# Management of COVID-19 using metformin: Repositioning against SARS-Cov-2

**Rajesh Kumar[1], Nita Bharti[2], Saurabh Kumar[3], Gian Prakash[4*], Gaurav Bhasker[5], Tarun Kumar[6], Md. Saquib Mokhtar[7], Vijay Prabhu SN[8], Uttoyan Chakraborti[9], Sutanay Bhattacharyya[10]**

[1]Associate Professor, [2,5-10]Senior Resident, [1]Dept. of Nephrology, [1,3-10]V.M.M.C. & Safdarjung Hospital, New Delhi, [2]Medanta The Medicine, Gurugram, Haryana, India

***Corresponding Author: Gian Prakash**
Email: ankurprakash3000@yahoo.com

## Abstract
Metformin is an inexpensive, widely available, safe and well-tolerated drug used for the management of type 2 diabetes mellitus. Its broad spectrum of activities has encouraged researchers to allude its efficacy in treating COVID-19 infection in affected population. Its immunomodulatory effect, ability to reduce tumor necrosis factor-α, increase interleukin-6 and activation of AMP activated protein kinase are key aspects in protection against COVID-19 infection. Studies demonstrate that metformin may help treat deadly virus in the absence of a specific treatment or vaccine. It lowered the death rate of elderly patients with COVID-19, diabetes and obesity through decrease of weight and pneumonia. It has regenerative effect in lung fibrosis, thus benefiting the patients in acute, chronic as well as recovery phases of COVID-19 infection. However, more prospective studies are warranted to explore its precise mechanism and efficacy in diverse population. The current review provides an overview of cost-effective metformin's role in treatment or prophylaxis of COVID-19 due to its anti-viral property.

**Keywords:** Inexpensive, Interleukin-6, Pneumonia, Tumor necrosis factor-α, Virus.

## Introduction
The COVID-19 pandemic associated with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a ribonucleic acid (RNA) virus infection has taken a heavy toll of people all over the world; thus, accelerating the research and development towards an effective therapy. The Center for Drug Evaluation and Research (CDER) has taken action to safeguard and endorse public health during the COVID-19 outbreak;[1] while Food and Drug Administration (FDA) has formed a distinct emergency program for possible coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP) that is engaged to move new treatments to patients at the earliest and monitoring their safety and effectiveness. The clinical trials are conducted all over the globe to explore either new drugs or reconsider the established drugs for COVID-19 treatment. Treatments such as anti-viral drugs, gene therapy, immunomodulators and antibodies are being studied widely to learn their usefulness in treating COVID-19.[2]

Although, researchers are engaged in developing new drugs and vaccines, simultaneous efforts are being made to examine and repurpose the established drugs against the COVID-19 infection.[3] Metformin the first line of drug used to treat type 2 diabetes mellitus is one such drug claimed by the researchers to be beneficial in treating COVID-19 infection due to its anti-viral and anti-inflammatory properties; thus, reducing the mortality in such patients. Animal and few clinical reports suggest a reduction in neutrophil count in patients with diabetes, polycystic ovarian disease and myocardial infarction.[4-7] Correspondingly, patients with COVID-19 too have shown elevated levels of neutrophil extracellular traps capable of triggering inflammatory cascade responsible for fatalities in COVID-19.[8,9] It is efficacious in diabetic as well as non-diabetic patients providing with cost-effective alternative to the healthcare sector. Metformin is endowed with several other pharmacological actions including, weight management, amplified fibrinolysis, lowering lipid levels, anti-cancer activity and improved endothelial function.[10-12] Furthermore, metformin provides activity against various pathogens through gut modulating action and AMP-activated protein kinase (AMPK) activation; thus, resulting in broadening of its therapeutic use against pathogenic diseases.[13].

The current review provides an overview of role of the metformin in treatment or prophylaxis of COVID-19 due to its antiviral property. In addition, the cost-effectiveness of metformin over other drugs has been briefly discussed in this review.

### Metformin – clinical profile and mechanism of action
Metformin is a biguanide anti-hyperglycemic obtained naturally. It is commonly used drug having good safety profile, few side-effects and is inexpensive. Originally, metformin was established to treat influenza while lowering blood glucose level was observed as a side effect of this drug. Researchers and Chinese doctors claim that metformin can help defeat the novel coronavirus infection successfully.

