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Mini Review

Metformin and COVID-19: From cellular mechanisms to reduced mortality

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with both poorer clinical outcomes during the COVID-19 pandemic and an increased risk of death in such hospitalized patients. While the role of glucose control has been emphasized to improve the prognosis, the impact of different glucose-lowering agents remains largely unknown. Metformin remains the first-line pharmacological choice for the management of hyperglycaemia in T2DM. Because metformin exerts various effects beyond its glucose-lowering action, among which are anti-inflammatory effects, it may be speculated that this biguanide might positively influence the prognosis of patients with T2DM hospitalized for COVID-19. The present concise review summarizes the available data from observational retrospective studies that have shown a reduction in mortality in metformin users compared with non-users, and briefly discusses the potential underlying mechanisms that might perhaps explain this favourable impact. However, given the potential confounders inherently found in observational studies, caution is required before drawing any firm conclusions in the absence of randomized controlled trials.

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Introduction

During the coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, several observational studies around the world have shown that type 2 diabetes mellitus (T2DM) is a risk factor for more severe disease, leading to acute respiratory distress syndrome and artificial ventilation in intensive care units, and almost doubling the death rate [1–3]. Among hospitalized patients with both T2DM and COVID-19, several prognostic factors have been identified, among which are older age and obesity [4]. However, while the role of the quality of glucose control has been repeatedly emphasized [5,6], the potential influence of the class of glucose-lowering medication remains unclear [2,7,8].

The pharmacotherapy of T2DM now comprises several new drugs that compete with older oral antidiabetic agents. Nevertheless, metformin remains the first-choice drug for the management of hyperglycaemia in T2DM patients [9]. Indeed, it has been the most popular glucose-lowering agent during the past two decades worldwide, and around two-thirds to three-quarters of patients with T2DM are treated with metformin alone or in combination. The United Kingdom Prospective Diabetes Study (UKPDS) [10]

showed that metformin reduces mortality in obese patients with newly diagnosed T2DM, and obesity has been reported to be a major risk factor for developing severe COVID-19 [11,12]. Thus, it is of major importance to know the effect of metformin on the clinical outcomes of patients with T2DM during the COVID-19 outbreak. Inflammation due to cytokine storms is recognized to play a crucial role in the poor prognosis of patients infected with the SARS-CoV-2 [13] and, as metformin has been shown to exert some anti-inflammatory effects irrespective of diabetes status [14,15], it may be speculated that this glucose-lowering agent could favourably influence the clinical outcomes of patients with T2DM hospitalized for COVID-19 beyond its effects on glucose control [16–18].

The aim of this short narrative review was to summarize the available data from observational studies in patients with T2DM comparing rates of death in metformin users vs non-users who were hospitalized for COVID-19, and to discuss the potential underlying mechanisms that might positively influence outcomes.

Possible mechanisms leading to beneficial effects

Over the past few weeks, several authors have written letters to editors and commentaries to speculate about the possible beneficial effects of metformin in diabetes patients with COVID-19 [17] based on the pleiotropic effects of this medication,

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characterized by a complex mode of action [19], and the multiple pathogenic mechanisms that contribute to worsen the prognosis of patients with COVID-19, especially when T2DM is present [13]. The most important mechanisms of metformin activity in relation to COVID-19 are summarized in Table 1 [16,17,20–25]. It is noteworthy, however, that all such proposed mechanisms remain, at present, theoretical.

In contrast, some authors have challenged the prescription of metformin and raised concerns about its use in patients with T2DM hospitalized for COVID-19, in particular by pointing out the possible risk of lactic acidosis in cases of multiple organ failure [26–28].

