Impact of COVID-19 on glycaemic control: a retrospective cohort study in a local district general hospital

The aim of our study was to review how COVID-19 infection affects glycaemic control. We retrospectively reviewed case notes of 55 patients and found no episodes of uncontrolled hyperglycaemia in patients without pre-existing diabetes. Uncontrolled hyperglycaemia was only seen in patients with elevated HbA1c, indicating pre-existing diabetes. While it is established that the presence of diabetes predisposes to severe clinical forms of COVID-19, it is yet to be determined if COVID-19 predisposes to diabetes or adverse glycaemic outcomes.

Introduction
In late 2019, a novel coronavirus, SARS-CoV-2, was identified as the cause of an outbreak of viral pneumonia in Wuhan, China. The disease, later named coronavirus disease 2019 (COVID-19), subsequently spread globally. Previously known severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are also caused by coronaviruses.

During the 2003 SARS epidemic, acute hyperglycaemia in previously healthy patients without known diabetes (as well as patients with known diabetes) was identified as a complication of SARS illness and a risk factor for respiratory failure and death. This was attributed to ACE2 receptors present in the islets of Langerhans within the pancreas, raising the possibility that the virus could directly affect the endocrine pancreas causing uncontrolled hyperglycaemia by binding to ACE2 receptors. SARS was also shown to induce a state of transient insulin resistance. Currently, there is no published evidence to show that COVID-19 causes new-onset diabetes.

There have been anecdotal reports of COVID-19 associated with atypical ketosis and hyperglycaemia in patients without known diabetes. It has also been reported that the presence of hyperglycaemia in hospitalised patients without known diabetes is an independent marker for in-hospital mortality associated with COVID-19.

Stress hyperglycaemia, defined by the American Diabetes Association as a transient elevation in blood glucose in the setting of acute illness or after surgery in a patient with an HbA1c <48mmol/mol, is directly associated with longer hospital length of stay, longer ventilator management time and increased mortality. People living with diabetes are more likely to develop severe illness if they are infected with COVID-19. A recent report from the Office for National Statistics showed a 31.3% mortality in type 2 diabetes and 1.5% incidence in type 1 diabetes who are infected with COVID-19.

The aim of our study was to review how COVID-19 infection affects glycaemic control in patients admitted to hospital with or without pre-existing diabetes. We retrospectively reviewed case notes of patients with confirmed COVID-19 infection admitted to our local hospital to establish the incidence of uncontrolled hyperglycaemia, ketosis, diabetic ketoacidosis or hyperosmolar hyperglycaemic state on or during admission. The presence of pre-existing diabetes and patient glucose balance pre-admission was also reviewed.

Method
There were a total of 171 patients with confirmed COVID-19 infection admitted to our hospital from 15 March to 3 April 2020. We were able to access case notes for 55 patients. These notes were obtained mainly from mortuary and research teams; some were related to active inpatients on general medical wards. It was difficult to get access to all paper records as most of the patients were admitted to intensive care units or high dependency areas.

We retrospectively reviewed admission case notes, laboratory results and electronic discharge records. We collected data on HbA1c (pre- and during admission), glucose levels, acid-base status, blood ketones and COVID-19 blood panel. All patients with hyperglycaemia were further reviewed in detail to assess the management of hyperglycaemia during admission.

A diagnosis of COVID-19 was defined as a positive SARS-CoV-2 PCR nasopharyngeal swab test result; hospital admission was defined as in-hospital stay of more than 24 hours; diabetes was defined as HbA1c >48mmol/mol (6.5%) or a previous diagnosis of diabetes; uncontrolled hyperglycaemia was defined as two or more capillary blood glucose values >10mmol/L within a 24-hour period.
Results
Among all the 171 admitted patients with COVID-19, 50 (29%) had diabetes. Of the 50 patients who had diabetes, their average HbA1c was 74.9mmol/mol, ranging from 49–135mmol/mol. Sixty-nine out of these 171 patients passed away giving a total case fatality rate of 40%. Of the 50 patients admitted with diabetes 22 passed away (44% mortality). (Figure 1.)

