
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

factors—explain the increased risk of morbidity and mortality observed in transgender women as opposed to transgender men. Increased publication of data on the safety of gender-affirming hormone therapy in the transgender population, which is lifesaving for many people, is encouraging. Continued refinement of delivery of care for transgender people will help to improve the lives of a clinically vulnerable growing population.

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# Diabetic ketoacidosis risk during the COVID-19 pandemic

Diabetic ketoacidosis (DKA) is the most common acute hyperglycaemic emergency in people with diabetes. DKA most often occurs in people with type 1 diabetes, but can also occur in patients with poorly controlled type 2 diabetes under stressful conditions.[1] Studies have reported an increased prevalence of DKA in patients with type 1 or type 2 diabetes with COVID-19 infection. Patients admitted to hospital with severe hyperglycaemia and DKA with COVID-19 infection have been shown to have increased severity of complications and a higher rate of mortality compared with patients without COVID-19.[2]

The Article by Shivani Misra and colleagues[3] examined the incidence of emergency hospital admissions coded with DKA in a country-wide database in England. The study focused on three discrete time periods during the COVID-19 pandemic: from March 1 to June 30, 2020 (first wave), July 1 to Oct 31, 2020 (post-first wave), and Nov 1, 2020, to Feb 28, 2021 (second wave), and compared the incidence of DKA admissions during these periods with the mean incidence during the equivalent time periods in the 3 years before the pandemic (2017–20). The authors found that DKA admissions in England were increased by 6% (95% CI 4–9) during the first wave of the pandemic compared with in the prepandemic years. The increase in DKA admissions was accounted for by a 41% (35–47) increased incidence of DKA in patients with pre-existing type 2 diabetes and 57% (48–66) increased incidence in patients with new-onset of diabetes, but a 19% (16–21) decreased incidence in those with pre-existing type 1 diabetes. Furthermore, DKA admissions were increased in older patients (60 years or older) with pre-existing type 2 diabetes and of non-White ethnicities. Patients admitted with DKA with new-onset diabetes had a median age of 30 years (IQR 13–51) and comprised a higher proportion of men and people of non-White ethnicities than in the prepandemic years. Among DKA admissions during the first wave, 12% had a diagnosis of COVID-19. 6% (5–7) of admissions with type 1 diabetes, 23% (21–24) with type 2 diabetes, and 7% (6–9) with newly diagnosed diabetes had concurrent COVID-19.

The authors found that incidence of DKA admissions had increased in people with type 2 diabetes even


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without concurrent COVID-19 infection. Before the pandemic, a trend of increased DKA hospitalisations was reported in patients with type 1 diabetes and type 2 diabetes during the past decade in England.[4] The risk factors for DKA include low socioeconomic status, young age, female sex, high $HbA_{1c}$ levels, and a previous episode of DKA. An important finding from the study by Misra and colleagues is that increased incidence of DKA admissions during the COVID-19 pandemic occurred primarily in type 2 diabetes and newly diagnosed diabetes, and not in type 1 diabetes. Possible reasons for increased DKA incidence during the pandemic are that due to social restrictions, less medical care is sought by people with type 2 diabetes, and there is worsening glycaemic control and increased sedentary lifestyle. Furthermore, new-onset diabetes that presents with DKA has been recognised as ketosis-prone diabetes,[5] and has been described mostly in people of African origin with overweight or obesity, with a prevalence two to three times higher in men than in women. At presentation, these patients were found to have impaired insulin secretion but without the autoimmune markers of type 1 diabetes, and after initial insulin treatment, about 70% were able to discontinue insulin due to recovery of pancreatic β-cell function.[5] Although the true incidence is not known, ketosis-prone diabetes phenotype might account for DKA occurring in people with type 2 diabetes with severe COVID-19 infection.

The cause of increased incidence of DKA with COVID-19 infection is likely to be multifactorial. Enteric and respiratory viral infections have been associated with autoimmune-mediated destruction of β cells in people with underlying genetic risk of type 1 diabetes, either through molecular mimicry or altered immune response.[6] Infections can cause increased insulin resistance leading to glycaemic decompensation in patients with a history of diabetes. Pancreatic islets express low levels of the angiotensin converting enzyme 2 (ACE2) receptor that is necessary for SARS-CoV-2 infection.[7] One study of human donor islets in patients with severe COVID-19 showed that, despite low levels of ACE2 expression, SARS-CoV-2 was present in pancreatic β cells, which suggests that SARS-CoV-2 might cause β-cell dysfunction and subsequent hyperglycaemia.[7,8]

In addition, severe hyperglycaemia and DKA, as well as COVID-19 with severe disease, have been associated with increased oxidative stress markers and high concentrations of pro-inflammatory cytokines.[9] Severe hyperglycaemia induces liver production of C-reactive protein under the influence of activated macrophages that produce pro-inflammatory cytokines, such as IL-6, IL-1β, and tumour necrosis factor. These cytokines in turn impair insulin secretion and reduce insulin action. IL-6 in particular has been highlighted as likely to play a role in a maladaptive immune response to SARS-CoV-2. Whether the inflammatory cascades engaged in DKA and severe COVID-19 are synergistic in leading to worse clinical outcomes remains to be seen.

The increased rates of hospitalisations for DKA in patients with type 1 and type 2 diabetes during the pandemic highlight the need to be vigilant in patients with COVID-19. The trend of increasing DKA admissions that started before the pandemic has been exacerbated by COVID-19, particularly in patients with poorly controlled type 2 diabetes.

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