

REVIEW

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COVID-19: Impact of and on Diabetes

Jonathan Schofield • Lalantha Leelarathna • Hood Thabit

J. Schofield (✉) • L. Leelarathna • H. Thabit

Manchester Diabetes Centre, Manchester University Hospitals NHS Foundation Trust

Email: jschofield@doctors.org.uk

J. Schofield • L. Leelarathna • H. Thabit

Faculty of Biology Medicine and Health, University of Manchester

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ABSTRACT

Diabetes has been identified as a pre-existing health condition linked with worse outcomes following Coronavirus Disease 2019 infection. Here we explore the association between hyperglycaemia and more severe illness, the impact of the pandemic on diabetes service delivery, and the resultant opportunities for innovation.

Keywords: Coronavirus; COVID-19; Diabetes; Hyperglycaemia; Service Development

Key Summary Points

- Diabetes has been linked to worse outcomes following COVID-19 infection.
- COVID-19 infection is associated with atypical diabetes presentations.
- The current pandemic has required significant service redesign.
- The challenge presents opportunities for innovation in diabetes care.

BACKGROUND

On 31 December 2019, the World Health Organisation (WHO) was informed of a cluster of cases of pneumonia of unknown aetiology in Wuhan City, Hubei Province, China. On 12 January 2020 it was announced that a novel coronavirus had been identified (Public Health England, 2020). Coronaviruses are a large family of viruses and although most are responsible for mild disease, such as the common cold, they have also been responsible for more severe disease outbreaks such as Severe Acute Respiratory Syndrome (SARS-CoV) in 2002-2003 and Middle East Respiratory Syndrome (MERS-CoV) in 2012 (Song, et al., 2019).

Having declared this outbreak a Public Health Emergency of International Concern, WHO named the syndrome caused by this novel coronavirus COVID-19 (Coronavirus Disease 2019), associated with Severe Acute Respiratory Syndrome (SARS-CoV-2) (World Health Organization, 2020). The clinical spectrum of COVID-19 infection appears remarkably heterogeneous, ranging from very mild symptoms to multi-organ failure and death.

DIABETES AS A PRE-EXISTING HEALTH CONDITION

There is a perception that people with diabetes are at higher risk both of infection and severe disease from COVID-19 (Ma & Holt, 2020). People with type 1 diabetes who have glucose values close to target may not be at greater risk of developing SARS-CoV-2 (JDRF, 2020). Similarly, as evidence accumulates that many people infected with COVID-19 remain asymptomatic (World Health Organization, 2020), it remains uncertain exactly what additional risk pre-existing diabetes poses. Although the risk of contracting COVID-19 may be no greater, viral infections can cause more severe symptoms and complications in people with diabetes (Kaiser, et al., 2020). It should also be noted that a number of people with

diabetes are at increased risk due to concomitant immunosuppression following solid organ transplantation (Weinrauch, et al., 2018).

Early reports from Wuhan province revealed that those with diabetes mellitus were over-represented among the most severely ill patients with COVID-19 (Guan, et al., 2020) (Huang, et al., 2020). This finding is in keeping with an analysis of people hospitalised by Sars-CoV, where even transient hyperglycaemia was associated with increased mortality (Yang, et al., 2010). Diabetes was also identified as being one of the most common comorbidities in a case series of 5700 patients in the New York City area requiring hospitalisation for SARS-CoV-2 (Richardson, et al., 2020).

Proposed mechanisms to explain the observed association between diabetes and SARS-CoV-2 include chronic inflammation, an impaired immune response, increased coagulation activity, and direct pancreatic islet cell injury (Hussain, et al., 2020). Well-controlled diabetes is associated with better outcomes than poorly-controlled diabetes (Zhu, et al., 2020), but even short-term hyperglycaemia can stun the innate immune system (Jafar, et al., 2016). Emerging evidence suggests that in the context of COVID-19, acute hyperglycaemia may be a greater risk factor for adverse outcomes than a diagnosis of diabetes (Bode, et al., 2020).

The SARS-CoV-2 pandemic highlights the importance of understanding shared disease pathophysiology, particularly where it might inform therapeutic choices for people with diabetes. Emerging data suggests that SARS-CoV-2 is also common in patients with hypertension and cardiovascular disease, although the prevalence rate has varied in different studies as well as globally (Singh, et al., 2020). Obesity is also a risk factor for more severe COVID-19-related illness (Drucker, 2020). In a meta-analysis of 8 studies (n=46,248) the odds ratio of severe SARS-CoV-2 was not significantly higher in patients with diabetes, unlike hypertension and cardiovascular disease (Yang, et al., 2020). It may therefore be more appropriate to say that complications and co-morbidities linked to diabetes are associated with a higher mortality rate than the presence of diabetes *per se* (Guo, et al., 2020). The apparent association with worse outcomes might also reflect the higher prevalence of type 2 diabetes in older people (Bornstein, et al., 2020).

