Asclepius

Should Metformin Be Continued after Hospital Admission in Patients with Coronavirus Disease 2019?

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ABSTRACT

Background: In most patients with diabetes, guidelines recommend discontinuation of oral anti-diabetic agents. Preliminary data suggest that pre-admission metformin use may have a mortality benefit in patients with coronavirus disease (COVID)-19 admitted to the hospital. **Objective:** The objective of the study was to review the impact of metformin on morbidity and mortality among hospitalized patients with COVID-19. **Methods:** Review of English literature by PUBMED search until November 10, 2020. Search terms included diabetes, COVID-19, metformin, retrospective studies, meta-analyses, pertinent reviews, pre-print articles, and consensus guidelines are reviewed. **Results:** Retrospective studies suggest that metformin use before hospital admission may be associated with a reduction in mortality by 21–67% among patients with diabetes admitted to the hospital with COVID-19. Meanwhile, in one large retrospective study (n = 1231), continuing metformin administration after hospital admission did not have a significant impact on 28-day all-cause mortality. Metformin use after hospitalization of patients with COVID-19 was associated with approximately 4.6 times increase risk of lactic acidosis among patients with severe symptoms of COVID-19, those taking 2 g/d of metformin or higher, and patients with estimated glomerular filtration rate <60 ml/min/1.73 kg/m². Metformin intake in hospital was associated with a significant decrease risk of heart failure and acute respiratory distress syndrome. In another smaller study (n = 110), continuing metformin use after hospitalization was associated with increased risk of life-threatening complications of COVID-19; odds ratio 3.96; 95% confidence interval = 1.03–15.19, P = 0.045. **Conclusions:** In patients with COVID-19, metformin use before hospitalization might be associated with reduction in mortality. However, after admission, metformin should be discontinued due to an increased risk of life-threatening complications and lactic acidosis.

Key words: Coronavirus disease-19, diabetes, lactic acidosis, metformin, mortality, safety

INTRODUCTION

The prevalence of diabetes in coronavirus disease (COVID)-19 patients ranges from 5.3% to 58%, representing the second comorbidity after hypertension.[1,2] Available data suggest that diabetes confers a poor prognosis in COVID-19 patients admitted to the hospital. In a meta-analysis of 30 retrospective studies (n = 6452), Huang *et al.*[3] showed that diabetes was associated with excess mortality: Risk ratio (RR) 2.12 (95% confidence interval (CI) 1.44–3.03, P < 0.001, severe degree of COVID-19: RR 2.45, 95% CI, 1.79–3.35, P < 0.001, acute respiratory distress syndrome (ARDS): RR 4.64, 95% CI, 1.86–11.58, P < 0.001, and disease progression: RR 3.31, 95% CI, 1.08–10.14, P = 0.04. Hence, adequate glycemic control is necessary after patient admission. Metformin is the most common anti-diabetic drug worldwide due to its well-established long-term overall high efficacy and safety profile and low cost.[4] It is still unclear whether to continue or stop metformin after the admission of patients with COVID-19. The American Diabetes Association (ADA) generally recommends stopping all oral anti-diabetic agents in most

patients after hospital admission admitted to the hospital due to due to lack of efficacy data, presence of adverse effects, and limited efficacy.[5] The ADA recommends insulin as the standard therapy for hyperglycemia in hospital.[5] However, one possible exception is metformin due to emerging data showing several clinical benefits in patients with COVID-19. This review discusses the impact of metformin on mortality and morbidity in patients with type 2 diabetes and COVID-19 when metformin was used before and after hospitalization. Specifically, the authors attempt to determine whether metformin should be continued or not in patients with COVID-19 and diabetes after admission to the hospital.

EFFECT OF METFORMIN ON MORTALITY AND MORBIDITY IN HOSPITALIZED PATIENTS WITH COVID-19

Effect of pre-admission use of etformin on mortality

The most comprehensive data in this respect may be derived from the recent meta-analysis conducted by Kow and Hassan.[6] In this study, the authors analyzed data (up to August 8, 2020) of 5 studies, including 8121 patients with diabetes and COVID-19 who were using metformin before hospital admission. Their pooled analysis revealed a significantly reduced risk for mortality with the use of metformin before admission, pooled odds ratio (OR) being 0.62 (95% CI, 0.43–0.89) compared to patients with diabetes who were non-users of metformin.[6] Interestingly, the largest study included in this meta-analysis by Bramante et al.[7] that contributed to 48.7% of the meta-analysis weight showed that pre-admission metformin use was associated with decreased in-hospital mortality in women only; OR 0.79 (95% CI 0.64–0.98), but not in men. Another retrospective study from the University of Alabama included in the previous meta-analysis[6] provided information on mortality in a diverse population of 604 patients (55% women, 51% African-American) with COVID-19 and diabetes admitted to the hospital.[8] In the latter study, Crouse et al.[8] reported that metformin treatment was independently associated with a significant reduction in mortality; OR = 0.33 (95% CI, 0.13–0.84; P = 0.02). Moreover, the absolute reduction in mortality was substantial.[8] Thus, whereas the mortality rate in patients with COVID-19 and diabetes who were not taking metformin was 23%, this rate dropped to 11% in patients who were using metformin.[8] Contrary to the study of Bramante et al.,[7] who found that metformin mortality reduction was limited to women, Crouse et al.[8] did not observe a significant differential effect of metformin on mortality based on gender.