### Mechanism of action
This age-old anti-diabetic drug is yet to be understood completely and studies suggest different mechanisms of actions responsible for different pharmacological activities including its action against SARS-Cov-2. Studies indicate that AMP-activated protein kinase (AMPK) activation is chiefly responsible for the metabolic effects of metformin and down streaming effects in Covid-19.[6] However, several studies have further revealed elucidations for the activity and efficacy of metformin due to mitochondrial complex I inhibition and modification of gut microbiota; thus, reducing the inflammation.[14,17] It is also observed to reduce tumor necrosis factor- α (TNF-α) and interleukin-6 (IL-6) while

augments the level of interleukin-10, and these advantageous effects are more prominent in females than males.[6,18-20]

The potential ways in which metformin might cause sex-specific responses in Covid-19 are inhibition of IgE- and aryl hydrocarbon-mediated mast cell activation. The activation of mast cell is an initial indicator of inflammatory response to SARS-CoV-2 and possibly cytokine storm.[21,22] The *in vitro* and *in vivo* studies indicate that metformin might cause virus inhibition, specifically hepatitis C virus. Virus infection affects glucose metabolism resulting in insulin resistance in prediabetic and those with type 2 diabetes and the insulin-sensitizing action of metformin benefits body's anti-virus function.[23] In addition, it reduces inflammation and boosts the immune system by promoting the formation of M2 macrophages, T-regulatory and CD8 memory T cells.[24] It also curbs down the expression of genes encoding cytokines and chemokines associated with inflammatory response.[25] Furthermore, metformin causes autophagy that kills or contains pathogens, controls inflammation, and activates immune response in the host.[26]

**In vitro data**

Gordan et al. conducted computational studies to investigate the antiviral activity of drugs including metformin as an option for repurposing against SARS-CoV-2 and HCoV-OC43. They cloned, tagged and expressed SARS-CoV-2 proteins in human cells and recognized the human proteins that physically interacted with each of the SARS-CoV-2 proteins. In total 66 druggable human proteins were identified that were targeted by 69 drugs, of which 29 drugs are approved by the USFDA.[27] Rodrigo et al. also performed chemoinformatic analyses to test the interaction of commonly prescribed FDA-approved molecules with the SARS-CoV-2 RNA-dependent RNA polymerase or main protease enzymes. This study was conducted to explore reconsidering the drugs including flupentixol, reserpine, fluoxetine, trifluoperazine, sunitinib, atorvastatin, raloxifene, butoconazole, and metformin against COVID-19.[28]

**Pharmacokinetics**

Metformin has a half-life of about 5 h that remains unmetabolized and hence excreted as it is by tubular secretion in the urine.[29] The drug is widely distributed into the intestine, liver, and kidney by organic cation transporters. Studies show variation in trough steady-state metformin plasma concentration indicating a large interindividual variability in its pharmacokinetics. Post 24 h of metformin single dose administration an undetectable blood plasma levels are observed. Metformin is a strongly basic having pKa of 12.4 and predicted to enhance the pH of the acidic vesicles holding viruses that could be an important mechanism of metformin against SARS-CoV-2.[30,31]

**Indications, contraindications and safety profile**

Metformin has some side effects such as heartburn, nausea, bloating, stomachache, muscle pain and potentially fatal lactic acidosis. Lactic acidosis is marked by increased lactic acid levels in the body causing symptoms such as muscle and abdominal pain and respiratory distress. COVID-19 infection too shows lactic acidosis; hence metformin needs to be used cautiously in this condition.[32] It is contraindicated in those with acute renal impairment, those hypersensitive to this drug or having metabolic acidosis or diabetic ketoacidosis.[33]

**Interactions**

It is observed that food decreases the absorption of metformin by 40% and delays the time it takes to reach the maximum concentration in blood (Tmax).[33] The drug interaction studies demonstrate inhibition of metformin uptake when co-administered with proton-pump inhibitors by obstructing OCT1, OCT2, and OCT3. Oral antidiabetic drugs repaglinide and rosiglitazone interfere with metformin transport *in vitro* and H2 blocker cimetidine reduces renal tubular secretion of metformin when co-administered.[34] Animal studies show an increased risk of fatalities when metformin is co-administered with hydroxychloroquine as compared to administration of single drug.[35,36]