Out of the 171 admitted, a total of 55 patient records with confirmed COVID-19 were analysed between 15 March and 3 April 2020. The age range of selected patients was between 31–94 years. Forty-two percent (23) had pre-existing diabetes; 58% (32) had no history of pre-existing diabetes. The pre-admission HbA1c among the cohorts with pre-existing diabetes ranged from 50–135mmol/mol, with an average HbA1c of 86.5mmol/mol; nine out of these 55 patients were admitted to ITU/HDU.

In the cohort with confirmed pre-existing diabetes, 39% (9/23) developed uncontrolled hyperglycaemia during admission defined as elevated blood glucose >10mmol/L on several occasions during hospital stay. In the nine patients with diabetes who developed uncontrolled hyperglycaemia, the average HbA1c was 87mmol/mol indicating sub-optimal pre-existing diabetes control.

Out of the patients with pre-existing diabetes (n=23), there was a 4% (1/23) incidence of hyperosmolar hyperglycaemic state (HHS) identified on admission. There were no episodes of reported diabetic ketoacidosis among our cohort of patients.

Among the patients not known to have diabetes on admission (32/55), only one patient had uncontrolled hyperglycaemia, but HbA1c done during admission was elevated at 68mmol/mol, leading to a new diabetes diagnosis. Of all the 55 notes audited, one patient received steroids during admission, but they were not diagnosed with diabetes and they were not hyperglycaemic. Out of the 10 patients who had uncontrolled hyperglycaemia during admission, six passed away.

This means that among patients without pre-existing diabetes, there were no episodes of uncontrolled hyperglycaemia, ketosis, HHS or diabetic ketoacidosis. Indeed, among all the patients included, with or without pre-existing diabetes, only 18% (10/55) of cases developed uncontrolled hyperglycaemia. (Figure 2.)

Summary
Among the 55 cases of single centre hospitalised patients with COVID-19 there were no episodes of uncontrolled hyperglycaemia in patients without pre-existing diabetes. Uncontrolled hyperglycaemia was only seen in patients with pre-existing diabetes and the presence of elevated HbA1c prior to or during admission.

This is a relatively small single centre study. As the data were collected during the COVID-19 pandemic, it was difficult to get access to all paper records and most of the notes that were audited were for patients who were either discharged home or had passed away; hence this needs to be taken into account when interpreting these data.

However, stress hyperglycaemia is common in critically ill patients and is an independent marker of disease severity. Furthermore, both the admission as well as the mean glucose levels during the hospital stay are strongly associated with patient outcomes. It is also important to take into account the neuroendocrine response to stress, which is characterised by excessive gluconeogenesis, glycogenolysis and insulin resistance in non-COVID illnesses. This stress response can contribute to hyperglycaemia in extreme sickness irrespective of the cause.

Long-term outcomes on the patients admitted with uncontrolled hyperglycaemia and COVID-19 are yet to be determined. Further large studies need to be conducted to demonstrate whether there is an association between COVID-19 and worsening glycaemic control leading to new diabetes diagnosis. As we collected data during the early stages of the pandemic, only one patient received steroids. However, following the preliminary reports from the RECOVERY trial providing evidence that treatment with dexamethasone at a dose of 6mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support, there will be an increased usage of dexamethasone for patients admitted with COVID-19 which will potentially increase the occurrence of uncontrolled hyperglycaemia.

We recommend not only checking blood glucose in all patients admitted to hospital with COVID-19 on at least two occasions 24 hours apart but also that all patients with hyperglycaemia must have their HbA1c tested to ensure we do not miss out a new diabetes diagnosis. Also patients admitted with COVID-19 who developed dysglycaemia during acute sickness need to be
followed up to assess the long-lasting effect on glycaemic control. While it is established that the presence of diabetes predisposes to severe clinical forms of COVID-19, it is yet to be determined if COVID-19 predisposes to diabetes or adverse glycaemic outcomes.

