**Comparison of diabetic ketoacidosis in adults, during the SARS-CoV-2 outbreak and over the same time period for the 3 preceding years**

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*Dear Editor*

Diabetic ketoacidosis (DKA) is a life-threatening metabolic decompensation occurring with any diabetes subtype, often precipitated by infection. During the SARS-CoV-2 outbreak, reports emerged suggesting Coronavirus disease-19 (Covid-19) is associated with a higher frequency of DKA with atypical presentations (1,2) and led some to hypothesise a direct effect of SARS-CoV-2 on the pancreas itself (3).

We addressed the observational bias of such reports, by comparing DKA cases and characteristics in adults during the outbreak, to matched 4-month periods (1st February – 31st May) from 2017-2019, at a large London NHS Trust.

Analysing 175 biochemically confirmed DKA cases, the 3-year average for cases admitted over the 4-month period was 44 (exact Poisson confidence interval, 32-59) versus 43 (31-58) during the outbreak. Although adult medical admissions reduced by 33% (3-year average for the same time period 26,831 vs 19,267) the proportion of individuals presenting with DKA during the outbreak was 0.22% of all admissions compared to a 3-year average of 0.16%, p=0.16.

Among those presenting with DKA, the proportion with a diagnosis of type 2 diabetes during the SARS-CoV-2 outbreak was higher compared to the preceding 3-years (37% vs 17%, p=0.01) (table 1) and type 1 diabetes cases reduced from 68% pre-pandemic to 44%. Adults with type 2 diabetes had a significantly higher proportion of positivity to SARS-CoV-2 than those with other types of diabetes; 89% vs 27% respectively, p=0.009.

Adults (n=43) presenting during the outbreak were older than those (n=132) in preceding years, median age 53 vs 44 years, p=0.03 and fewer were insulin-treated; 89% vs 60%, p<0.0001.

Comparing n=89 type 1 diabetes DKA cases pre-pandemic to n=19 during the outbreak, we observed no significant differences in demographic or biochemical characteristics (pH, ketone or bicarbonate level) of DKA and noted markedly elevated HbA1c (11.1% /98 mmol/mol pre-pandemic vs 12.9%/118 (p=0.1)) across both timeframes.

Adults (n=22) with type 2 diabetes in DKA during the outbreak were of similar age to pre-pandemic (69 vs 63 years p=0.5) and no demographic or biochemical differences were observed including SGLT-2 inhibitor use (table 1).

People with type 2 diabetes in DKA who had Covid-19 (n=8) were more likely to be of non-white ethnicity (100% vs 35%, p=0.015) than cases pre-pandemic (n=22) and equally likely to not be insulin treated (50% vs 50%). In total 5/43 (12%) individuals (all with type 2 diabetes and 4/5 with Covid-19) died during their admission with DKA compared to 3/130 (2.3%), p=0.023, pre-pandemic (table 1). Those who died had significant comorbidities or multi-organ failure at admission and were not deemed appropriate for intensive care or ventilatory support.

In this systematic analysis of DKA presentations during the SARS-CoV-2 pandemic compared to previous years, no significant changes in absolute numbers of DKA cases were observed but adults with type 2 diabetes disproportionately contributed to cases. The presentations of DKA in people with type 2 diabetes were significantly associated with Covid-19 infection, whilst proportions of people presenting in DKA with known type 1 diabetes reduced and were less likely to test positive.

We hypothesise that the characteristics of those over-represented in the DKA cohort during the pandemic, reflect the characteristics of those most at risk of the severe manifestations of Covid-19 (4); older individuals, with suboptimal glycaemic control and a propensity towards people from non-white ethnic groups, in those with Covid-19. A study of n=35 hyperglycaemic emergencies (2) in SARS-CoV-2 positive patients supports our observation of excess type 2 diabetes presentations.

The ‘stress response’ associated with Covid-19 may account for the higher proportion of DKA in those with type 2 diabetes; relative insulin deficiency from rising glucagon and cortisol contributes to DKA development, particularly in those not insulin-treated. Excess DKA was noted in a previous influenza epidemic when ~70% of the typical DKA cases/ year occurred in an 8 week period (5), suggesting DKA in at risk individuals may be an expected feature of any severe viral infection.