**Clinical evidences**

Metformin is also called a magic drug due to its broad spectrum of activities that makes it a potential drug to be used substantially against other diseases, besides being an effective anti-diabetic drug.[37] This drug was explored in search of anti-malarial drug that was observed to have an anti-viral activity and was evidenced to be beneficial in influenza treatment; however, lowering of blood glucose levels was a side effect.[38] Recently, several clinical studies reported the potential efficacy of metformin to have anti-cancer, anti-aging, anti-obesity and anti-inflammatory properties.[39] Additionally, it showed beneficial results in polycystic ovary syndrome, cardiac diseases, metabolic syndrome, and neurological disorders.[40,41] Findings from recent studies prove its unique action in treating autoimmune diseases and lowering of macrophage cytokines synthesis. Apart from its metabolic and neurological actions, findings propose that metformin might exert an inhibitory effect on the virus through elevating insulin sensitivity.[41]

A retrospective cohort study conducted in USA in patients older than 65 years of age with a prior history of diabetes and who were hospitalized with pneumonia demonstrated that former administration of metformin significantly lowered the 30-day mortality in these patients (odds ratio 0.80, 95% confidence interval 0.72-0.88.).[42] Noticeably, advancing age and presence of co-morbidities such as diabetes, asthma, obesity increases the risk towards COVID-19 infection than young and healthy individuals.[43-47] Therefore, the mortality rate of elderly patients with COVID-19 infection is 30-100-fold greater than that of young and middle-aged patients.[48] Investigations in patients with COVID-19 presented with respiratory symptoms, further advancing to acute respiratory disease syndrome (ARDS) that is closely associated with a cytokine storm, in particular IL-6, and metformin can manage these symptoms by reducing the levels of inflammatory mediators as well as controlling the prevailing co-morbidities such as diabetes and obesity.[49] Therefore, metformin can be a supplemental

therapy enabling the lowered death rate of elderly patients with COVID-19, diabetes and obesity through the decrease of weight and pneumonia.

Metformin's effects on the cytokines is sex dependent with favorable effects in female over male mice, particularly for TNF-α. It improves hemodynamic recovery in aging male and female mice after hemorrhage and precisely its cardioprotective and anti-inflammatory effects are gender-dependent.[19] Correspondingly, an observational study was conducted in a series of 6256 patients hospitalized with Covid-19 and had either diabetes or obesity, of which 52.8% were women.[50] The findings of this study showed a significantly lowered mortality (OR 0.792 [0.640, 0.979]) in women suggesting a strong sex-specific response to metformin in COVID-19. It is probably due to TNF-α reduction and boosting levels of IL-10, in females more than males.[51]

A French multicenter observational study in patients with diabetes hospitalized for COVID-19 showed majority (56.6%) received metformin and mortality was higher in patients with lower metformin use. On the other hand, patients receiving medications such as insulin, renin–angiotensin–aldosterone system blockers, β-blockers, loop diuretics and mineralocorticoid-receptor antagonists were found to be associated with early death. However, metformin use was associated with a lowered mortality, probably indicating a less advanced stage of diabetes with fewer comorbidities.[52] Similarly, Chen et al. reported higher levels of albumin and lower urea and IL-6 in metformin users, thus reducing mortality, hospital stay and prognosis as compared to non-metformin users or insulin users.[53]

Metformin being a strong base serve as a regulator of vacuolar ATPase and endosomal Na+/H+ exchangers that exerts a regenerative effect in lung fibrosis, thus benefiting the patients in acute, chronic as well as recovery phases of COVID-19 disease. Additionally, the strong basicity of metformin is predicted to raise the pH of the acidic vesicles containing viruses that seems to be a vital mechanism of metformin against SARS-CoV-2.[31]

Moreover, another large 6-year cohort study conducted in a series of 23,920 patients with asthma and diabetes, showed lower hazard ratio (0.92) of asthma exacerbation, lower hazards of asthma-related emergency department visits (0.81) and hospitalizations (0.67) with implementation of metformin therapy suggesting a possible advantage of metformin in more severe asthma exacerbations.[54] Investigations by Yu et al. showed that metformin inhibited pulmonary oedema, vascular leakage and neutrophil accumulation, and lowered the levels of TNF-α, IL-1β, IL-6 and IL-17 in an ARDS model. Similarly, patients with severe SARS-CoV-2 develop ARDS causing a cytokine storm in response to aberrant immunological response. Further research is needed to establish the role of metformin as a host-directed treatment for severe COVID -19.[55,56]

