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Review

Should metformin be continued after hospital admission in patients with COVID-19?

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Abstract

In most patients with diabetes, guidelines recommend discontinuation of oral anti-diabetic agents. Preliminary data suggest that pre-admission metformin use may have mortality benefit in patients with coronavirus disease 2019 (COVID-19) admitted to the hospital. To review metformin safety, particularly its impact on mortality among hospitalized patients with COVID-19. Review of English literature by PubMed search until September 18, 2020. Search terms included diabetes, COVID-19, metformin, retrospective studies, meta-analyses, pertinent reviews, pre-print articles and consensus guidelines are reviewed. Retrospective studies suggest that metformin use prior to hospital admission may be associated with reduction in mortality among patients with diabetes admitted to the hospital with COVID-19. Meanwhile, continuing metformin administration after hospital admission did not have 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 in patients with severe symptoms of COVID-19, patients taking 2 gm/d of metformin or higher, and patients with estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 kg/m^2. Metformin intake in hospital was associated with significant decrease risk of heart failure and acute respiratory distress syndrome (ARDS). In patients with diabetes and COVID-19 admitted to the hospital, metformin should not be used in presence of severe symptoms of COVID-19, kidney dysfunction (eGFR < 60 ml/min/1.73 m^2), and with daily doses of 2 gm or more due to increased risk of lactic acidosis.

Keywords: COVID-19, Diabetes, Metformin, Safety, Mortality, Lactic acidosis

1. Introduction

The prevalence of diabetes in coronavirus disease 2019 (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=6,452), Huang et al. [3] showed that diabetes was associated with excess mortality: risk ratio (RR) 2.12 (95% 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, 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 admission of patients with COVID-19. The American Diabetes Association (ADA) generally recommends stopping all oral anti-diabetic agents in

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most patients after hospital admission admitted to the hospital due to due to lack of 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 safety profile of metformin in COVID-19 in the hospital setting, with special emphasis on its impact on mortality. Based on available data, the authors attempt to determine whether metformin should be continued or not in patients with COVID-19 and diabetes after admission to the hospital.

2. Effect of metformin on mortality in hospitalized patients with COVID-19

2.1 Effect of pre-admission use of metformin 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 8,121 patients with diabetes and COVID-19 who were using metformin prior to hospital admission. Their pooled analysis revealed a significantly reduced risk for mortality with the use of metformin prior to 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). 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.

3. Effect of continuing metformin intake during hospitalization

To the best of authors' knowledge, there is only one study that evaluated the effects of continuing metformin after admission on mortality in patients with diabetes and COVID-19 [9]. Thus, in this large (n=1,213) retrospective study from China, Cheng et al. [9] have shown that metformin administration during hospitalization was not associated with 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. These data, although based on a retrospective study, may provide reassuring information about metformin safety in the hospital setting among patients with COVID-19.

4. Adverse effects of metformin use during hospitalization of patients with COVID-19

4.1 Effect of metformin on lactic acidosis

Lactic acidosis is a rare, but potentially lethal adverse effect of metformin [10]. 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 gm/d or higher, and in presence of kidney

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dysfunction defined as eGFR <60 ml/min/1.73 kg/m^2 [9].

4.2 Effect of metformin on heart failure and acute respiratory distress syndrome

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].

5. Potential mechanisms underlying metformin clinical benefits

Metformin has been shown to improve the immune response and reduce inflammation [11]. 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, Chen et al. [12] 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. However, it should be emphasized that metformin should not be used in 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 [10].

6. Conclusions and future needs

Preliminary data suggest that metformin use prior to hospitalization of patients with diabetes and COVID-19 might reduce mortality. Meanwhile, continuing metformin after hospitalization did not affect mortality, but increased risk of lactic acidosis. The risk of lactic acidosis was evident only in patients with severe symptoms of COVID-19, those with kidney dysfunction, and in patients taking 2 gm of metformin or more daily. Accordingly, metformin should be discontinued in cases of severe COVID-19 and kidney disease, and its daily doses should not exceed 2 gm. On the other hand, metformin in lower doses may be continued in mild cases, and in presence of normal kidney function in view of its possible benefits in reducing risk of heart failure and ARDS.

Table 1. Conditions in which metformin may be continued after admission of patients with COVID-19 and type 2 diabetes

COVID-19 of mild severity
Absence of kidney dysfunction defined as eGFR* < 60 ml/min/m^2
Absence of any type of acidosis, including diabetic ketoacidosis
Absence of hypoxia
Absence of hemodynamic shock or decreased tissue perfusion
Absence of concomitant infection
Metformin doses should be less than 2 gm/day

* eGFR= Estimated glomerular filtration rate

Table 1 summarizes the conditions in which metformin may be continued after hospital admission in patients with COVID-19 and diabetes based on available data. Unfortunately, all current data related to COVID-19 and metformin are based on retrospective studies prone for multiple bias and confounding factors. Randomized trials are urgently needed to determine safety and efficacy of metformin in hospitalized COVID-19 patients.

Author contributions

All authors contributed equally to this manuscript and approved the final version of manuscripts.

Conflict of Interests

The authors do not have any conflict of interest to disclose.

Ethical declarations

Not applicable.

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