Metformin in COVID-19: clinical trials are needed to prove its benefits

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The retrospective cohort study reported by Saygili and colleagues [1] is the latest addition to the literature on the use of metformin in patients with coronavirus disease 2019 (COVID-19). The authors aimed to determine the effect of preadmission use of metformin on COVID-19-related mortality in 240 propensity score-matched patients hospitalized with COVID-19 [1]. The study reported reduced all-cause mortality (adjusted hazard ratio = 0.585; 95% confidence interval 0.371 to 0.920) with preadmission use of metformin relative to non-use of metformin [1]. In fact, the findings of the study were in agreement with the previously published systematic reviews and meta-analyses investigating the same topic. At least eight systematic reviews and meta-analyses [2–9] have been published (indexed in PubMed); the latest systematic review and meta-analysis [2], which included 19 observational studies, reported that the use of metformin is associated with significantly reduced COVID-19-related mortality (odds ratio = 0.66; 95% confidence interval 0.56 to 0.78).

The beneficial clinical effects of metformin in patients with serious infection have been reported even before the beginning of the COVID-19 pandemic [10]; a meta-analysis [11] of five observational studies with 1282 patients demonstrated benefits with the use of metformin in patients with sepsis and concurrent diabetes in which there were significantly reduced odds of death (pooled OR = 0.59; 95% confidence interval 0.43 to 0.79). The mechanisms of clinical benefits with the use of metformin in COVID-19 have been recently reviewed [12]. Since it is evident that hyperglycemia clearly increases disease severity and risk of death in patients with COVID-19, blood glucose levels must be adequately monitored and maintained, which could be achieved by the use of metformin. Besides, metformin could reduce the detrimental effects of COVID-19 through several mechanisms, which include its anti-inflammatory and immunomodulatory action, effect on viral entry and ACE2 stability, reduced viral survival by its effect on endosomal pH, mTOR inhibition, and positive influence on gut microbiota. Therefore, in patients with COVID-19, metformin provides metabolic protection in addition to protection of COVID-19-related complications, including thrombotic events and exaggerated immune response.

Thus far, there has not been a keen interest among the medical fraternity to trial the use of metformin in patients with COVID-19 compared to most of the other repurposed drugs; for instance, only three active trials investigating the use of metformin in patients with COVID-19 had been registered in the registry of clinical trials (ClinicalTrials.gov) whereas over 80 trials had been registered in the same registry investigating the use of ivermectin in patients with COVID-19. The heightened interest to trial the use of ivermectin [13] in patients with COVID-19 stems merely from an in vitro study [14] demonstrating its ability to inhibit the replication of SARS-CoV-2, the causative pathogen of COVID-19, prior to the availability of strong observational evidence. Despite positive observational evidence [2–9] demonstrating potential benefits, the use of metformin in patients with COVID-19 never comes under the limelight.

We believe that metformin should be given a fair chance in clinical trials to establish its clinical benefits in patients with COVID-19. Metformin is inexpensive and readily available, and hence the feasibility to perform clinical trials investigating the use of metformin in patients with COVID-19, especially in countries with limited resources to purchase high-end drugs for COVID-19 such as molnupiravir and Paxlovid. Nevertheless, physicians must also carefully evaluate the eligibility of the use of metformin for patients with COVID-19 mortality since it is associated wih lactic acidosis. In the meantime, the prescription of metformin to

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eligible patients in primary care should be encouraged since the clinical benefits of metformin in COVID-19 extends to its preadmission/prediagnosis use.

Declarations

Conflict of interest The authors declare no competing interests.

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