International Journal of Pharmacy and Infections Therapy
Review Article

Metformin For Treatment of Covid-19: Evidence From Randomized Trials

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Received: 13 May 2023; **Accepted:** 18 May 2023; **Published:** 27 May 2023

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Abstract

Background: Many observational studies suggest a possible benefit of metformin in treatment of severe coronavirus disease 2019 (Covid-19), but evidence from randomized trials is limited.

Objective: To evaluate the therapeutic role of metformin in Covid-19 based on randomized trials.

Methods: PubMed review until May 12, 2023. Key words are Covid-19, metformin, long Covid, mortality. Randomized trials, retrospective studies, pre-print articles, and meta-analyses are included.

Results: Only 2 double-blind, placebo-controlled randomized trials, TOGETHER (n= 418) and COVID-OUT (n= 1,323), examined the effects of metformin in outpatients with COVID-19. Metformin therapy was started within 7 days after onset of symptoms. In TOGETHER trial, extended release metformin 750 mg bid for 10 days did not have any significant effects on the primary outcome, emergency department (ED) visit > 6 h or hospitalization at 28 days. In COVID-OUT trial, immediate release metformin, up to 1500 mg/d for 14 days did not have a significant effect on the primary composite end point including hypoxemia, ED visits, hospitalization, or death at 14 days, adjusted odds ratio (OR) vs placebo 0.84 (95% CI, 0.66-1.09; P=0.19). Likewise, metformin had no effect on early symptoms of Covid-19 in the first 14 days following infection. However, prespecified secondary analyses of COVID-OUT suggested a possible benefit of metformin in reduction of ED visits, hospitalization, or death, adjusted OR 0.58 (95% CI, 0.35-0.94). In addition, long-term follow-up of COVID-OUT showed a significant

42% reduction in the incidence of long Covid diagnosed by a medical provider after 10 months, hazard ratio (HR) vs. control group 0.58% (95% CI, 0.38-0.88).

Conclusions: Early treatment of symptomatic patients with Covid-19 might reduce frequency of ED visits, hospitalizations, and long Covid but had no effects on hypoxemia and severity of symptoms. Further randomized trials are needed to clarify the therapeutic role of metformin in Covid-19 in outpatient and inpatient settings.

Key words: metformin, Covid-19, long Covid, hospitalization, mortality

Introduction

Many retrospective and observational studies suggest that metformin may decrease hospitalization and mortality from Covid-19 [1-2]. These results were consistent with animal and human data showing that metformin may exert anti-viral and anti-inflammatory actions [3]. However, the results of observational studies are prone for different types of bias and unmeasured confounding factors. Therefore, stronger level of evidence with respect to the role of metformin in management of COVID-19 should be based on well-designed randomized trials. Research of the literature revealed 2 trials, TOGETHER and COVID-OUT that evaluated metformin for outpatient treatment of Covid-19 [4,5]. The main purpose of this mini-review is to provide an appraisal of the potential therapeutic role of metformin in Covid-19 based exclusively on evidence derived from randomized trials. Table 1 depicts an overview of design and main results of the TOGETHER and COVID-OUT trials [4, 5].

The TOGETHER trial

The first randomized double-blind, placebo-controlled study to examine the effect of metformin on the course and complications of Covid-19 was the TOGETHER trial [4]. This trial, conducted in Brazil, included 418 outpatients with Covid-19 (table 1). Patients were randomized to receive extended-release metformin 750 mg bid (n=215) or matching placebo (n=203) for 10 days. The primary outcome was hospitalization (defined as either retention in ED for > 6 h or admission to a tertiary hospital) at 28 days. Secondary outcomes were viral clearance at day 7, time to hospitalization, mortality and adverse drug reactions. No significant difference or even a trend was found between the metformin group and placebo group in any outcome. Thus, in the intention to treat analysis, relative risk of the primary outcome with metformin vs placebo was 1.14 (95% Bayesian Credible Interval 0.73-1.81) [4]. Accordingly, the Data and Safety Monitoring Committee recommended stopping enrollment in the metformin arm due to futility [4].

The COVID-OUT Trial

The COVID-OUT, conducted in the USA, is the second and largest double-blind placebo-controlled trial to test the effectiveness of metformin and 2 other repurposed drugs: ivermectin (anti-viral) and fluvoxamine (anti-inflammatory) on the severity and course of Covid-19 [5]. The primary outcome of COVID-OUT trial was a composite of hypoxemia (defined as ≤93% oxygen saturation on home oximetry), ED visits, hospitalization, or death at 14 days [5]. Immediate release metformin was given as 500 mg once on day 1, 500 mg bid on day 2-5, and 500 mg in the morning and 1,000 mg in the evening on days 6-14. No significant effects were demonstrated in any treatment group compared with placebo regarding the composite primary endpoint; adjusted ORs being 0.84 (95% CI, 0.66-1.09; P=0.19) with metformin, 1.05 (95% CI 0.76-1.45; P=0.78) with ivermectin, and 0.94 (95% CI, 0.66-1.36; P=0.75) with fluvoxamine [5]. Likewise, symptom severity, a key secondary end point,

was not affected in any treatment group. Meanwhile, in the metformin group, there was a trend towards amelioration of several components of the primary end point. Thus, adjusted OR for ED visits, hospitalization or death was 0.58 (95% CI, 0.35-0.94) and adjusted OR for hospitalization or death was 0.47 (95% CI, 0.20-1.11) (P values were not calculated) [5].

