-CoV-2 protection[8].

HOW DOES EXERCISE IMPROVE IMMUNITY?

Several reviews have described numerous immune mechanisms which may explain how exercise training mechanistically confers protection against COVID-19. First, exercise downregulates the expression/activation of proinflammatory Toll-like receptors (TLR)[5]. Second, exercise training demonstrates an anti-inflammatory cytokine profile with increased levels of anti-inflammatory interleukin (IL)-10, IL-1 receptor antagonist (IL-1ra), and IL-37, which in turn inhibits the TLR-inflammation pathway and counteracts the inflammatory response induced by the inflammasomes[5]. In general, exercise promotes the recirculation of key immune cells and mediates an anti-inflammatory and antioxidant state through multiple mechanisms[5]. Effective rehabilitation programs for sarcopenia, could reduce inflammation and the need for IL-37 to exert its negative feedback to control the release of inflammatory cytokines[9].

NEWER PERSPECTIVES ON EXERCISE PROTECTION IN COVID-19

AMPK

A more specific mechanism with immediate antiviral effects involves AMPK. We propose two new perspectives through which high CRF may protect from SARS-CoV-2. AMPK is an energy-sensing heterotrimeric enzyme, able to detect minute changes in cellular ADP and AMP as well as glucose availability[10]. Located in various cells and organs, AMPK modulates numerous downstream targets through switching phosphorylation on-off, including targets in the RAS[11]. AMPK is activated through several physiological and pathological conditions, such as hypoxia, caloric restriction, and physiological exercise but also *via* certain well known pharmacological agents as metformin, aspirin, canagliflozin, telmisartan, and herbal substances such as resveratrol, berberine, and quercetin[11,12]. Since activating AMPK has been shown to suppresses the Angiotensin II-induced vascular smooth muscle proliferative pathway and improve cardiometabolic disease, we believe that physical exercise-induced AMPK regulation of diverse cellular pathways is a reasonable mechanism in mediating both immediate and delayed SARS-CoV-2 protection (Figure 1)[11,13,14]. Physiological exercise induces AMPK activation as an important molecular mechanism of adaptation after physical activity. AMPK-eNOS phosphorylation-activated formation of NO appears to be a signal that impacts metabolic activity[15]. Mice with an eNOS mutation that prevents AMPK-dependent phosphorylation and impedes NO-biosynthesis develop hyperinsulinemia and insulin resistance with high fasting blood sugar, increased adiposity, elevated inflammatory markers and weight gain when fed a high-fat diet[16]. eNOS phosphorylation through AMPK will lead to increased NO generation and NO bio-availability in the lung and blood vessels[17]. Host endothelium is where the critical COVID-19 battle between SARS-CoV-2 and the host is fought with NO as one of the main contenders (Figure 1)[18]. SARS-CoV-2 spike (S) protein induces endotheliitis *via* downregulation of angiotensin-converting enzyme 2 (ACE2) and NO impairment[18]. At the same time, increased generation and bio-availability of NO inhibits SARS-CoV-1/2[19] replication through two clearly different mechanisms: (1) Decline in the production of viral RNA in the very first stages of viral replication; and (2) decrease in the palmitoylation of nascently-expressed S protein that impacts the fusion of the S protein with ACE2[20]. Similar NO effects are presumed for SARS-CoV-2, given both SARS-CoV-1/2 engage ACE2 in the same manner[21]. Palmitoylation of SARS-CoV-2 S protein is critical in controlling membrane fusion and virion infectivity[22]. Inhibition of acetyl-CoA carboxylase by AMPK will directly inhibit palmitate synthesis thus engendering additional SARS-CoV-2 protection[23]. In addition, orlistat, a pharmaceutical substance used in weight loss treatment also inhibits fatty acid synthase[23]. Through both mechanisms of increased NO bio-availability and directly reducing palmitate synthesis, physical exercise engenders specific and immediate SARS-CoV-2 protection[20,22,23].

