# Metformin: an inexpensive and effective treatment in people with diabetes and COVID-19?

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People with diabetes have been reported to have more severe outcomes, as compared with non-diabetic people, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Numerous reports have shown how the risk of intensive care unit admission, intubation for mechanical ventilation, and mortality have been greater among people with diabetes, as compared with people without diabetes.[1] In people with diabetes, glycaemic control might contribute to reducing the risk of these outcomes because lower plasma glucose levels at the time of admission[2] and during hospitalisation[3] have been associated with improved prognosis. Whether it is glycaemic control per se that accounts for improved outcomes, or whether some anti-hyperglycaemic agents confer some advantage has been a matter of discussion.[1] In *The Lancet Healthy Longevity*, Carolyn T Bramante and colleagues report[4] the results of a large retrospective cohort analysis, including 3923 people without a metformin prescription (55·4% women, median age 76·0 years) and 2333 people with a metformin prescription (48·4% women, mean age 73·0 years), exploring whether use of metformin before admission to hospital for COVID-19 (based on filled pharmacy prescriptions of at least 90 days within 12 months of COVID-19 diagnosis) could affect in-hospital mortality of people with type 2 diabetes and obesity and, if so, the extent of this effect. According to Bramante and colleagues' analysis, metformin was associated with a significant reduction in the risk of mortality in women, but not in men. Although other retrospective studies have suggested a potential benefit of metformin[5–7] this gender effect was not previously reported. The authors explain this result might be due to a more specific effect of the drug in reducing TNFα in females, which is greater than in men. Metformin has been suggested to have anti-inflammatory properties, as shown by activation of autophagy, conversion of M2 macrophages, and stimulation of CD8 memory T-regulatory cells. Moreover, metformin can exert antioxidant actions and these effects could lend support to a potential benefit in the occasion of major inflammatory reactions as it occurs with COVID-19.[8] Metformin has been suggested to be associated with reduced mortality during sepsis and in patients with pulmonary disease[8]—ie, the possibility of a beneficial effect, as shown by Bramante and colleagues, is plausible. However, some caution should be taken when drawing final conclusion from their results. First, their analysis is based on administrative records of filled pharmacy prescription of metformin, which does not provide information on effective use of the prescribed drug, duration of treatment, whether metformin was actually taken at the time of hospital admission, and dose. Similarly, whether metformin therapy was maintained or withdrawn on admission to hospital cannot be established. Extrapolation of beneficial effect of metformin into a recommendation for implementing or continuing its use at the time of hospital admission would require taking into consideration potential side-effects. Metformin is potentially associated with lactic acidosis under conditions of hypoxaemia or organ failure because lactic acidosis might occur in people with acute respiratory distress syndrome due to COVID-19. A retrospective study[9] involving more than 2500 people with confirmed COVID-19 with type 2 diabetes from 16 hospitals in China found an increased incidence of acidosis, although this incidence was not associated with greater mortality in people treated with metformin during hospitalisation.

The retrospective nature of Bramante and colleagues' study, and other similar studies, needs to be carefully considered due to the large number of potential confounders, including confounding by indication. In Bramante and colleagues' study, among those who had metformin prescription, there were more young individuals (age <75 years; with metformin 59·2%, with no metformin 48·7%) with lower prevalence of coronary artery disease, heart failure, chronic kidney disease, and end-stage renal disease—all conditions that have been associated with poorer outcomes in people with type 2 diabetes and COVID-19.[1] The extent to which these differences might be even greater when comparing men and women with type 2 diabetes and obesity remains to be fully elucidated. Finally, Bramante and colleagues' study and other retrospective studies have collected survival data from different hospitals, which might have adopted different treatment protocols for COVID-19, including

decisions concerning intubation and resuscitation procedures. All these limitations have been acknowledged by the authors, who have tried accounting for all these variables by using different statistical methods; however, it might not be possible to take all of them into account in spite of logistic, Cox proportional-hazard regressions, and propensity matching. Nonetheless, the results of these studies add up to the well establish pleiotropic effect of metformin. After the cardiovascular protection initially reported in the UK Prospective Diabetes Study, metformin has been suggested to protect from diabetes-related and non-diabetes-related comorbidities, including renal, neurological, and neoplastic diseases, and reducing consequences under several stress conditions.[10] Nonetheless, this evidence is largely indirect, and based on retrospective, observational studies. Large, randomised, prospective controlled trials might be difficult to do, particularly at the time of challenging situations like the COVID-19 pandemic. Moreover, randomised trials are unlikely to be initiated because of the lack of consistent investment in a potentially powerful, yet out-of-patent, drug. However, it is because of the low cost of metformin that randomised trials could prove a very high cost-effectiveness, particularly when dealing with highly expensive diseases, such as COVID-19.

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