Insulin resistance impacts sustained virological response and metformin is known to increase the insulin sensitivity. In a randomized controlled study involving 98 patients with genotype 1 chronic hepatitis C and insulin resistance, a combination of metformin, peginterferon alfa-2a, and ribavirin enhanced insulin sensitivity and reinforced the virological response in these patients with a good safety profile.[57]

Another retrospective study from Wuhan, China conducted in hospitalized patients (n=283) showed a decreased mortality (2.9%) in patients treated with metformin compared with diabetics not receiving metformin (12.3%).[58] This suggests metformin's potential to reduce the mortality due to COVID-19 and repurpose it as host-directed therapies for COVID-19 patients with or without diabetes. Metformin can effectively decrease the comorbidity, rate and severity of infections, fatality of SARS-CoV-2 infection, particularly in the high-risk elderly patients being majorly impacted with COVID-19 infection and is a cost-saving geroprotector for prevention of SARS-CoV-2.[59,60] Although reasons are unclear, SARS-Cov 2 is found to be associated with liver impairment or damage and literature has evidenced the liver protection activity of metformin allowing to presume that metformin could offer liver protection in patients with diabetes and infected with COVID-19.[61-65]

Zumla et al. noted that high dose therapy using some drugs such as metformin, glitazone, and atorvastatin are observed to lower immune response and proved to be safe and effective that might be responsible for a reduced mortality rate in COVID-19 [66]. Investigations show that metformin surges the formation of mitochondrial reactive oxygen species and elevates autophagy in macrophages.[67] Experiments in mice confirms that metformin inhibits the level of mitochondrial complex I in the lungs leading to improvement in lung condition.[68]

A meta-analysis was conducted to evaluate the clinical outcomes of metformin in first-trimester of pregnancy. This study encompassed eight studies including 200 women and findings of this analysis showed positive results without any associated incidence of major malformations [OR = 0.50 (95%CI: 0.15, 1.60)].[69] Similarly, Li et al.[70] conducted another meta-analysis in women with gestational diabetes (11 studies, n=2712). The results demonstrated favorable outcomes with metformin that significantly decreased adverse maternal and neonatal consequences mainly gestational high blood pressure, hypoglycemia and neonatal intensive care. Thus, it can be a safe and effective alternative for insulin in women with gestational diabetes that could be promising for pregnant women with COVID-19 infection.

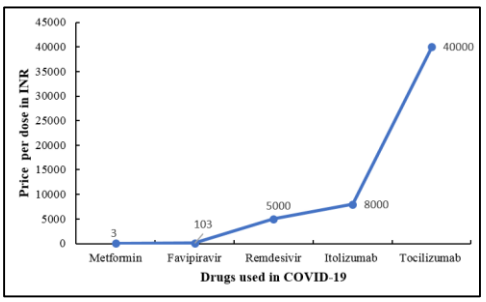


**Figure 1:** Cost differences of currently used drugs to treat COVID-19 patients in India[80]

**Recommendations**

There is a paucity in data supporting the repurposing of metformin in patients severely infected by COVID-19. The current guidelines recommend discontinuation of metformin upon hospitalization. Insulin therapy is preferred over metformin for management of diabetes in patients hospitalized with COVID-19.[71]. Association of British Clinical Diabetologists (ABCD) endorses to stop sodium-dependent glucose cotransporters-2 inhibitors and metformin in all the patients, post-hospitalization and review the safety of other concomitant medications. The researchers are yet struggling with the innovation of therapeutically and economically effective therapy or vaccine and the urgency has endeavored reconsidering the older established drugs together with metformin during the COVID-19 outbreak. Despite limited animal and clinical studies reporting the usage of metformin for treating COVID-19, real world data with regards to its utility and safety is essential for a conclusive judgment. Additional clinical data would aid the national authorities and guidelines to include or propose metformin as an adjuvant therapy for COVID-19 infection.