Chronic exercise induces EPO elevation, a well-known neuroprotective hormone, which mediates COVID-19 protection[3]. EPO's protective effects are mediated through AMPK-dependent signaling, leading to enhanced phosphorylation of the beta common receptor (βcR) and eNOS, increased βcR-AMPK-eNOS complex formation, NO production, increased NO bio-availability, and ultimately tissue protection (Figure 1)[24]. Elevated, protective EPO mRNA levels were recently reported to be 2.6 times higher in nasopharyngeal swab samples of adult SARS-CoV-2 patients that were asymptomatic or showing mild COVID-19 symptoms, as compared to a control group[25]. Patients with acute respiratory distress syndrome (ARDS) in a moderate-sized COVID-19 cohort showed lower soluble eNOS levels, implying that greater eNOS activity and the presumed increased NO synthesis probably prevent patients from serious lung complications[26]. Fluvoxamine, intensely investigated as a SARS-CoV-2 protective agent, also mediates its action through sigma-1 receptor (S1R) agonism that induces eNOS, albeit *via* phosphatidylinositol-3-kinase and protein kinase B signaling[27].

Moreover, AMPK signaling exerts beneficial effects through RAS by elevating the protective arm of ACE2 and angiotensin (Ang) 1-7 through the Mas receptor (MasR) (Figure 1)[11]. Phosphorylation of ACE2 by AMPK enhances the stability of ACE2 and increases Ang 1-7 and eNOS-derived NO bio-availability further sustaining increased, protective NO levels[28]. Reduced inflammatory responses in lung emphysema, mitigation of pulmonary hypertension and protection against lipopolysaccharide-induced acute lung injury and ARDS have been reported with increased AMPK signaling[28-30]. Later in the course of SARS-CoV-2 infection, AMPK/ACE2/Ang 1-7/MasR-induced NO-increase may be cardio-, and renoprotective through lower oxidative stress, apoptosis, and systemic inflammatory responses[11,31].

Irisin perspectives in COVID-19

Irisin is a myokine, cleaved as a peptide hormone of 112 amino acids from fibronectin type III domain containing 5 in skeletal muscle and secreted during aerobic exercise[32]. Irisin is positively correlated with an active lifestyle and vigorous intensity physical activity[32]. Both aerobic and resistance exercise are associated with high irisin levels, especially in older age groups[32]. Irisin is involved in muscle hyper-trophy and controls energy levels in muscle, participates in glucose homeostasis and browning of white adipose tissue, and has been implicated in exercise-induced neuroprotection as it is highly expressed in the brain[33,34]. Furthermore, exercise-derived irisin reduces arterial stiffness and lowers