Angiotensin-converting enzyme 2 (ACE2) is now established as the SARS-CoV receptor but with conflicting data as to its translational relevance (Yan, et al., 2020). A role for ACE2 in explaining the association between cardiovascular disease in diabetes and SARS-CoV-2 has been suggested. ACE2 expression is reduced in people with diabetes possibly due to glycosylation, but expression is increased in patients taking ACE Inhibitors or Angiotensin receptor blockers (Pal & Bhansali, 2020). Speculation around possible adverse or protective effects has not proven helpful, and people prescribed ACE Inhibitor drugs and Angiotensin receptor blockers have been advised to continue taking them (European Society of Cardiology, 2020). Membrane-associated Dipeptidyl Peptidase-4 (DPP4) also functions as a coronavirus receptor (Raj, et al., 2013) but there is currently no evidence to support clinically meaningful effects on immune function through DPP4 inhibition (Drucker, 2020).

Acute viral infection has previously been linked to the rapid development of transient insulin resistance (Sestan, et al., 2018). Infection with COVID-19 is also generally associated with an increased insulin requirement (Guo, et al., 2020).

There are many unanswered questions regarding the course of clinical recovery following SARS-CoV-2, and it is of interest that diabetes appears to be associated with increased time for viral clearance (Chen, et al., 2020).

SERVICE DESIGN

COVID-19 will also impact on the health of people with diabetes who are not infected with the virus but find that their clinical care is compromised due to service disruption. Clinical teams have been challenged to fulfil their general responsibilities and prioritise acute care in relation to COVID-19 whilst ensuring that essential diabetes care continues (Kaiser, et al., 2020).

People with diabetes continue to require emergency admissions and medical management and specialists have an important role to play expediting treatment and minimising length of stay (NHS England, 2020). Many inpatient diabetes services have looked to increase their capacity in recognition of the reported association between diabetes and hospitalisation

with COVID-19 infection, and to mitigate against the impact of a potentially reduced workforce.

Direction has been given to minimise outpatient attendances, with movement towards virtual consultations, including support for those recently discharged from hospital to reduce the risk of readmission. Community services should not underestimate the importance of their contributions to maintaining diabetes care. Triaging of clinic lists supports the identification of those patients who might still require face-to-face review. Specialist teams should also acknowledge that clinic postponement will equate to cancellation in a proportion of cases. Traditional reliance on biochemical parameters to inform management decisions in diabetes does mean that access to phlebotomy services must also be considered where useful information cannot be obtained from shared data (NHS England, 2020).

Secondary care services that may need to continue at close to full capacity include multidisciplinary diabetic foot services and pregnancy and diabetes services. The International Working Group on the Diabetic Foot has looked to remind clinicians that most patients with diabetic foot disease do not need to be hospitalised (IWGDF, 2020). Inpatient teams should also ensure that acute foot infection is not missed as non-specific symptoms are attributed to SARS-CoV-2. The precautionary identification of pregnant women as being at higher risk of severe COVID-19-related illness has led to the rapid implementation of remote antenatal care, including diabetes management. Modifications have also been made to the screening pathway for gestational diabetes (RCOG, 2020).

CHALLENGES

National and locally driven crisis management plans must look to manage anxiety, about the health of clinical staff and the people they care for, but also around redeployment and service reconfiguration. Redeployment and new ways of working will inevitably impact the education and training of healthcare providers in diabetes management, and alternative approaches will need to be adopted.

The longer-term healthcare impact of social lockdown may not be apparent for some time. In the short term, interruption of daily activities, including diet and exercise, may have a significant impact on glucose control, as may anxiety and sleep disturbance. Structured diabetes education has been recommended by the National Institute for Health and Care Excellence (NICE) since 2003 (Diabetes UK, 2015). Much of this is delivered through group education, which has been suspended, and may not be able to restart for some time.

While technology companies have been quick to reassure users around their supply chains (ABHI, 2020), centres where diabetes technology supplies have traditionally been delivered to the clinical site rather than directly to users have had to recognise the additional risk this carries. Companies have agreed to extend warranties for insulin pumps but have also offered remote pump upgrade services where appropriate.