**Cost implications with usage of metformin**

Along with therapeutic efficacy and safety accompanies the third aspect of successful treatment regimen that is the cost of the drug. The current medications used for COVID-19 treatment are not available in generic form and hence are far more expensive to be affordable for patients belonging to middle/lower socio-economic strata. Thus, during such emergency situations where recommended drugs are unaffordable or inaccessible due to shortage of supply; metformin, the cheapest anti-diabetic drug can be reconsidered as an adjuvant in treating COVID-19. Metformin is well-tolerated by majority of patients and its low price makes it an affordable drug and hence it is covered by Medicare and most insurance plans.[72]

Metformin is widely prescribed in its generic form. In the United Kingdom, a 56-tablet pack of 500 mg dosage costs £1.67; in USA 100 tablet pack of 500 mg is around $8 and in India a 10-tablet pack cost INR 22/-,[73] depending on the pharmacy visited.[74] Hill et al. calculated the production costs and estimated generic prices for 148 drugs on the WHO essential medicine list revealing that most essential drugs can be manufactured at low cost. They reported the average API price per kilogram to be in the range of US$1–US$10/kg for five drugs including metformin. Most importantly, the cost-effectiveness of metformin is linked to the prevention or delay of diabetes-associated complications. Conceivably, the usage of metformin would be of greater cost-effectiveness in metabolically high-risk and non-diabetic recipients to avert the inception of new-onset diabetes after transplantation (NODAT).[75] Drugs including tocilizumab, remdesivir, favipiravir listed in the protocol for clinical management of COVID-19 are either expensive, have broken supply chain, have black markets or associated with side effects.[76] However, the production costs of these drugs were far less than their current prices.[77] Dexamethasone is another low-priced and widely available drug used for COVID-19 treatment; however, its safety concerns does not permit its long-term use.[78,79] These challenges can be overcome by incorporating the dirt-cheap drug, metformin in the therapy to treat COVID-19 infection even in developing and underdeveloped countries.

## Conclusion

The findings from the *in vitro*, animal and clinical studies pertaining to metformin use in COVID-19 indicates its ability to be re-purposed against COVID-19. It has shown favourable outcomes in diabetic and non-diabetic recipients including elderly and pregnant women. Thus, fast-tracking the clinical trials will help to understand metformin's precise mechanism and effectiveness. This will enable to gain approval for its use in the current pandemic for providing the best therapeutic care to the patients.

**Key highlights**

1. Metformin inhibits virus through AMP-activated protein kinase (AMPK) activation, raises the pH of the acidic vesicles containing viruses, reduces inflammation and boosts the immune system; thus, down streaming effects in Covid-19 [6].
2. Prior administration of metformin reduces mortality in patients with pneumonia and has advantage in severe asthma exacerbations.
3. Metformin can be a supplemental therapy enabling the lowered death rate of elderly patients with COVID-19, diabetes and obesity.
4. Metformin is safe and effective alternative for insulin in women with gestational diabetes that could be promising for pregnant women with COVID-19 infection.

## Acknowledgement

All healthcare worker and essential service providers who are providing their services in the name of humanity to save many lives, to control this pandemic and standing on frontline keeping their and their family members life at risk.

## Conflict of Interest

None.

## Funding Support

None.

## References

1. Coronavirus (COVID-19) | Drugs. Available from: https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs. Accessed on 14 September 2020.
2. Coronavirus Treatment Acceleration Program (CTAP). Available from https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap. Accessed on 14 September 2020.
3. Serafin MB, Bottega A, Foletto VS, da Rosa TF, Hörner A, Hörner R et al. Drug repositioning is an alternative for the treatment of coronavirus COVID-19. *Int J Antimicrob Agents*. 2020;55:105969.
4. Soraya H, Rameshrad M, Mokarizadeh A, Garjani A. Metformin attenuates myocardial remodelling and