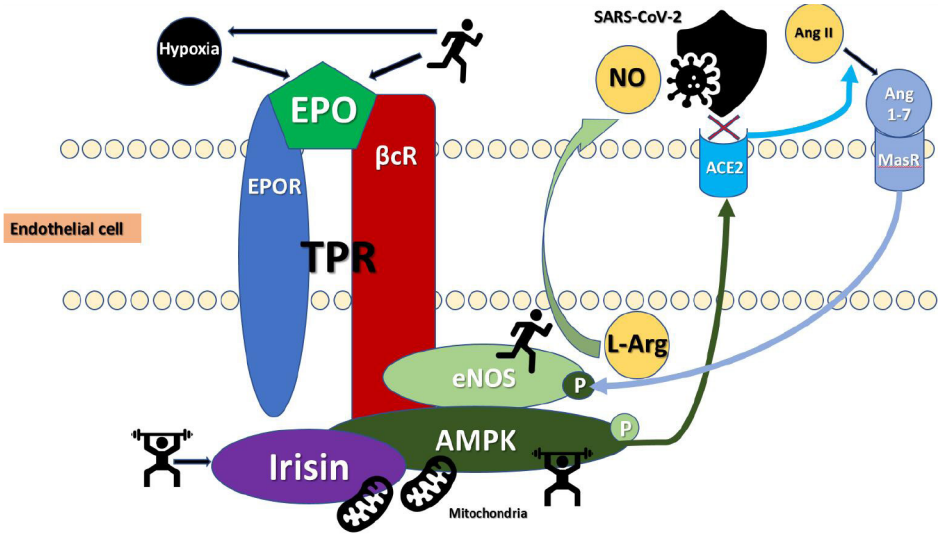

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Figure 1 Molecular mechanisms of exercise. Chronic exercise induces transient hypoxia and elevates erythropoietin (EPO) that induces endothelial nitric oxide synthase (eNOS) *via* the tissue protective receptor (EPOR/βcR). Exercise activates adenosine monophosphate-activated protein kinase (AMPK) and releases Irisin, resulting in eNOS activation and subsequent nitric oxide production inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication and mitigating cell entry (X). AMPK stabilizes angiotensin-converting enzyme (ACE) 2 and increases protective angiotensin (Ang) 1-7 conversion which in turn activates eNOS *via* the MasR. Irisin also exerts protective functions on mitochondria. AMPK: Adenosine monophosphate-activated protein kinase; EPO: Erythropoietin; EPOR: EPO receptor; βcR: β-common receptor; TPR: Tissue protective receptor; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; L-Arg: Arginine; ACE2: Angiotensin-converting enzyme 2; Ang II: Angiotensin II; Ang1-7: Angiotensin 1-7; MasR: Mas receptor; P: Phosphorylation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

blood pressure through activation of the AMPK/Akt-eNOS/NO pathway and has thus the potential to impact cardiovascular health (Figure 1)[8,35]. Irisin also protects mitochondrial function in endothelial cells and benefits endothelial barrier integrity through the integrin αVβ5 receptor and activated AMPK signaling[36]. Moreover, irisin can directly antagonize Ang II-induced cardiac profibrotic response *in vitro* as well as *in vivo*[37]. In addition, serum irisin levels were decreased and negatively correlated with disease severity and mortality in ARDS patients[36]. Recently, irisin modulation of genes associated with severe COVID-19 outcomes was reported in human subcutaneous adipocyte cell culture[38].

Collectively, all the above findings point to the fact that increased AMPK and irisin activity with exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection.

CONCLUSION

Evolution arms us with ingenious and adaptive defense structures - our immune system, musculature, and cardiovascular system. Increased CRF through regular aerobic exertion and resistance exercise, greatly benefits all the above systems promoting survival and longevity[5]. Regular physical exercise enhances vaccination response and immunoprotection[5]. Maintaining regular physical activity levels along with prudent and balanced nutrition are safe and affordable lifestyle strategies against the current and future pandemics. Physical exercise may also reverse insulin resistance, alleviate hypertension, and mitigate against obesity and cardiometabolic disease syndemics[39]. While observing social distancing, exercise is still possible in public indoor spaces or outdoors. Exercise prescription for vulnerable groups and free or subsidized use of digital technology with online platforms delivering exercise classes could be employed to achieve the recommended exercise guidelines. For greater health benefits, 300 min of aerobic activity is recommended along with strength training exercises for all major muscle groups at least two times a week[40]. "Work from home" directives along with time savings from daily commuting have potentially freed up time for exercise that can be achievable in the home environment. The beneficial effects of exercise training in communicable and non-communicable disease prevention must remain central when deciding appropriate public health policies and subsidies. Government bodies should heed the Damoclean warning in this pandemic of the excess mortality threatening over 500 million people affected with obesity and diabetes worldwide or risk new hecatombs. We may have to learn to live with the virus for many years to come. It is thus imperative, on an individual level, to devise personal strategies for exercise training that do not depend on access to public gymnasiums. The takeaway message is once again to move more because a moving target is harder to kill.

FOOTNOTES

Author contributions: Papadopoulos KI had the original idea on the hypothesis concept and composed the manuscript; Sutheesophon W and Aw TC assisted in literature search, and all have made substantial, direct, and intellectual contributions to the work; all authors critically assessed the manuscript and approved it for publication.

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LETTER TO THE EDITOR

Therapeutic potential of N-acetyl cysteine during COVID-19 epoch

Ajita Kapur, Munish Sharma, Geetanjali Sageena

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Abstract

N-acetyl cysteine (NAC) is a promising drug for prophylaxis and treatment of coronavirus disease 2019 (COVID-19) based on antioxidant and anti-inflammatory mechanisms. Further studies with cautious approach are needed to establish the benefits and risks before considering NAC as an adjuvant treatment for COVID-19.