It should be emphasized that while the results of the previous studies are encouraging, they should be considered preliminary due to the following limitations. First, all included studies were retrospective prone for confounding factors. Second, it was not possible to know to what extent patients were adherent to metformin intake prior to hospital admission. Third, the duration and dosage of metformin were not known. Fourth, it was not clear in any of these studies, whether patients continued to take metformin or discontinued it after admission to the hospital.

Effect of continuing metformin intake during hospitalization

To the best of authors' knowledge, there are two retrospective Chinese studies that evaluated the effects of continuing metformin after admission on mortality and severity of COVID-19 in patients with type 2 diabetes.[9,10] In the first larger study (n = 1213), Cheng et al.[9] have shown that metformin administration during hospitalization was not associated with an increase in 28-day all-cause mortality compared with metformin non-users; adjusted hazard ratio (HR) 0.87 (95% CI 0.36–2.12); P = 0.75. In the second smaller study (n = 110), Gao et al.[10] found that risk of life-threatening complications was significantly higher in patients with COVID-19 receiving metformin compared with patients not taking metformin; OR 3.96 (95% CI 1.03–15.09; P = 0.045). Furthermore, 28.6% (16 of 56) of metformin users developed life-threatening complications of COVID-19, mostly admission to the intensive care unit, compared with 7.4% (4 of 54) of non-users of metformin, P = 0.004.[10]

ADVERSE EFFECTS OF METFORMIN USE DURING HOSPITALIZATION OF PATIENTS WITH COVID-19

Effect of metformin on lactic acidosis

Lactic acidosis is a rare but potentially lethal adverse effect of metformin.[11] The large study of Cheng et al.[9] allowed the evaluation of metformin safety in different subgroups of patients. Thus, they found that lactic acidosis was increased in patients with COVID-19 compared with metformin non-users, adjusted HR 4.66, 95% 1.45–14.99; P = 0.01.[9] However, this increased risk of lactic acidosis was limited to the following subgroups of patients: Those with severe COVID-19, patients using metformin in doses of 2 g/d or higher, and in the presence of kidney dysfunction defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 kg/m^2.[9] It should be emphasized that metformin should not be used in the presence of hypoxia, decreased tissue perfusion, sepsis, acute or chronic kidney disease, and acute heart and liver failure to avoid the risk of lactic acidosis.[11]

Effect of metformin on heart failure and ARDS

In the study of Cheng et al.,[9] metformin in-hospital use was shown to be associated with decreased risk of heart failure

adjusted HR 0.61 (95% CI 0.43–0.87; $P = 0.006$) and ARDS, adjusted HR 0.66 (95% CI 0.46–0.96; $P = 0.03$). There was no significant effect of metformin on acute kidney injury or disseminated intravascular coagulation.[9]

POTENTIAL MECHANISMS UNDERLYING METFORMIN CLINICAL BENEFITS AND HARMS

There are some potential mechanisms whereby metformin could decrease mortality before hospitalization of patients with COVID-19. Thus, metformin has been shown to improve the immune response and reduce inflammation.[12] Indeed, Cheng *et al.*[9] found that serum levels of pro-inflammatory cytokines known to mediate cytokine storm in COVID-19 were increased to a lesser extent among metformin-users versus metformin non-users. Such pro-inflammatory cytokines included: Interleukin-6, interleukin-2, and tumor necrosis-alpha (TNF-α).[9] Likewise, Cheng *et al.*[9] found that levels of IL-6 were lower in metformin users than non-users. Moreover, Cheng *et al.*[9] recorded lower neutrophil count among metformin users compared with non-users. On the other hand, when metformin use was continued after hospital admission, no mortality benefit was demonstrated.[9] On the contrary, in-hospital metformin use was associated with increased severity of COVID-19 and lactic acidosis.[9,10]

CONCLUSIONS AND FUTURE NEEDS

Preliminary data suggest that metformin use before hospitalization of patients with diabetes and COVID-19 might reduce mortality. Meanwhile, continuing metformin after hospitalization did not affect mortality but was associated with an increased risk of lactic acidosis in patients admitted with diabetes and COVID-19. The risk of lactic acidosis was evident in patients with severe symptoms of COVID-19, those with kidney dysfunction, and in patients taking 2 g of metformin or more daily.[9] In addition, Gao *et al.*[10] reported increase admissions to the intensive care unit and the occurrence of life-threatening complications in association with in-hospital use of metformin. Accordingly, metformin should be discontinued in patients with COVID-19 and diabetes upon admission to the hospital. Unfortunately, all current data related to COVID-19 and metformin are based on retrospective studies prone for multiple biases and confounding factors. Randomized trials are urgently needed to determine safety and efficacy of metformin in hospitalized COVID-19 patients.

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