neutrophil recruitment after myocardial infarction in rat. *Bioimpacts*. 2015;5:3-8.
5. Chen X, Walther FJ, Sengers RM, Laghmani el H, Salam A, Folkerts G, et al. Metformin attenuates hyperoxia-induced lung injury in neonatal rats by reducing the inflammatory response. Am J Physiol Lung Cell Mol Physiol. 2015; 309: L262-70.
6. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. *Circ Res*. 2016;119:652-65.
7. Ibanez L, Jaramillo AM, Ferrer A, de Zegher F. High neutrophil count in girls and women with hyperinsulinaemic hyperandrogenism: normalization with metformin and flutamide overcomes the aggravation by oral contraception. *Hum Rep*. 2005; 20: 2457-62.
8. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. *JCI Insight*. 2020; 5: e138999.
9. Laridan E, Martinod K, De Meyer SF. Neutrophil extracellular traps in arterial and venous thrombosis. *Semin Thromb Hemost*. 2019;45:86-93.
10. Seifarth C, Schehler B, Schneider HJ. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. *Exp Clin Endocrinol Diabetes*. 2013;121:27-31.
11. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug?. *Mol Cancer Ther*. 2010;9:1092-9.
12. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. *J Res Med Sci*. 2014;19:658-64.
13. Malik F, Mehdi SF, Ali H, Patel P, Basharat A, Kumar A, et al. Is metformin poised for a second career as an antimicrobial?. *Diabetes Metab Res Rev*. 2018;34:e2975.
14. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108:1167-74.
15. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60:1577-85.
16. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Manneras-Holm L, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat Med*. 2017;23:850-8.
17. Ouyang J, Isnard S, Lin J, Fombuena B, Marette A, Routy B, et al. Metformin effect on gut microbiota: insights for HIV-related inflammation. *AIDS Res Ther*. 2020;17:10.
18. Kelly B, Tannahill GM, Murphy MP, O'Neill LA. Metformin Inhibits the Production of Reactive Oxygen Species from NADH: Ubiquinone Oxidoreductase to Limit Induction of Interleukin-1β (IL-1β) and Boosts Interleukin-10 (IL-10) in Lipopolysaccharide (LPS)-activated Macrophages. *J Biol Chem*. 2015;290:20348-59.
19. Matsiukevich D, Piraino G, Lahni P, Hake PW, Wolfe V, O'Connor M, et al. Metformin ameliorates gender-and age-dependent hemodynamic instability and myocardial injury in murine hemorrhagic shock. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863:2680-91.
20. Quan H, Zhang H, Wei W, Fang T. Gender-related different effects of a combined therapy of Exenatide and Metformin on overweight or obesity patients with type 2 diabetes mellitus. J Diabetes Complications. 2016;30:686-92.
21. Wang HC, Huang SK. Metformin inhibits IgE- and aryl hydrocarbon receptor-mediated mast cell activation in vitro and in vivo. *Eur J Immunol*. 2018;48:1989-96.
22. Kritas SK, Ronconi G, Caraffa A, Gallenga CE, Ross R, Conti P et al. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *J Biol Regul Homeost Agents*. 2020;34:9-14.