We observed no differences in the biochemical characteristics or severity of DKA, however despite this, a higher death rate was observed, specifically in those with Covid-19. With larger numbers biochemical differences may emerge, however the higher frequency of type 2 diabetes may account for observations of ‘atypical presentations’ as practitioners maybe more accustomed to managing DKA in people with type 1 diabetes.

We acknowledge national testing strategies employed early in the outbreak may have missed some cases of Covid-19; up until 26th April, specific criteria had to be met (fever, cough, breathlessness) to be tested, however beyond this, all admissions were tested.

In conclusion, the SARS-CoV-2 outbreak was associated with similar numbers of DKA cases in adults compared to previous years. However, an excess of cases occurred in older individuals with type 2 diabetes, less likely to be insulin-treated and these presentations were specifically associated with positivity to SARS-CoV-2 in non-white ethnic groups.

Further work is needed to determine whether this represents a specific SARS-CoV-2 effect on the beta-cell or if they reflect the effects of widespread infection on risk of DKA, in susceptible individuals.

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*Contributions*

Study design & methodology; SM, TT, DG, VB & JV. Literature search; PHJ, SM. Data collection; SM, BK, PHJ, KM, MR, VS and GT. Data curation; SM, BK, PHJ. Formal analysis; SM, BK, TT, DG, VB & JV All authors helped draft, edit and review the submitted manuscript.

Disclosures

All authors disclose no conflicts of interest

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**Table 1:** Proportion of cases presenting with diabetic ketoacidosis (DKA) during the outbreak and in comparison to the 4-month period from 1st Feb- 31st May between 2017-2019. Sub-analysis by subtype of diabetes and SARS-CoV-2 status along with treatment and mortality data. p-values using a Fishers exact test.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total2017 2019 n (%) | During Outbreak n (%) | p-value (before vs outbreak) | n (%) Tested for SARS-CoV-2 | SARS-CoV-2 Positive n (%)  | SARS-Cov-2 Negative n (%) | p-value (positive vs negative) |
| Total DKA cases (biochemically confirmed) | 133 | 43 |  | 24 (56) | 12 (50) | 12 (50) |  |
| Subtypes of diabetes |  |  |  |  |  |  |  |
| Known type 1 diabetes | 89(68) | 19(44) | 0.019 | 9 (47) | 1 (11) | 8 (89) | 0.002 |
| Known type 2 diabetes | 22(17) | 16(37) | 9 (56) | 8 (89) | 1 (11) |
| Known other type | 4(3) | 2(5) | 2 (100) | 1 (50) | 1 (50) |
| New presentation | 15(12) | 6(14)& | 4 (67) | 2 (50) | 2 (50) |
| All non-type 2 diabetes | 108(83) | 27(63) | 0.01\* | 15 (56) | 4 (27) | 11 (73) | 0.009\* |
| All known diabetes | 115(88) | 37(86) | 0.79$ | 20 (54) | 10 (50) | 10 (5) | 1.0$ |
| Treatment of type 2 diabetes at admission |  |  |  |  |  |  |  |
| Insulin-treated at admission n (%) | 11 (58) | 6 (38) | 0.32 | -- | -- | -- | -- |
|  SGLT2-inhibtor n (%)  | 3 (14) | 1 (6) | 0.62 | -- | -- | -- | -- |
| Mortality |  |  |  |  |  |  |  |
| Overall n (%) | 3/130 (2.3) | 5/43 (12) | 0.023 | 4/5 (80) | 4/4 (100) | 0 | -- |
| Type 2 diabetes n (%) | 2/22 (9) | 5/16 (31) | 0.12 | 4/5 (80) | 4/4 (100) | 0 | -- |

\*Statistical comparison of all non-type 2 diabetes cases vs type 2 diabetes

$ Statistical comparison of all known diabetes DKA cases versus new diabetes presentation DKA cases

& Of the six new diagnoses, reviewed retrospectively; three had type 1 diabetes (positive pancreatic-autoantibodies), one had type 2 diabetes, one had pancreatic type 3c diabetes and the final developed insulin-deficient diabetes after immune checkpoint inhibitor use, with negative autoantibodies. The checkpoint inhibitor case and a type 1 diabetes case were positive to SARS-CoV-2.