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COMMENTARY

Is metformin a miracle or a menace in COVID-19 patients with type 2 diabetes?

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic since March 2020. Diabetes mellitus, especially type 2 diabetes, has been linked to worse COVID-19-related outcomes. It has been shown that glycemic control is important in COVID-19 patients with diabetes. Individuals with well-controlled blood glucose levels had lower mortality compared with those with poor control, and glucose management might potentially influence the prognosis and outcomes of COVID-19 infection. Recommendations from an expert consensus panel on the management of diabetes in patients with COVID-19 have been released. In terms of the choice of glucose-lowering agents, it has been suggested that metformin should be avoided in diabetes patients with COVID-19 because of the concern about lactic acidosis in cases of multi-organ dysfunction[1]. However, experimental studies have shown that metformin has anti-inflammatory and anti-viral action beyond its glucose-lowering effect. It has been speculated that these pleiotropic effects of metformin might potentially be beneficial amidst the cytokine storm related to COVID-19[2]. Through activation of adenosine monophosphate-activated protein kinase, metformin inhibits nuclear factor kappa B pathway and reduces inflammation. Metformin also has immunomodulatory properties and restores immune homeostasis in T cells, B cells, monocytes, macrophages and neutrophils. Furthermore, it has been postulated that adenosine monophosphate-activated protein kinase activation by metformin leads to phosphorylation of angiotensin-converting enzyme 2 receptor. This results in conformational and functional changes in the angiotensin-converting enzyme 2 receptor, which in turn could lead to reduced binding by SARS-CoV-2. So, does metformin have a role in the treatment of individuals with diabetes and COVID-19?

The association between metformin use and mortality in patients with diabetes and COVID-19 has been examined in a number of retrospective studies, and these are summarized in Table 1. Two Chinese studies of COVID-19 patients with diabetes from Wuhan in the early stage of the pandemic suggested potential beneficial effects of metformin. Luo *et al.*[3] reported that the in-patient mortality rate was significantly lower in the metformin-treated COVID-19 patients with diabetes than the non-metformin-treated group. The length of hospitalization was similar between the two groups, and the benefit in mortality was observed despite higher fasting glucose levels on admission among the metformin-treated group[3]. A trend toward lower in-patient mortality among metformin users was also observed in the other Chinese study, which involved a smaller number of participants[4]. Data from a single tertiary healthcare center in the USA also showed that metformin treatment was independently associated with a significant reduction in mortality in individuals with diabetes and COVID-19 after correcting for multiple covariates[5]. The CORONADO (Coronavirus SARS-CoV-2and Diabetes Outcomes) study, a French multicenter study including 1,317 COVID-19 patients with diabetes, showed that patients who were taking metformin before admission had a lower 7-day mortality rate (odds ratio 0.59, 95% confidence interval [CI] 0.42–0.84), but this was no longer significant after adjusting for confounding factors[6]. The relationship between metformin and mortality in patients with diabetes and COVID-19 has also been investigated using big data collected from national claims databases. No definite association could be shown between metformin and mortality in a South Korean study[7]. A much larger study using United Health insurance claims from all 50 states in the USA showed that pre-admission metformin use was associated with reduced COVID-19-related mortality only in women hospitalized with COVID-19, but not in men. The sex-specific phenomenon was thought to be due to the tumor necrosis factor-alpha-lowering effect of metformin, which was more prominent in women[8]. The number of patients in most of these observational studies was small and lacked statistical power. Meta-analyses have been carried out and metformin use was associated with a significant reduction in mortality (pooled odds ratio 0.75, 95% CI 0.67–0.85)[2].

Given that there is evidence suggesting that metformin might be associated with reduced mortality, should metformin be continued in individuals with COVID-19 and pre-existing type 2 diabetes? Does metformin have any favorable effects beyond its glucose-lowering action in COVID-19 patients? In response to this controversy, Cheng *et al.*[9] carried out a retrospective analysis on the use of metformin in 1,213 COVID-19 patients with pre-existing type 2 diabetes from 16 hospitals in the Hubei province of China. Patients with contraindications to metformin use, such as cirrhosis and estimated glomerular filtration rate <30 mL/min, were excluded. Patients using insulin as the only anti-diabetic drugs were also excluded. They compared patients treated with metformin alone/metformin plus other anti-diabetic agents with those treated with non-metformin anti-diabetic agents. Propensity score matching was

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Table 1 | Retrospectives studies comparing mortality rates between metformin and non-metformin users in patients with COVID-19 and type 2 diabetes