**Dr Aaisha Saqib,** RCP Chief Registrar and Specialist Registrar in Diabetes and Endocrinology  
**Dr Pratik Solanki,** Specialist Registrar  
**Dr Matthew Carroll,** Specialist Registrar  

**Dr Andrew Gough,** Consultant Diabetologist  
**Dr Victor Oguntolu,** Consultant Diabetologist  
1 Medway Hospital NHS Trust, Gillingham Kent, UK

**Correspondence to:** Dr Aaisha Saqib, Medway NHS Foundation Trust, Medway Maritime Hospital, Windmill Road, Gillingham ME7 5NY, UK; email: aaishasaqib@nhs.net

**Declaration of interests**

There are no conflicts of interest declared.

---

**References**

1. Yang J-K, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–9.  
2. Guillermo E, et al. Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002; 87(3):978–82.  
3. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 – United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69:382–6.  
4. Office for National Statistics. COVID related death 2020. https://www.ons.gov.uk/.  
5. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response? Crit Care 2013;17(2):305.  
6. RECOVERY Collaborative Group, Horby P, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. N Engl J Med 2020 Jul 17;NEJMoa2021436.
LETTER

Are we moving towards direct-to-consumer medication?

Sir, We recently saw a patient admitted with ketoacidosis after injecting GLP-1 analogue which she was able to buy over the internet. This illustrates the serious risks of taking medication without proper medical oversight.

A 37-year-old patient with no previous medical history came to hospital with history of vomiting and feeling generally unwell for four days. She had been drinking fluids, but not able to keep food down over this period. The day prior to admission she had taken a dose of semaglutide 1mg which she was able to buy online from a UK based website – this was marketed as ‘skinny pen plus’. She was dehydrated; otherwise clinical examination was unremarkable.

Venous blood gas showed significant acidosis with pH of 7.22 (7.35–7.45), bicarbonate of 12.8mmol/L (22–26) and normal lactate of 1.5mmol/L (0.6–2.5). Blood glucose was 3.7mmol/L with blood ketone of 6.8mmol/L. She had mild acute kidney injury with creatinine of 79µmol/L (baseline creatinine 47µmol/L). A diagnosis of starvation ketoacidosis was made and she was treated with intravenous dextrose and crystalloids. She improved clinically and all biochemical abnormalities resolved over the next 48 hours. She was discharged and advised not to take any further doses of semaglutide.

On visiting this particular website, it is surprisingly easy to buy GLP-1 analogues. The website identifies them as ‘skinny pen’ and clients are able to choose either a daily or weekly preparation based on preference and cost. After making the choice the customer is required to fill out a medical questionnaire, following which the medication arrives by post. The website mentions that ‘an experienced medical team will assess suitability for medication based on information provided and the drug is dispensed from a UK based pharmacy’. This patient did not have a phone or video consultation and did not receive any information other than the leaflet along with the drug. It is of note that GLP-1 analogues are currently not licensed in the UK as treatment for weight management. It is well known that they induce significant weight loss; however, the licence is for treatment of type 2 diabetes.

A search of the internet revealed at least half a dozen other websites offering similar prescriptions. GLP-1 analogues commonly cause gastrointestinal side effects and in about 5% of cases this can be serious enough to discontinue the drug. As there is no contact with a health care professional, it is unclear how much information is given to patients buying the drug online. Clearly this patient did not know what to expect and when to seek help.

It is likely that we will be encountering more of such cases with potential harm to some patients. This practice is blurring the boundary line of ‘Direct-to-Consumer Pharmaceutical Advertising’ which is common practice in the USA, but not allowed in the UK. All online pharmacies in the UK are regulated by the General Pharmaceutical Council; however, the NHS advises caution when ordering online drugs. Regulations about online consultations and prescriptions may need to be reviewed to ensure safe and appropriate use of GLP-1 analogues.

Dr Subash Sivaraman, 1 MRCP, MD, Consultant Physician and Diabetologist
Dr Mohandas Kozhippally, 1 MRCP, Consultant Physician
1University Hospital of North Midlands NHS Trust, Stoke-on-Trent, UK

Correspondence to: Dr Sivaraman, email: subashsivaraman@nhs.net

References
1. https://bnf.nice.org.uk/drug/semaglutide.html#indicationsAndDoses.
2. Cefalu WT, et al. Beyond metformin: safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management – reflections from a Diabetes Care editors’ expert forum. Diabetes Care 2014;37(9):