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Commentary

Is metformin ahead in the race as a repurposed host-directed therapy for patients with diabetes and COVID-19?

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Most of the expert consensus to date have suggested avoiding metformin in patients with diabetes and coronavirus disease-19 (COVID-19), due to an anticipated fear of lactic acidosis in the background of multi-organ dysfunction including hepatic and renal impairment [1–6]. However, these earlier advisories were made in the absence of studies conducted with anti-diabetic drugs in patients with diabetes and COVID-19.

Historically, host-directed anti-viral properties of metformin were utilized during the treatment of influenza outbreak in Philippines in 1949 [7]. Proguanil, an immediate predecessor of metformin is still used in the prevention and treatment of malaria. Serendipitously, both these drugs were found to have a glucose lowering properties since the 1940s [8]. This ability of metformin was further pursued by French physician Jean Sterne, in the treatment of diabetes in 1957 and is being used for the same in United Kingdom and Europe, since 1958 [9]. United States permitted the use of metformin in diabetes only after an intensive scrutiny in 1995, despite all the reverberations of lactic acidosis associated with phenformin and buformin of the same biguanide family [10]. While both phenformin and buformin were withdrawn in the 1970s, metformin came out to become the first line anti-diabetic drug in the treatment of type 2 diabetes, after passing a series of tests and trials, including the epic United Kingdom Prospective Diabetes Study-34 [11]. Interestingly, the historical use of metformin during influenza and malaria outbreak is somehow analogous to the recent use of anti-influenza and anti-malarial drug as a repurposed agent in the treatment of COVID-19, in the absence of any licensed agent.

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We aimed to analyze the host-directed outcomes with metformin in the context of, a. Its anti-inflammatory effect in experimental studies, b. Outcomes in pulmonary disease prior to the COVID-19 pandemic, and c. Outcomes in patients with diabetes with COVID-19.

1. Anti-inflammatory properties of metformin

Metformin may have an ability to improve host-directed response by virtue of inducing adenosine monophosphate (AMP) activated protein kinase. The mechanism by which metformin can reduce inflammation and improve both adaptive and innate immune response include, induction of autophagy, formation of M2 macrophages and CD8 memory T-regulatory cells, besides its ability to reduce the expression of genes that encode chemokines and cytokines [12–14]. In addition, metformin may have a role as an anti-oxidant by altering the activities of catalase and superoxide dismutase [15]. Furthermore, metformin may also reduce inflammation by altering the composition of gut microbiota [16]. Collectively, these anticipated immunomodulatory, anti-oxidative and antiproliferative properties suggest that metformin could be beneficial in combating the cytokine storm induced host-directed damage in patients with diabetes and COVID-19.

2. Role of metformin in pulmonary disease and sepsis

Metformin has shown its protective role in *legionella* pneumonia, in the mouse models [17]. Human studies in the past, that studied metformin in sepsis and lung diseases have consistently shown benefit. In a meta-analysis of 5 observational studies, Liang et al. [18] showed that metformin uses in patients with diabetes prior to the hospital admission had a significantly less mortality during the sepsis (odds ratio [OR] 0.59; 95% CI, 0.43–0.79, p = 0.001), compared to the non-users. In a meta-analysis of 17 observational studies, Zhang et al. [19] found metformin users had a significantly lesser incidence of active tuberculosis (relative risk [RR] 0.51; 95% CI, 0.38–0.69, p < 0.001) as well as mortality (RR 0.34; 95% CI, 0.20–0.57, p < 0.001), compared to the non-users, in patients with diabetes. In a median 6.2 years of follow up (n = 5266), Mendy et al. [20] found metformin users had a significantly decreased risk of mortality in patients with chronic obstructive pulmonary disease (COPD) with diabetes (hazard ratio [HR] 0.30; 95% CI, 0.10–0.93, compared to the non-users, even after the adjustment for multiple confounding factors. Another 2-year follow up study of 4321 patients with diabetes and COPD, Ho et al. [21] showed a significantly lower risk of death in metformin-users (HR 0.46; 95% CI, 0.23–0.92), compared to the non-users. Collectively, these data suggest a beneficial effect of metformin in patients with pulmonary disease including a consistent reduction in mortality.

3. Metformin in patients with diabetes and COVID-19

Accumulating evidence now points that continuing treatment with metformin in patients of diabetes with COVID-19 is not harmful and could possibly be beneficial. Study by Zhu et al. [22] that looked for the proportion of patients receiving different anti-diabetic agents, found no harm with metformin. In the comparative analysis (1:1 propensity-matched to other comorbidities) of well-controlled group (blood glucose 70–180 mg/dL) that showed a significant reduction in all-cause mortality (adjusted HR 0.13; 95% CI, 0.04–0.44, p < 0.001), compared to the poorly-controlled arm (blood glucose > 180 mg/dL); a significantly higher proportion of the patients were receiving metformin in the former group, compared to the latter (39.2% vs. 26.4% respectively, p = 0.003). While the beneficial outcome is attributed to the good glycemic control, this also hints at no anticipated harm with metformin.