Retrospective analyses of observational human studies

A few retrospective analyses of observational studies in patients with T2DM hospitalized for severe COVID-19 suggested that the use of metformin might be associated with a reduction in mortality [18]. The main characteristics of those studies are presented in Table 2, and the relative effects of metformin on mortality rates are summarized in a meta-analysis (Fig. 1). A positive effect (whether significant or not) was observed in all four studies with an overall reduction of death by 25% ($P < 0.00001$), but with moderate-to-high heterogeneity ($I^2 = 61\%$). The size of the four studies varied considerably, with two big cohorts from the US [29] and France [4], but two more limited samples from China [30,31]. Mean ages ranged from 65 to 75 years and the gender ratio showed a slight predominance of males. Unfortunately, detailed information on body mass index (BMI) was missing in most of the studies. Greater reductions of mortality in metformin users vs non-users were observed in the two trials that recruited smaller numbers of patients [30,31]. The results of these four studies have been briefly discussed elsewhere [18].

In one large US study of 6256 subjects (>95% T2DM, 52.8% female, mean age 75 years), metformin was significantly associated with reduced mortality in women (but not in men) in an observational analysis of claims data from individuals hospitalized with COVID-19 with an odds ratio (OR) of 0.759 [95% confidence interval (CI): 0.601–0.960] after propensity matching [29].

The Coronavirus-SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, as with many other observational studies, was not specifically designed to investigate the potential influence of previous antidiabetic medications [4]. Nevertheless, in this large observational multicentre French study, metformin users prior to hospital admission had a lower death rate at day 7 compared with metformin non-users in an unadjusted analysis (OR: 0.59, 95% CI:

0.42–0.84). After full adjustment, a non-statistically significant trend for fewer deaths still remained in metformin users compared with non-users (OR: 0.80, 95% CI: 0.45–1.43), as previously described elsewhere [18].

In a smaller retrospective study of T2DM patients hospitalized for COVID-19, a reduced trend for in-hospital deaths was observed in metformin users ($n = 43$) compared with non-users ($n = 77$): 9.3% vs 19.5%, respectively. A noteworthy finding was that metformin users had a significantly lower increase in interleukin (IL)-6 compared with non-users: 4.1 pg/mL vs 11.1 pg/mL, respectively ($P = 0.02$) [30].

In another study, despite having similar baseline characteristics, laboratory parameters and treatment interventions between metformin users ($n = 104$) and metformin non-users ($n = 179$), there was a significantly lower in-hospital mortality rate in patients treated with metformin vs not (2.9% vs 12.3%, respectively; $P = 0.01$). Interestingly, this difference was observed despite significantly higher baseline fasting plasma glucose levels in metformin users compared with non-users. In a multivariate analysis, a more than fourfold reduction in in-hospital mortality was noted in metformin users compared with non-users (OR: 4.36, 95% CI: 1.22–15.59; $P = 0.02$) [31].

Finally, one study could not be included in the meta-analysis because it did not provide enough precise data regarding the relationship between the use of metformin and death [32]. In this comparative analysis that mainly focused on the effect of glucose control (1:1 propensity-matching for other comorbidities), a significant reduction in all-cause mortality was observed in the well-controlled compared with poorly controlled T2DM patients (adjusted HR: 0.13, 95% CI: 0.04–0.44; $P < 0.001$). Of potential interest, a significantly greater proportion of patients were taking metformin in the well-controlled arm vs poorly controlled arm (39.2% vs 26.4%, respectively; $P = 0.003$). While the beneficial outcome was attributed to good glycaemic control, a potential benefit resulting from metformin use itself could not be excluded when considering the data reported in the four above-mentioned studies [32].

Discussion

The available retrospective studies, albeit still limited in number, have all shown a reduction in mortality in metformin users compared with non-users among patients with T2DM hospitalized for COVID-19. However, caution is required before drawing any firm conclusions. Indeed, as with every observational study, potential confounders could influence the final results, and

Table 1
Suggested mechanisms to explain the possible positive effects of metformin on COVID-19 outcomes.