Initial insights suggested that COVID-19 infection increased the risk of emergency states of hyperglycaemia with ketones, diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (National Inpatient COVID-19 Response Team, 2020). These atypical presentations have challenged inpatient diabetes teams and led to some anxiety around the prescription of sodium-glucose co-transporter (SGLT)-2 inhibitors. It remains important that people with both type 1 and type 2 diabetes follow the sick day rules should they become unwell from any illness.

SGLT-2 inhibitors have significant cardiovascular and renal benefits in people with type 2 diabetes but are associated with a small but increased risk of ketoacidosis. There are to date only anecdotal reports of ketoacidosis in patients with SARS-CoV-2 taking SGLT-2 inhibitors, but they should be suspended in any acute medical admission, vomiting or dehydration (ABCD, 2020). Metformin should also be used with caution in unwell patients. Interestingly metformin has been proposed to have immunomodulatory actions (Cameron, et al., 2016). Glucagon-like Peptide (GLP-1) Receptor agonists also exert anti-inflammatory actions and may even attenuate pulmonary inflammation (Zhou, et al., 2016). Although the short-term safety of GLP-1 agonists has been demonstrated in critically unwell patients (Lee, et al., 2013) there is still insufficient experience to make recommendations around their use in patients with SARS-CoV-2.

With perhaps the exception of SGLT-2 inhibitors, most patients with mild COVID-19 symptoms and normal oral intake can continue their usual anti-hyperglycaemic medications. Review of glucose-lowering medications should be carefully considered given the possible implications of increased glycaemic variability (Ceriello, et al., 2019). Insulin has been used most extensively in the management of hyperglycaemia in critically ill patients (Drucker, 2020). Insulin also exerts anti-inflammatory actions (Hansen, et al., 2003).

Challenges in fluid replacement in DKA due to concerns over acute respiratory distress syndrome and with the availability of infusion pumps for intravenous insulin administration have also been reported (National Inpatient COVID-19 Response Team, 2020). Here subcutaneous insulin regimes may prove helpful in the management of hyperglycaemia where tissue perfusion has not been compromised.

Analysis of capillary blood glucose tests in patients with SARS-CoV-2 admitted to a medical centre in Wuhan suggested suboptimal adherence to current best practice for the management of hyperglycaemia (Zhou & Tan, 2020). This is perhaps not surprising given the pressure on healthcare systems, and the increased exposure of healthcare staff associated with frequent capillary blood glucose monitoring and adjustment of insulin infusions, but emerging evidence suggests good glycaemic control is associated with improved outcomes in patients hospitalised with SARS-CoV-2 (Zhu, et al., 2020). Automated closed-loop insulin-delivery systems have been proven safe and effective in non-critical care environments (Bally, et al., 2018). The feasibility of fully automated closed-loop glucose control has also been studied in critical illness (Leelarathna, et al., 2013) and may be an option. The finding that patients admitted with SARS-CoV-2 often developed acute hyperglycaemia following hospitalisation suggests an opportunity exists for more interventional glycaemic management (Bode, et al., 2020).

OPPORTUNITIES

The prevalence of diabetes or stress hyperglycaemia in people hospitalised with COVID-19 infection, and recognition that improved glycaemic control might improve outcomes and

reduce length of stay in patients with SARS-CoV-2 has underlined the importance of specialist inpatient diabetes teams to acute care.

The current pandemic has also highlighted opportunities for continuing and expanding innovations in the delivery of diabetes care, through virtual consultations between healthcare providers and people with diabetes, and the use of diabetes technology (Drucker, 2020). Crisis management has created unprecedented interest in remote care from both patients and providers, and removed many long-standing regulatory barriers. The US Food and Drug Administration has also allowed the use of personal blood glucose meters and continuous glucose monitoring devices in hospital for the duration of the pandemic (Abbott, 2020) (Dexcom, 2020).

Virtual consultations might also support people with diabetes to be seen by the 'right person at the right time' instead of waiting months between routine clinic appointments. This might be a physician, specialist nurse / diabetes educator, dietician or clinical psychologist (Peters & Garg, 2020).

While group face-to-face structured diabetes education may not be possible for some time, there are opportunities to pilot alternative forms of delivery. Patient-led remote models of structured diabetes education have been reported to improve both uptake and clinical outcomes. The digital version of DESMOND, an evidence-based type 2 diabetes structured education programme was made free to everyone with type 2 diabetes in the United Kingdom in April 2020 (Desmond, 2020). BERTIE Online offers fully remote diabetes structured education for people with type 1 diabetes (BERTIE, 2016).

Enforced service redesign through this pandemic will also enable other innovations in diabetes care, which might only become apparent over the coming months. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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