Effect of metformin on long Covid

The COVID-OUT trial was extended to evaluate the effects of metformin, ivermectin, and fluvoxamine on the incidence of long Covid. In fact, long Covid diagnosed by a medical provider at 10 month-follow-up was a pre-specified secondary outcome of the COVID-OUT trial [6]. Thus, after 10 months, 6.3% of patients in the metformin group received the diagnosis of long Covid compared with 10.6% in the control group, HR 0.58 (95% CI, 0.38-0.88) [6]. No effects on incidence of long Covid was demonstrated in the ivermectin group [HR 0.99 (95% CI, 0.59-1.64)] and fluvoxamine group [HR 1.36 (95% CI, 0.78-2.38)] [6]. Risk of bias remained low because blinding was maintained during the 10-month follow-up period [6].

The TOGETHER trial versus COVID-OUT trial

There were important differences between the TOGETHER and COVID-OUT trials in terms of patients' demographics, vaccination status against severe acute respiratory syndrome coronavirus 2 (SARS-Co-2), metformin formulation (extended vs. immediate release), duration of therapy, and dosing regimen (table 1). In general, the COVID-OUT trial was better designed compared with the TOGETHER trial due to enrollment of a greater number of patients, longer duration of follow-up and higher adherence to metformin regimen (table 1). In fact, only 22% of patients in the TOGETHER trial received metformin as dictated by the study protocol compared to 73% in the COVID-OUT trial (table 1). While the 2 trials did not show a significant impact of metformin on their primary endpoints, significant differences between metformin and control groups emerged in the COVID-OUT trial in terms of several prespecified secondary outcomes. Such outcomes included a composite of ED visits, hospitalization, or death, and in incidence of long Covid [5, 6].

Conclusions and current needs

Only 2 randomized trials examined the effects of metformin on the course and complications of covid-19. Overall, the balance of evidence derived from the better designed COVID-OUT trial suggests a possible benefit of metformin in reducing risk of clinically important outcomes including a composite of ED visits, hospitalization, or death. Despite the lack of efficacy of metformin in reducing symptoms of Covid-19, long-term follow-up of patients in COVID-OUT trial showed an impressive 42% reduction in diagnosis of long Covid. Indeed, metformin is the first drug shown to decrease risk of long Covid in the setting of a randomized blinded trial [6]. Further randomized studies are urgently needed to clarify the role of metformin for treatment and prevention of short-term and long-term complications of Covid-19. These studies should help determine the optimum dose and duration of metformin, its safety and efficacy in the outpatient and inpatient setting, as well as patients' subgroups that mostly benefit from such therapy.

Conflict of interest: The authors do not have conflict of interest to declare.

Table 1. **Randomized clinical trials of metformin for treatment of Covid-19**

	TOGETHER [4]	COVID-OUT [5,6]
Subjects	n=214, 57% F, median age 52, 91% mixed race, 45% had BMI ≥30 kg/m2, SARS-CoV-2 vaccination excluded	n=1,323, 56% F, median age 46, 82% Whites, approximately 48% had BMI ≥30 kg/m2, 52% vaccinated against SARS-CoV-2
Country	Brazil	USA
Timing of subject enrollment	Within 3 days after confirmed diagnosis of COVID-19 and less than 7 days after onset of symptoms	Within 7 days of onset of symptoms after confirmation with positive rapid antigen test for SARS-Co-V-2
Metformin regimen	Extended release 750 mg bid (n=215) vs. matching placebo (n=203)	Immediate release with gradual dose increase over 6 days to 1500 mg/d (n=663) vs. placebo (n=660)
Duration of metformin therapy	10 days	14 days
Adherence to metformin per protocol	22% in metformin group vs. 12% in placebo group	73% metformin vs 73% with placebo
Primary outcome	Hospitalization at 28 days	Composite of hypoxemia, ED visits, hospitalization, or death
Secondary outcomes	Viral clearance at day 7, time to hospitalization, mortality, adverse drug reactions	Symptom severity, Long Covid by day 300 (i.e. 10 months)
Follow-up	28 days	14 days. For the long Covid outcome: 300 days
Results	No significant differences between metformin and placebo in any outcome	No significant differences in composite outcome or symptom severity. Significant reduction by metformin in ED visits, hospitalization or death, HR 0.58 (95% CI, 0.35-0.94)
Long Covid	Not evaluated	10.6% in control group vs 6.3% in metformin group, HR 0.58 (95% CI, 0.38 to 0.88)
Comments	Enrollment in metformin arm was stopped due to futility	Blinding was maintained up to 300 days follow-up

Abbreviations: Covid-19: severe coronavirus disease 2019, F; females, BMI, body mass index, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ED: emergency department, HR: hazard ratio

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Citation: Nasser Mikhail , Soma Wali (2023), "**Metformin For Treatment of Covid-19: Evidence From Randomized Trials**", Int J Phar Inft Thrp ; 6(1)-101: 1-5.

DOI:10.31829/2765-852X/ijpit2023-6(1)-101