Key Words: N-acetyl cysteine; COVID-19; Coagulopathy; Therapeutic potential; Prophylaxis; Treatment

Core Tip: Risk of coagulopathy is noteworthy in coronavirus disease 2019 (COVID-19) and cerebral hemorrhage could be a potential risk in COVID-19 patients receiving N-acetyl cysteine (NAC). Results of well-designed randomized controlled trials should be awaited before NAC becomes a common practice for prophylaxis and treatment of patients with COVID-19.

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TO THE EDITOR

The impact of coronavirus disease 2019 (COVID-19) pandemic resulting in substantial mortalities and morbidities has driven the quest to accelerate the treatment options for containment of this public health emergency. We read with interest the review by Dominari *et al*[1]. The authors have reviewed the pharmacology, efficacy, and safety of N-acetyl cysteine (NAC) as an adjuvant therapy of COVID-19. NAC is a nutraceutical precursor of vital antioxidant glutathione. Based on a broad range of antioxidant and anti-inflammatory mechanisms, NAC seems to be a promising drug to attenuate the risk of developing COVID-19, and in high doses might play an adjuvant role in the treatment of severe COVID-19 and alleviate its fatal complications[2]. We agree with author's insight that NAC is a worthy candidate to be evaluated for COVID-19; however, we consider that a cautiously optimistic approach is required to assess the risk–benefit profile of this medication in the current scenario.

Patients with COVID-19 suffer from coagulopathy and prolonged prothrombin time (PT)[3]. Hypercoagulation due to elevated D dimer and fibrinogen could lead to ischemic stroke in COVID-19 patients. Though less common, intracerebral haemorrhage resulting from consumption coagulopathy related to fibrinogen depletion has been reported in more than 10% of COVID-19 patients with stroke [4].

As documented in the review, adverse effects from NAC could vary from mild gastrointestinal symptoms to severe anaphylactoid reactions[1]. Abnormal hemostatic activity, such as anticoagulant and platelet-inhibiting properties with increased bleeding risk, has been documented in patients receiving NAC[5]. NAC interacts with human vitamin K epoxide reductase at the same binding site and causes interruption in the vitamin K reduction pathway. A recent study warns regarding prolonged use of NAC in COVID-19 patients and suggests the monitoring of international normalized ratio, PT, and partial thromboplastin time. In addition, considering the lipophilicity, and hence, easy passage of NAC through blood brain barrier, this study cautioned about the risk of cerebral hemorrhage in COVID-19[6].

The possible benefits of NAC in COVID-19 seem to outweigh the risks, but an important issue plaguing the usefulness of NAC is its uncertain efficacy in mild cases[7] and potential of unregulated use in the current scenario where there are limited drugs available for the management of COVID-19. Hence, as is rightly stressed upon by the author[1], before the use of NAC in COVID-19 spreads, further research is warranted to avoid another failure story[8]. Clinical trials are already underway to establish efficacy of NAC in COVID-19[9,10], and recent review by Wong *et al*[11] (2021) elaborated the potential role of NAC as adjunctive remedy for COVID-19[11]. However, there is no in vivo research to specifically examine its effects in COVID-19.

A retrospective cohort study of hospitalized patients with moderate or severe COVID-19 pneumonia documented lower risk of progression to serious respiratory failure in patients treated with NAC[12]. However, we would like to emphasize that the results of the randomized controlled trials should be awaited before incorporating NAC to improve prognosis and clinical outcomes in the treatment of COVID-19.

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LETTER TO THE EDITOR

Bacterial and fungal co-infection is a major barrier in COVID-19 patients: A specific management and therapeutic strategy is required

Tarun Sahu, Henu Kumar Verma, Lakkakula V K S Bhaskar

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Abstract

Microbial co-infections are another primary concern in patients with coronavirus disease 2019 (COVID-19), yet it is an untouched area among researchers. Preliminary data and systematic reviews only show the type of pathogens responsible for that, but its pathophysiology is still unknown. Studies show that these microbial co-infections are hospital-acquired/nosocomial infections, and patients admitted to intensive care units with invasive mechanical ventilation are highly susceptible to it. Patients with COVID-19 had elevated inflammatory cytokines and a weakened cell-mediated immune response, with lower $CD4^+$ T and $CD8^+$ T cell counts, indicating vulnerability to various co-infections. Despite this, there are only a few studies that recommend the management of co-infections.