Mechanisms	References
Improved glucose control	Ceriello et al. [5,6]
Reduction in body weight	El-Arabey and Abdalla [20]
Reduction in insulin resistance	Penlioglou et al. [16] Sharma et al. [17]
AMPK activation leads to phosphorylation of ACE2, thereby inhibition of virus penetration	Sharma et al. [17]
Inhibition of mTOR pathway and prevention of immune hyperactivation	Sharma et al. [17] Bolourian and Mojtahedi [21]
Action on endosomal Na ⁺ /H ⁺ exchanger, thereby increasing cellular pH and interference with viral endocytic cycle	Lehrer [22]
Anti-inflammatory properties	Esam [23] Kumar Singh and Singh [18]
Reduction in neutrophils	Dalan [24]
Inhibition of mitochondrial complex 1, suppression of mitochondrial reactive oxygen species (ROS) signalling, ROS prevention: CRAC-mediated interleukin-6 release	Menendez [25]

AMPK: AMP-activated protein kinase; ACE2: angiotensin-converting enzyme 2; mTOR: mammalian target of rapamycin; CRAC: Ca²⁺ release-activated Ca²⁺ channels.

Table 2

Characteristics of four observational studies comparing death rates in metformin users vs non-users among patients with type 2 diabetes hospitalized for COVID-19.

References	Country	Endpoint	Metformin users/non-users			
			Patients (n)	Mean age (years)	Gender (% male)	BMI (kg/m ²)
Bramante et al. [29]	US	In-hospital mortality	2333/3923	73/76	52/45	NA
Cariou et al. [4]	France	Death at ≤7 days of admission	746/571	70	65	28.5
				(both groups)	(both groups)	(both groups)
Chen et al. [30]	China	In-hospital mortality	43/77	62/67	NA	NA
Luo et al. [31]	China	In-hospital mortality	104/179	63/65	51/57	NA

BMI: body mass index; NA: not available.

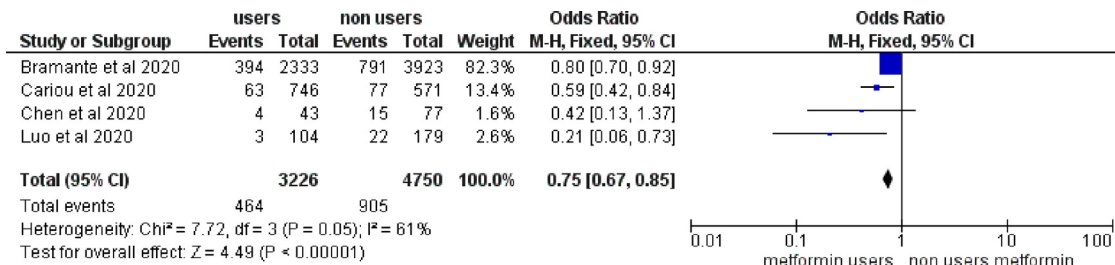


Fig. 1. Mortality rates in metformin users compared with non-users among patients with type 2 diabetes hospitalized for COVID-19 infection. M–H: Mantel–Haenszel (test).

it is not possible to eliminate all of them even after multiple adjustments and propensity matching. Of note, metformin non-users may represent patients with relevant contraindications to the prescription of metformin, such as old age, renal insufficiency and/or cardiovascular disease, even though these contraindications have been alleviated in recent years [33]. These conditions all represent risk factors that could trigger poorer prognoses in cases of COVID-19 [11]. On the other hand, metformin is more commonly used in obese patients with T2DM [10], and obesity has been demonstrated to be associated with a greater risk of severe COVID-19 infection and a higher mortality rate [11,12].