Study	Country	Study design	Metformin vs non-metformin (*n*)	Multivariable adjusted odds ratio (95% confidence interval)	Adjustment
Luo *et al.*[3]	China	Single site	104 vs 179	0.23 (0.06–0.82), $P = 0.01$	Therapies for COVID-19
Chen *et al.*[4]	China	Single site	43 vs 77	0.62 (0.17–2.20), $P = 0.456$	Age, albumin, creatinine, C-reactive protein, glucose
Crouse *et al.*[5]	USA	Single site	76 vs 144	0.33 (0.13–0.84), $P = 0.021$	Age, sex, race, obesity status, hypertension, insulin
Cariou *et al.*[6]	France	Multicenter (53 sites)	746 vs 571	0.80 (0.45–1.43), $P = 0.453$	Age, sex, comorbidities, micro- and macrovascular complications, routine medications, insulin
Do *et al.*[7]	Korea	Analysis of claims database	469 vs 95	0.77 (0.44–1.35), $P = 0.052$	Age, sex, Charlson Comorbidity Index, hypertension
Bramante *et al.*[8]	USA	Analysis of claims database	2333 vs 3923	All patients: 0.90 (0.78–1.05) Female subgroup: 0.79 (0.64–0.98), $P = 0.01$	Age, sex, comorbidities, body mass index, home medications

COVID-19, coronavirus disease 2019.

used to balance potentially confounding variables, and the Cox regression model with time-varying exposure was used in the data analysis to take into account that the status of metformin use could be influenced by changes in clinical condition during hospitalization. The effect of metformin on both the 28-day all-cause mortality rate and the length of hospitalization was essentially neutral. There were no significant differences between the metformin and non-metformin groups, despite the fact that metformin use was associated with an increased incidence of both acidosis (adjusted hazard ratio 2.45, 95% CI 1.08–5.54, $P = 0.032$) and specifically lactic acidosis (adjusted hazard ratio 4.66, 95% CI 1.45–14.99, $P = 0.010$). More in-depth analysis had identified factors that were associated with the development of acidosis or lactic acidosis. These included higher doses of metformin (≥2 g), impaired kidney function and COVID-19 severity. No events of acidosis or lactic acidosis were seen in the subgroup with mild COVID-19 treated with metformin.

Cheng *et al.*[9] further showed that metformin use was associated with a significant reduction in heart failure (adjusted hazard ratio 0.61, 95% CI 0.43–0.87, $P = 0.006$) as well as inflammatory responses. Markers of cardiac injury, heart failure and inflammation were consistently lower in the metformin group compared with the non-metformin group. Subgroup analysis showed that the magnitude of reduction in these markers was even more pronounced in patients with severe COVID-19. There was also a lower incidence of acute respiratory distress syndrome in the metformin group, but the reduction was only significant in the Cox regression model with time-varying exposure. Taken together, the authors suggested that the adverse events of lactic acidosis in COVID-19 patients with pre-existing type 2 diabetes might be offset by the beneficial effects of metformin on heart failure and inflammation, which were seen even in the more severe cases. Their findings that metformin had no effect on mortality in the current study were in contrast to the positive findings from another center in Wuhan reported by Luo *et al.*[3] These differences were partly attributed to the inclusion of COVID-19 patients treated with only insulin in the non-metformin control group in the study by Luo *et al.*, leading to a potential bias in the results.

In conclusion, the study of Cheng *et al.*[9] was the first study to examine the pros and cons of metformin therapy in patients with type 2 diabetes and COVID-19. The balance between risks and benefits was evaluated by analysis of data derived from a relatively large cohort of participants. Attempts were made to control for potential confounding factors by using multiple adjustments and propensity score matching. Nevertheless, inherent to the retrospective observational nature of the study, there might still be residual confounders that could not be accounted for. Despite all the limitations, their results have helped to clarify some of the concerns on the use of metformin in COVID-19 patients with type 2 diabetes. As expected, metformin was associated with a higher incidence of acidosis. However, this was accompanied by a reduction in heart failure and inflammation, and there was no overall unfavorable effect on COVID-19-related mortality. Risk factors identified for the development of lactic acidosis included higher doses of metformin, impaired kidney function and the severity of COVID-19. Hence, in mild cases of COVID-19, metformin therapy is safe and there is no reason to discontinue the medication. In more severe cases, metformin should be used judiciously. If metformin is to be continued, close monitoring for the development of adverse events is necessary and high doses of the drug should be avoided. Regardless of the evidence from all the recent observational studies, whether there is any definitive causal relationship between metformin and COVID-19-related clinical outcomes can only be determined by future prospective randomized controlled trials.

DISCLOSURE

The authors declare no conflict of interest.

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