Key Words: COVID-19; Co-infection; Bacterial co-infection; Fungal co-infection

Core Tip: The immune systems of coronavirus disease 2019 patients are already compromised, making them vulnerable to bacterial, fungal, and viral co-infections. These secondary infections, also known as co-infections, are hospital-acquired/nosocomial infections, and mechanically ventilated patients are especially vulnerable. There are no specific guidelines or treatment options for these types of co-infections at the moment, which is contributing to an increase in morbidity and mortality among these patients.

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TO THE EDITOR

The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China, in December 2019, and the World Health Organization declared it a pandemic in March 2019. Approximately one-third of patients experienced severe complications of COVID-19 and required hospitalization[1]. Recently, secondary bacterial/fungal infections or co-infections are another major concern in COVID-19 patients, impacting mortality but lacking attention. Less evidence of bacterial and fungal infection was documented in earlier coronavirus pandemics and epidemics, such as severe acute respiratory syndrome (SARS)-1 and Middle East respiratory syndrome[2]. Recently, we have seen a paper by Saeed *et al*[3] entitled "Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain"[3] in your well-regarded journal *World J Virol*. We appreciate the work done by Saeed *et al*[3] as they reported the microbial infections in patients with COVID-19 in the Kingdom of Bahrain.

The most common bacterial species they reported were *K. pneumonia, P. aeruginosa, A. baumannii, E. coli, S. aureus, E. faecalis,* and *E. faecium*. Among all of these, hospital-acquired (HAI)/nosocomial infection was higher (73.8%) than community-acquired infection. Similar results were reported by Mahmoudi[4] and Sharifipour *et al*[5] in the neighboring country Iran. Both authors reported the same species of bacterial strains, which are the most common. Later on, a descriptive study conducted in the United Arab Emirates found bacterial co-infection in patients with COVID-19 and especially *Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus,* and *Acinetobacter baumannii* were most predominant strains[6]. The recent reviews and meta-analysis also show that *Klebsiella pneumonia, Haemophiles influenzae, Streptococcus pneumoniae,* and *Staphylococcus aureus* are the most frequently identified bacteria among co-infected patients[7,8]. A unique case series from Saudi Arabia reported Middle East respiratory syndrome coronavirus co-infection in 12% of patients already suffering from severe acute respiratory syndrome coronavirus 2[9]. At the same time, another case series from Saudi Arabia by Shabrawishi *et al*[10] reported 7 cases of COVID-19 and tuberculosis co-infection[10]. The interesting results of Hashemi *et al*[11] showed influenza A (H1N1) virus, human metapneumovirus, bocavirus, adenovirus, respiratory syncytial virus (RSV), and parainfluenza viruses in 105 dead patients with COVID-19 in northeastern Iran[11].

Other than bacteria, fungal and viral co-infections are also severe issues with COVID-19 patients. In the present article, the authors reported fungal co-infection in about 10% of total microbial co-infection. The most common isolated fungi were *Candida galabrata, Candida tropicalis, Candida albicans,* and *Aspergillus fumigatus*. They also found that the death rates in patients with fungal co-infection were very high (70.4%)[3]. Studies from other different regions found aspergillosis or invasive candidiasis as the common fungal co-infections[12]. In contrast, influenza type A, type B, and RSV were the most common viral co-infections in patients with COVID-19[7]. These co-infections are associated with an increased probability of death. Most of the articles reported that microbial co-infections were HAI/nosocomial infections, similar to Saeed *et al*[3], who found 71% were HAI.

Further, the authors have described well different microbial co-infections in patients of COVID-19. Furthermore, the study has some limitations, such as the authors not providing any treatment or management options for COVID-19 infected patients. That is the most crucial concern for the patient's benefit. In this context, we would like to draw your attention to the management and recommendations for the infection. Chedid *et al*[13] reviewed the most common antibiotics used by COVID-19 hospitalized patients, primarily in an intensive situation, by analyzing the use of antibiotics in different types of bacterial secondary and co-infection[13].