23. Chen Y, Gu F, Guan JL. Metformin Might Inhibit Virus through Increasing Insulin Sensitivity. *Chin Med J*. 2018;131: 376-7.
24. Schuiveling M, Vazirpanah N, Radstake TRDJ, Zimmermann M, Broen JCA. Metformin, A New Era for an Old Drug in the Treatment of Immune Mediated Disease?. *Curr Drug Targets*. 2018;19:945-59.
25. Ba W, Xu Y, Yin G, Yang J, Wang R, Chi S, et al. Metformin inhibits pro-inflammatory responses via targeting nuclear factor-κB in HaCaT cells. *Cell Biochem Funct*. 2019;37:4-10.
26. Yew WW, Chang KC, Chan DP, Zhang Y. Metformin as a host-directed therapeutic in tuberculosis: Is there a promise?. *Tuberculosis (Edinb)*. 2019; 115: 76-80.
27. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, O'Meara MJ, et al. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. Preprint. bioRxiv. 2020; 2020.03.22.002386.
28. Duarte RRR, Copertino DC, Iñiguez, LP, Marston JL, Nixon DF, Powell TR et al. Repurposing FDA-Approved Drugs for COVID-19 Using a Data-Driven Approach. ChemRxiv. Preprint. 2020; chemrxiv.12148764.
29. Graham GG, Punt J, Arora M, Richard OD, Matthew PD, Janna K, et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*. 2011;50:81-98.
30. Krogstad DJ, Schlesinger PH. The basis of antimalarial action: non-weak base effects of chloroquine on acid vesicle pH. *Am J Trop Med Hyg*. 1987; 36: 213-20.
31. Esam Z. A proposed mechanism for the possible therapeutic potential of Metformin in COVID-19. *Diabetes Res Clin Pract*. 2020;108282.
32. Kow CS, Hasan SS. Metformin use amid coronavirus disease 2019 pandemic [published online ahead of print, 2020 May 29]. *J Med Virol*. 2020.
33. GLUCOPHAGE® XR (metformin hydrochloride) Extended-Release Tablets. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf. Accessed on 14 September 2020.
34. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genom*. 2012; 22: 820-7.
35. Montastruc JL, Toutain PL. A New Drug-Drug Interaction Between Hydroxychloroquine and Metformin? A Signal Detection Study. *Drug Saf*. 2020;43:657-60.
36. Rajeshkumar NV, Yabuuchi S, Pai SG, Maitra A, Hidalgo M, Dang CV et al. Fatal toxicity of chloroquine or hydroxychloroquine with metformin in mice. *Biorxiv*. 2020.
37. El-Arabey AA. Update on off label use of metformin for obesity. *Prim Care Diabetes*. 2018;12:284-5.
38. Bailey CJ. Metformin: historical overview. *Diabetologia*. 2017;60:1566-76.
39. Soukas AA, Hao H, Wu L. Metformin as Anti-Aging Therapy: Is It for Everyone?. *Trends Endocrinol Metab*. 2019;30:745-55.
40. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*. 2003;327:951-3.
41. EL-Arabey AA, Abdalla M, Eltayb WA. Metformin: Ongoing journey with superdrug revolution. *Adv Pharm Bull*. 2019;9:1-4.
42. Eric M, Antonio A. Association of metformin and mortality for patients with diabetes who are hospitalized with pneumonia. *Eur Respir J*. 2018;52:PA2639.
43. Riddle MC, Buse JB, Franks PW, Knowler WC, Ratner RE, Selvin E, et al. COVID-19 in People With Diabetes:

