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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1 Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017; **102:** 3869–903.
2 Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals. *J Clin Transl Endocrinol* 2015; **2:** 55–60.
3 Wierckx K, Van Caenegem E, Schreiner T, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med* 2014; **11:** 1999–2011.
4 de Blok CJM, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol* 2021; published online Sept 2. https://doi.org/10.1016/S2213-8587(21)00185-6.
5 Fung R, Hellstern-Layefsky M, Tastenhoye C, Lega I, Steele L. Differential effects of cyproterone acetate vs spironolactone on serum high-density lipoprotein and prolactin concentrations in the hormonal treatment of transgender women. *J Sex Med* 2016; **13:** 1765–72.
6 Nota NM, Wiepjes CM, de Blok CJM, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain 2018; **141:** 2047–54.
7 Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics* 2020; **145:** e20191725.
8 van Velzen DM, Paldino A, Klaver M, et al. cardiometabolic effects of testosterone in transmen and estrogen plus cyproterone acetate in transwomen. *J Clin Endocrinol Metab* 2019; **104:** 1937–47.
9 Getahun D, Nash R, Flanders WD, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med* 2018; **169:** 205–13.
10 Chen D, Abrams M, Clark L, et al. Psychosocial characteristics of transgender youth seeking gender-affirming medical treatment: baseline findings from the trans youth care study. *J Adolesc Health* 2021; **68:** 1104–11.

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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1 Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers* 2020; **6:** 40.
2 Pasquel FJ, Messler J, Booth R, et al. Characteristics of and mortality associated with diabetic ketoacidosis among US patients hospitalized with or without COVID-19. *JAMA Netw Open* 2021; **4:** e211091.
3 Misra S, Barron E, Vamos E, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. *Lancet Diabetes Endocrinol* 2021; published online Sept 2. https://doi.org/10.1016/S2213-8587(21)00208-4.
4 Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. *Diabetes Care* 2018; **41:** 1870–77.
5 Vellanki P, Umpierrez GE. Diabetic ketoacidosis: a common debut of diabetes among African Americans with type 2 diabetes. *Endocr Pract* 2017; **23:** 971–78.
6 Craig ME, Kim KW, Isaacs SR, et al. Early-life factors contributing to type 1 diabetes. *Diabetologia* 2019; **62:** 1823–34.
7 Steenblock C, Richter S, Berger I, et al. Viral infiltration of pancreatic islets in patients with COVID-19. *Nat Commun* 2021; **12:** 3534.
8 Wu CT, Lidsky PV, Xiao Y, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab* 2021; **33:** 1565–76.e5.
9 Martinez-Urbistondo M, Mora-Vargas A, Expósito-Palomo E, et al. Inflammatory-related clinical and metabolic outcomes in COVID-19 patients. *Mediators Inflamm* 2020; **2020:** 2914275.