In a retrospective study by Chen and colleagues [23] that studied 120 patients with diabetes and COVID-19 (including confirmed and unconfirmed but clinically diagnosed cases), metformin users (n = 43) had a significantly less increase in interleukin-6 (4.1 vs. 11.1 pg/mL, respectively; p = 0.02) compared to the metformin non-users (n = 77). A reduced trend of in-hospital deaths was also observed in metformin users, compared to the non-users (9.3 vs. 19.5%, respectively; p = 0.19). In addition, a significant increase in albumin level was observed in patients receiving metformin compared to the non-users (38.6 vs. 36.7 g/L, respectively; p = 0.04). Whether these differences are attributable to the beneficial effect of metformin or due to the difference in glycemic equipoise between the two arms or due to the other confounders, is not clearly known. However, this data at least reaffirms that metformin produces no harm in patients with diabetes and COVID-19.

CORONADO (Coronavirus disease and diabetes outcome), was a dedicated trial conducted in patients with diabetes and COVID-19 (n = 1317) that looked for the composite of tracheal intubation and death as a primary outcome within 7 days of admission. CORONADO study found that an increase in body mass index was the only factor independently associated with a significant increase in the composite of primary outcome [24]. Notably, amongst all the anti-diabetic agents, only metformin users prior to the admission had a lower rate of death, compared to the metformin non-users (OR 0.59; 95% CI, 0.42–0.84), in an unadjusted analysis. A non-statistical trend of lower death was also observed in metformin users, even after the full adjustment (OR 0.80; 95% CI, 0.45–1.43; p = 0.45). This clearly hints of no harm with metformin in patients with diabetes and COVID-19.

In a retrospective study Luo et al. [25] analyzed the outcomes with metformin in 283 patients with diabetes of which 104 were receiving metformin while 179 were metformin non-users. Despite a similar baseline patient characteristics (no significant difference in age, sex, clinical severity of covid-19, oxygen requirement and other associated comorbidities such as hypertension, coronary heart disease, COPD, chronic kidney disease and malignancy), similar laboratory parameters (no significant difference in white blood cell count, lymphocyte and neutrophil count, liver enzymes, renal profile and C-reactive protein) and a similar treatment characteristics (no significant difference in the use of other anti-diabetic agents, statins, anti-viral drugs, anti-bacterial drugs, steroid and anti-coagulants) between metformin users versus non-users, there was a significantly less in-hospital mortality in

Table 1 – Effect of metformin on lung diseases and mortality in experimental studies and patients with diabetes with or without COVID-19.

Metformin	Outcomes
Studies in patients with diabetes and COPD or sepsis [18–21]	• Meta-analysis of 5 observational studies found metformin users had a significantly less mortality compared to the non-users, during the sepsis (OR 0.59; 95% CI, 0.43–0.79, p = 0.001). • Meta-analysis of 17 observational studies found metformin users had a significantly lesser incidence of active tuberculosis (RR 0.51; 95% CI, 0.38–0.69, p < 0.001) and mortality, compared to the non-users (RR 0.34; 95% CI, 0.20–0.57, p < 0.001). • After the adjustment for multiple confounding factors, metformin users had a significantly decreased risk of mortality in patients with COPD compared to the non-users, in a median 6.2 years of follow up (HR 0.30; 95% CI, 0.10–0.93). • Patients with COPD had a significantly lower risk of death in metformin users compared to the non-users, in a 2-year follow up study (HR 0.46; 95% CI, 0.23–0.92).
Studies in patients with diabetes and COVID-19 [22–25]	• Well-controlled cohorts with diabetes (receiving metformin in 39%) had a significant reduction in all-cause mortality, compared to the poorly-controlled cohorts (receiving metformin in 26%) after a 1:1 propensity matching (adjusted HR 0.13; 95% CI, 0.04–0.44, p < 0.001). • Metformin users had a significantly higher albumin level (38.6 vs. 36.7 g/L, p = 0.04) and lower IL-6 level (4.1 vs. 11.1 pg/mL, p = 0.02) compared to the non-users. A trend of decreased in-hospital deaths was observed in metformin users, compared to the non-users (9.3 vs. 19.5%, p = 0.19). • In an unadjusted analysis, metformin users had a lower rate of death, compared to the non-users (OR 0.59; 95% CI, 0.42–0.84, p = nr). A trend of lower rate of death was also observed in metformin users compared to non-users, even after the full adjustment (OR 0.80; 95% CI, 0.45–1.43; p = 0.45). • Metformin users had a significantly less in-hospital mortality compared to the non-users (2.9 vs. 12.3%, p = 0.01). Four-fold decrease in-hospital death in metformin users compared to the non-users, in a multi-variate analysis (OR 4.36; 95% CI, 1.22–15.59, p = 0.02).

OR: odds ratio, RR; risk ratio, HR: hazard ratio, COPD: chronic obstructive pulmonary diseases, IL-6: interlukin-6, nr: not reported, COVID-19: coronavirus disease-19.

the former groups, compared to the latter (2.9 vs. 12.3% respectively; p = 0.01). Interestingly, this significant reduction in mortality in metformin users was observed despite a significantly higher baseline fasting glucose, compared to the non-users (9.19 vs. 7.36 mmol/L respectively, p < 0.01). Notably, in the multi-variate analysis more than 4-fold decrease in in-hospital death was observed in metformin users, as compared to the non-users (OR 4.36; 95% CI, 1.22–15.59, p = 0.02). This retrospective study underscores the benefit of metformin in patients with diabetes and COVID-19. Table 1 summarizes the effects of metformin on various outcomes including lung diseases and mortality in patients with diabetes with or without COVID-19.

4. Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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