The findings of observational studies showing a reduction of death rates in patients treated with metformin while exposed to COVID-19 are in agreement with previous observations reporting significantly lower mortality rates in patients treated with metformin compared with metformin non-users during bacterial infections such as sepsis (OR: 0.59, 95% CI: 0.43–0.79; P=0.001) [34] and active tuberculosis [35]. Animal data have also shown a higher survival rate when mice exposed to experimental sepsis were treated with metformin [36]. As discussed in a previous review, in addition to its traditional effects on glucose metabolism, metformin also offers antimicrobial benefits in a very wide range of infections whether *in vitro* and *in vivo* [37]. Metformin has also been found to be associated with a markedly lower mortality rate in patients with respiratory pathologies such as chronic obstructive pulmonary disease [38,39]. Finally, in a recent randomized, double-blind, placebo-controlled, proof-of-concept phase-II trial, metformin reduced metabolic complications and inflammation in non-diabetes patients receiving systemic glucocorticoid therapy for inflammatory diseases. The results of this study further emphasize the anti-inflammatory effects of metformin independently of glucose control [15].

Both metformin therapy and COVID-19 can also share similar adverse gastrointestinal events. The most commonly reported side-effects of metformin are nausea, dyspepsia and diarrhoea, usually occurring within the first few days or weeks of starting therapy [40]. COVID-19 can also induce gastrointestinal disturbances beyond the classic systemic (fever) and respiratory (cough, dyspnoea) symptoms [41]. Of course, metformin should be stopped in cases of severe gastrointestinal symptoms. The risk

of lactic acidosis, pointed out by some authors as a possible complication [26–28], is in fact rarely seen with metformin and, even then, the drug may not necessarily be responsible for it, as previously explained [42]. However, lactic acidosis may arise in cases of multiple organ failure, particularly renal insufficiency and hepatic failure, and especially in the context of hypoxia triggering anaerobic glycolysis [26,27].

However, firm conclusions about the impact of metformin therapy can only be drawn from double-blind randomized controlled trials (RCTs), and such trials are almost impossible in the context of COVID-19, considering the known difficulties encountered in carrying out such RCTs (for example, the ambitious European DISCOVERY trial). Because metformin is out of patent and very inexpensive, no pharmaceutical company is likely to be interested in planning a study to demonstrate the benefits of metformin on COVID-19-related clinical outcomes. Nevertheless, it is worth noting that such an RCT is currently ongoing with dapagliflozin, a sodium–glucose cotransporter type-2 (SGLT2) inhibitor, in the Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial (ClinicalTrials.gov identifier: NCT04350593) [43]. Of potential interest, SGLT2 inhibitors have also demonstrated anti-inflammatory effects [44] that are somewhat similar to those described with metformin [14].

In addition, an intriguing finding was recently reported by Bramante et al. [29]: in their large observational study of patients hospitalized due to COVID-19, the reduction in mortality in metformin users compared with non-users was highly significant in women, but was not observed in men. According to those authors, this gender-specific finding is consistent with the greater reduction of tumour necrosis factor (TNF)-α by metformin in women than in men, and suggests that metformin conveys protection against COVID-19 through TNF-α-mediated effects. Nevertheless, the authors also recognize that prospective studies are now needed to understand the mechanisms and causality behind these effects. Other authors have pointed out the reduction in IL-6 levels in metformin-treated patients [30]. Whatever the case may be, these findings confirm the potential anti-inflammatory activity of metformin [14], which could be beneficial in an infection like COVID-19 where cytokine storms play such a

deleterious role and markedly worsen the prognosis, including survival [13].

Conclusion

Metformin, the marketplace leader among glucose-lowering agents for the management of T2DM, has a complex mechanism of action involving multiple mechanisms, some of which lead to anti-inflammatory activity that may help in reducing the risk of severe COVID-19 beyond the effects of glucose control. Some preliminary data from retrospective studies have confirmed a reduction in death rates in metformin users compared with non-users in patients with T2DM hospitalized for COVID-19. Caution is, however, required when interpreting these observational findings, as only RCTs can provide definitive conclusions. Nevertheless, there are at least no negative safety indications, so there is no reason to stop metformin therapy during COVID-19 infection except in cases of severe gastrointestinal symptoms, hypoxia and/or multiple organ failure.

Declaration of interest

None declared.

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