

# Metformin use amid coronavirus disease 2019 pandemic

To the Editor,

A recent article by EL-Arabey and Abdalla<sup>1</sup> entitled "Metformin and COVID-19: A novel deal of an Old Drug" presented a well-reasoned discussion on the possible protective mechanism of metformin towards novel coronavirus disease 2019 (COVID-19).


There are a few aspects that we would like to add to complement the discussion by EL-Arabey and Abdalla.<sup>1</sup> First, the authors suggested that the reduction of weight with the use of metformin, especially among obese patients, may have a protective effect on mortality from COVID-19. However, in individuals who are obese, metformin promotes at best only modest weight reduction. In a study aimed to determine the effectiveness of metformin on weight loss in nondiabetic individuals with obesity, the mean weight loss in the metformin-treated group was only 5.8 kg.<sup>2</sup> More than half of the included participants (52.6%) receiving metformin lost only less than 5% of their weight. This is in stark contrast with other established weight-loss drug therapy, such as orlistat where patients could lose 5 to 10 kg (8% of baseline weight) according to a meta-analysis.<sup>3</sup> Therefore, weight reduction by metformin may not be the main mechanism to protect against, if any, towards mortality from COVID-19.

Second, we would like to caution that metformin reduces intestinal absorption of vitamin B12 in up to 30% of metformin-treated patients and lowers serum vitamin B12 concentrations by 5% to 10%.<sup>4,5</sup> The prevalence of vitamin B12 deficiency (or borderline low levels) in metformin-treated patients may approach 20% over 5 years.<sup>5</sup> Since vitamin B12 plays an important role in immune system regulation, its deficiency may negate the potential protective effects, if any, from COVID-19 and its associated mortality. Specifically, cellular immunity, especially related to CD8+ cells and the natural killer cells, may be impaired in patients with vitamin B12 deficiency.<sup>6</sup> These cytotoxic lymphocytes (CD8+ T cells and natural killer cells) are important to contain viral infection and they have been observed to decrease significantly during the early stage of COVID-19, which suggests that exhaustion of these cytotoxic lymphocytes facilitates infection from COVID-19.<sup>7</sup>

Third, the risk of lactic acidosis from metformin treatment cannot be ignored. Though the incidence of lactic acidosis in metformin users appears to be very low, lactic acidosis related to metformin remains a concern because of the high case-fatality rate.<sup>8</sup> Predisposing factors to lactic acidosis with metformin include any conditions with hypoperfusion or hypoxemia, such as acute or renal impairment, acute heart failure, acute pulmonary decompensation, and sepsis.<sup>9</sup> These conditions can be very common among hospitalized patients with COVID-19 where metformin should be avoided in

most hospitalized COVID-19 patients than not. Patients with COVID-19 may have already elevated lactate levels.<sup>10</sup>

In conclusion, while evidence may not be sufficient to suggest the efficacy of metformin in COVID-19, the well-established harms should be cautioned. Metformin-treated patients should undergo routine B12 monitoring, especially in patients with poor dietary intake or absorption who may be at higher risk in vitamin B12 deficiency. This may be especially important amid COVID-19 pandemic to avoid disruption in immunity to combat severe acute respiratory syndrome coronavirus 2, the causative agent of COVID-19. Besides, the possible risk of lactic acidosis in hospitalized patients with COVID-19 receiving metformin should be recognized and acted upon preemptively.

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