Urgently Needed Lessons From Early Reports. *Diabetes Care*. 2020;43:1378-81.
44. Singh AK, Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review. *Diabetes Res Clin Pract*. 2020;165:108266.
45. Matsumoto K, Saito H. Does asthma affect morbidity or severity of COVID-19?. *J Allergy Clin Immunol*. 2020;146:55-7.
46. Flint SW, Tahrani AA. COVID-19 and obesity-lack of clarity, guidance, and implications for care. *Lancet Diabetes Endocrinol*. 2020;8:474-5.
47. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environ Res*. 2020;188:109890.
48. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *J Infect*. 2020;80:e14-8.
49. Lupia T, Scabini S, Mornese Pinna S, Di Perri G, De Rosa FG, Corcione S et al. 2019 novel coronavirus (2019-nCoV) outbreak: A new challenge. *J Glob Antimicrob Resist*. 2020;21:22-7.
50. Bramante C, Ingraham N, Murray T, Marmor S, Hoversten S, Gronski J, et al. Observational Study of Metformin and Risk of Mortality in Patients Hospitalized with Covid-19. Preprint. *medRxiv*. 2020.
51. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. New England Journal of Medicine. 2020. Published online May 15, 2020.
52. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study [published correction appears in Diabetologia. 2020 Jul 2;:]. Diabetologia. 2020;63:1500-15.
53. Chen Y, Yang D, Cheng B, Jian Chen, Anlin Peng, Chen Yang, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care*. 2020;43:1399-407.
54. Wu TD, Keet CA, Fawzy A, Segal JB, Brigham EP, McCormack MC et al. Association of Metformin Initiation and Risk of Asthma Exacerbation A Claims-based Cohort Study. *Ann Am Thorac Soc*. 2019;16:1527-33.
55. Yu LL, Zhu M, Huang Y, Zhao YM, Wen JJ, Yang XJ, et al. Metformin relieves acute respiratory distress syndrome by reducing miR-138 expression. *Eur Rev Med Pharmacol Sci*. 2018;22:5355-63.
56. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet*. 2020;395:e35-6.
57. Yu JW, Sun LJ, Zhao YH, Kang P, Yan BZ. The effect of metformin on the efficacy of antiviral therapy in patients with genotype 1 chronic hepatitis C and insulin resistance. *Int J Infect Dis*. 2012;16:e436-41.
58. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. *Am J Trop Med Hyg*. 2020;103:69-72.
59. Zhavoronkov A. Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. *Aging (Albany NY)*. 2020;12 6492-510.
60. Menendez JA. Metformin and SARS-CoV-2: mechanistic lessons on air pollution to weather the cytokine/thrombotic storm in COVID-19. *Aging (Albany NY)*. 2020;12:8760-5.
61. Doyle MA, Singer J, Lee T, Muir M, Cooper C. Improving treatment and liver fibrosis outcomes with metformin in HCV-HIV co-infected and HCV mono-infected patients with insulin resistance: study protocol for a randomized controlled trial. *Trials*. 2016;17:331.
62. Tai WL, Chang TH, Sun WC, Chan HH, Wu CC, Hsu PI, et al. Metformin activates type I interferon signaling against HCV via activation of adenosine monophosphate-activated protein kinase. *Oncotarget*. 2017; 8: 91928-37.
63. Iranshahy M, Rezaee R, Karimi G. Hepatoprotective activity of metformin: a new mission for an old drug. *Eur J Pharmacol*. 2019;850:1-7.
64. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol*. 2020;8:18-24.
65. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420-2.
66. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses- drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15:327-47.
67. Beigel JH, Nam HH, Adams PL, Krafft A, Ince WL, El-Kamary SS, et al. Advances in respiratory virus therapeutics- a meeting report from the 6th isirv antiviral group conference. *Antivir Res*. 2019;167:45-67.
68. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, et al. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. *Am J Respir Crit Care Med*. 2008;178:168-79.
69. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril*. 2006;86:658-63.
70. Li G, Zhao S, Cui S, Li L, Xu Y, Li Y et al. Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs. *Arch Gynecol Obstet.* 2015;292:111-20.
71. Melillo G. Experts Issue Guidance on Concurrent COVID-19, Diabetes Treatment. Available from: https://www.ajmc.com/newsroom/experts-issue-guidance-on-concurrent-covid19-diabetes-treatment. Accessed on 14 September 2020.
72. Kadanoff M, Hay T. Everything You Always Wanted to Know About Metformin, But Were Afraid to Ask. Available from: https://diatribe.org/everything-you-always-wanted-know-about-metformin-were-afraid-ask. Accessed on 14 September 2020.
73. Drug information on Glyciphage (500 mg) (Metformin) from Franco-Indian Pharmaceuticals Pvt. Ltd. Available from: https://www.medindia.net/drug-price/metformin/glyciphage-500-mg.html. Accessed on 14 September 2020.
74. Metformin Prices, Coupons and Patient Assistance Programs. Available from: https://www.drugs.com/price-guide/metformin. Accessed on 14 September 2020.
75. Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health*. 2018;3:e000571.
76. Bhuyan A. Life-Saving' COVID-19 Drug In Short Supply, Prices Shoot Up. Available from: https://www.indiaspend.com/life-saving-covid-19-drug-in-short-supply-prices-shoot-up/. Accessed on 14 September 2020.
77. Hill A, Wang J, Levi J, Heath K, Fortunak J. Minimum costs to manufacture new treatments for COVID-19. *J Virus Erad*. 2020;6:61-9.

78. Swaminathan S. Dexamethasone: Game-changer in the COVID-19 battle? Available from: https://health.economictimes.indiatimes.com/news/pharma/dexamethasone-game-changer-in-the-covid-19-battle/76817741. Accessed on 14 September 2020.
79. Salim Rezaie. The RECOVERY Trial: Dexamethasone for COVID-19?. Available from: https://rebelem.com/the-recovery-trial-dexamethasone-for-covid-19/. Accessed on 14 September 2020.
80. Murugan PA. How Effective Are the Drugs Approved to Treat COVID-19 Patients in India?. Available from: https://science.thewire.in/health/cdsco-remdesivir-favipiravir-dexamethasone-tocilizumab-itolizumab/. Accessed on 14 September 2020.

**How to cite:** Kumar R, Bharti N, Kumar S, Prakash G, Bhasker G, Kumar T, Mokhtar MS, Vijay Prabhu SN, Chakraborti U, Bhattacharyya S. Management of COVID-19 using metformin: Repositioning against SARS-Cov-2. *IP J Urol Nephrol Hepatol Sci* 2020;3(3):52-8.