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LETTER TO THE EDITOR

Metformin therapy in COVID-19: inhibition of NETosis

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We appreciate Usman et al. [1] for reporting the sub-analysis of the evaluation of hemostasis in hospitalized COVID-19 patients (TARGET-COVID) study which investigated the relationship among the use of metformin, laboratory biomarkers, and clinical outcomes in patients with coronavirus disease 2019 (COVID-19). In their multivariable analysis, the use of metformin at the time of hospital admission in patients with COVID-19 was associated with significantly fewer days in hospital (odds ratio = − 7.4; 95% confidence interval − 1.7 to − 13.1) as well as significantly lower intubation rate (odds ratio = − 0.2; 95% confidence interval − 0.04 to − 0.36). Indeed, the positive effect of metformin therapy in patients with COVID-19 has previously been confirmed in a meta-analysis of observational studies [2] which reported significantly reduced odds of death with pre-diagnosis metformin use (pooled odds ratio = 0.59; 95% confidence interval 0.43–0.79). Nevertheless, the findings of these observational studies [1, 2] contradict the findings of a recently reported randomized controlled trial [3] which investigated the efficacy of metformin among high-risk adult outpatients with COVID-19. The randomized trial reported that clinical improvement at day 28, defined as the time to reporting a score of 0 on the World Health Organization clinical worsening scale, was not significantly different between patients randomized to metformin compared to their counterparts randomized to placebo (odds ratio = 1.05; 95% confidence interval 0.71 to 1.56). In addition, the mortality rate was not significantly different between the metformin group and the placebo group (3.3% versus 4.4%; P = 0.53).

It is worthwhile to discuss the discrepancy in the findings with metformin therapy in patients with COVID-19 between real-life observational studies and randomized trial to avoid hampering further enthusiasm to investigate the efficacy of metformin therapy in this population of patients. We believe the discrepancy may be attributable to that the main driver of clinical benefits with metformin in COVID-19 is the ability of metformin to inhibit the formation of neutrophil extracellular trap (NET) induced by SARS-CoV-2, but not its anti-inflammatory activities [4]. Recently, it has been reported in patients with COVID-19 that, persistent elevations in NETs post-disease diagnosis were detected in those who were symptomatic, but not in their counterparts who were asymptomatic [5]. Therefore, NET formation is an important determinant of clinical severity in this population of patients. Patients with COVID-19 also displayed impaired NET degradation, which leads to the persistence of symptoms [5]. Moreover, NETs were detected in many organs of adult patients who died from COVID-19 related complications [5].

The findings where pre-diagnosis use of metformin was associated with clinical benefits (in observational studies [1, 2]) may be due to inhibited NET formation by metformin upon SARS-CoV-2 infection during the very initial stage of the disease (incubation period, when no symptoms are manifested). On the other hand, de novo introduction of metformin after diagnosis of COVID-19 and upon manifestation of flu-like symptoms (in the randomized trial [3]) did not lead to clinical benefits since dampened NET formation by metformin could no longer help in the disease course, where NETosis has already occurred and the impaired NET degradation becomes the contributor to the clinical severity.

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As discussed by Usman et al. [1], metformin could display anti-inflammatory activities in patients with COVID-19 through inhibition of the nuclear factor kappa B (NF-κB pathway), but it seems that the anti-inflammatory mechanism of metformin is not adequate to significantly improve the prognosis of patients with COVID-19, as reported in the randomized trial [3].

Our hypothesis where inhibition of NET formation by metformin plays a major role in its clinical benefits in patients with COVID-19 is also supported by the observations in the study reported by Usman et al. [1] where the level of D-dimer was significantly lower in the metformin group compared to the metformin naïve group (P = 0.04). The level of blood myeloperoxidase-DNA, which is a biomarker of NET formation as well as early response to SARS-CoV-2 infection, has been reported to positively correlate with the level of D-dimer in patients with COVID-19 [6]. Therefore, we believe future clinical trials investigating the clinical efficacy of metformin in COVID-19 should administer metformin for pre-exposure prophylaxis, and target especially high-risk patients prone to COVID-19 complications. In addition, we urge for widespread prescribing of metformin in the real-life clinical practice to patients who are indicated, especially those with type 2 diabetes, who are at high risk of severe course of COVID-19. Also, it would be interesting to investigate the thrombotic-related outcomes with metformin therapy in patients with COVID-19 due to its ability to inhibit NET formation which contributes to immunothrombosis in patients with COVID-19 [7, 8].

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