On the other hand, Sieswerda *et al*[14] gave evidence-based recommendations for antibacterial therapy for secondary microbial and co-infection[14]. Wu *et al*[15] described the management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19[15]. For the treatment of fungal co-infections, Song *et al*[16] suggested the regimen, which is currently in an induction phase and includes amphotericin B deoxycholate and flucytosine, followed by (1) Fluconazole; alternative options for fluconazole + flucytosine or amphotericin B deoxycholate +

fluconazole; (2) Consolidation phase for fluconazole; and (3) Maintenance (or secondary prophylaxis) phase for fluconazole[16].

Depending upon disease severity, patients with influenza A or B viral co-infection should be treated with oseltamivir or its substitute[17]. Treatment options for other viral co-infection, such as RSV, are restricted and beneficial only in specific circumstances, such as immunosuppression or hypogammaglobulinemia[18,19].

Patients with COVID-19 had elevated levels of inflammatory cytokines and a debilitated cell-mediated immune response, with lower $CD4^+$ T and $CD8^+$ T cell counts, indicating vulnerability to various co-infections. Furthermore, COVID-19 patients who are immunocompromised, such as those with extended neutropenia, hematopoietic stem cell transplantation, hereditary or acquired immunodeficiencies, or tumor, are more likely to develop co-infection. Co-infection and superinfection of pathogens in COVID-19 patients is a critical issue as it is difficult to distinguish the associated complications. Specific diagnostic tests should be recommended for proper treatment and management of these infections to reduce morbidity and mortality.

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LETTER TO THE EDITOR

Novel appearance of hyperglycemia/diabetes, associated with COVID-19

Ioannis Ilias

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Abstract

In a recent meta-analysis the prevalence of coronavirus disease 2019 (COVID-19)-associated hyperglycemia was 25%, and that of COVID-19-associated new-onset diabetes was 19%. An association between hyperglycemia or new-onset diabetes and COVID-19 has been suggested. In a recent relevant study of critically and non-critically ill patients with COVID-19, we found that indeed beta-cell function was compromised in critically ill patients with COVID-19 and that these patients showed a high glycemic gap. Nevertheless, one quarter of critically ill patients with no history of diabetes have stress hyperglycemia, a finding which could obscure the prevalence of hyperglycemia or new-onset diabetes that could be attributed to COVID-19 *per se*.

Key Words: Blood glucose; Pandemics; Severe acute respiratory syndrome coronavirus 2; Humans; Hyperglycemia; Hospitalization

Core Tip: An association between hyperglycemia or new-onset diabetes and coronavirus disease 2019 (COVID-19) has been suggested. Nevertheless, one quarter of critically ill patients with no history of diabetes have stress hyperglycemia, a finding which could obscure the prevalence of hyperglycemia or new-onset diabetes that could be attributed to COVID-19 *per se*.

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TO THE EDITOR

We have read with great interest the work by Shrestha *et al*[1] regarding new-onset hyperglycemia/diabetes (DM) in patients with coronavirus disease 2019 (COVID-19). With an erudite meta-analysis the authors found that the pooled prevalence of COVID-19-associated hyperglycemia was 25.23% and that the prevalence of COVID-19-associated new-onset DM was 19.70%[1].

An association between hyperglycemia/new-onset DM and COVID-19 has been suggested[2], *via* decreased insulin secretion and increased insulin resistance[2,3]. In a recent relevant study, of critically and non-critically ill patients with COVID-19, we found that indeed beta cell function (based on glucose and insulin measurements and using the Homeostasis Model Assessment HOMA2 estimate of steady state beta cell function[4]) was compromised in critically ill patients with COVID-19. Furthermore, these patients showed a high glycemic gap (based on admission glucose and glycated hemoglobin measurements)[5]. Nevertheless, we acknowledged that on average, 25% of critically ill patients with no history of DM have stress hyperglycemia[5-7], a finding which could obscure the prevalence of hyperglycemia/new-onset DM that could be attributed to COVID-19 *per se*.

Thus, it would be interesting if the results of the study by Shrestha *et al*[1] were presented separately-if possible-for critically and non-critically ill patients with COVID-19 and compared to non-COVID-19 patients.

FOOTNOTES

Author contributions: Ilias I conceived and wrote this letter.

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