A Physician's approach and experience of managing patients with diabetes during COVID-19

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Abstract

Since the start of the COVID-19 pandemic, the vulnerability of people with diabetes has been recognised with a greater risk of morbidity and mortality compared to the general population. The outcomes associated with diabetes may be a consequence of an impaired immune response, presence of composite comorbidities or the multi-organ infectivity of SARS-CoV-2 affecting the pancreas. Emerging evidence suggests that both acute and chronic hyperglycaemia can exacerbate the clinical consequences of COVID-19. Thus, the role of healthcare professionals in the observation and management of glucose control is increasingly recognised in people with diabetes in both the acute and chronic setting. In this review, we highlight the key biological implications of SARS-CoV-2 infection in people with diabetes, the clinical outcomes of COVID-19 in people with diabetes and management principles with respect to glucose control including our local experiences.

Introduction

The unprecedented global outbreak of novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection has defined 2020. Indeed, coronavirus disease 2019 (COVID-19) has resulted in a worldwide catastrophe, with an extraordinary impact on global healthcare systems and economy. Typically, patients with more severe SARS-CoV-2 infection have multiple medical comorbidity; particularly diabetes, hypertension, and cardiovascular disease [1]. In this article we review the impact of COVID-19 in people with diabetes and offer a practical approach to managing diabetes in this pandemic.

Biological associations between COVID-19 and diabetes

People with diabetes are more susceptible to contracting viral pneumonia [2, 3] and are usually recommended to receive the annual influenza vaccination. During previous coronavirus outbreaks such as the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), diabetes was associated with worse clinical outcomes including greater morbidity and mortality compared to people without diabetes [4]. Given this association, some authors argue there maybe be shared underlying pathophysiology between diabetes and coronavirus infection [5].

Diabetes is associated with greater risk of infection due not only to its effect on pro-inflammatory and pro-coagulative states but also due to metabolic dysfunction. Chronic hyperglycaemia and elevated HbA1c impairs macrophage and neutrophil function, as well as lymphocyte proliferation to diminish the response to bacterial and viral infection [5, 6, 7]. Indeed, there is a clear relationship observed such that innate immunity diminishes with increasing glucose levels [6]. Moreover, higher glucose levels may promote viral replication within pulmonary epithelial cells resulting in worsening pneumonitis [8]. Therefore, impaired

cell-mediated immunity and lymphocytic response negatively impact on overall immune function in individuals with chronic hyperglycaemia. However, some argue that hyperglycaemia may be consequence, rather than cause, of the inflammatory response seen in COVID-19. Nevertheless, the higher prevalence of diabetes, cardiovascular disease and impaired immune response seen in older patients increases their vulnerability. Thus, hyperglycaemia preceding COVID-19 illness or during hospital admission is associated with worse outcomes [5].

Further potential mechanisms to explain the graver impact of COVID-19 in people with diabetes include that SARS-CoV-2 enters the host cells via the ACE2 receptor, which is enhanced by hyperglycaemia-induced ACE2 receptor glycosylation [9, 10]. ACE2 is mostly expressed in the lung, kidney, heart, and islet cells of the pancreas [11]. COVID-19 infection reduces ACE2 expression [11, 12]. ACE2 is responsible in reducing angiotensin II levels, conferring some protective effect to the lungs. It was found that reduction of ACE2 levels would increase the level of Angiotensin II production locally, leading to activation of pulmonary renin-angiotensin-system (RAS), thus triggering pulmonary blood vessel leakage and may subsequently result in severe acute lung failure and acute respiratory distress syndrome (ARDS) [13, 14]. Hyperglycaemia in both acute and chronic settings can lead to undesirable consequences in COVID-19 infection. This is because acute hyperglycaemia upregulates *ACE2* cell expression and may facilitate viral entry through enhanced glycosylation [10]. On the other hand, others postulate that chronic hyperglycaemia downregulates *ACE2* expression which may make cells vulnerable to viral damage due to lack of anti-inflammatory effect of ACE2 [9].

Impact of COVID-19 on insulin resistance & beta cell function

As COVID-19 was first observed in Wuhan, China, it has been reported early in the pandemic that SARS-CoV-2 infection caused ketosis or ketoacidosis, and induced DKA in patients with diabetes [15, 16]. A further study subsequently illustrated a reliable association between SARS-CoV-2 infection with insulin resistance which also positively correlates with severity and mortality of COVID-19 patients [17]. As a result of the high pancreatic expression of *ACE2*, SARS-CoV-2 may enter the host cells causing damage to the pancreatic β-cells resulting in impaired insulin secretion and may even precipitate ketoacidosis [11]. The relative insulin deficiency caused by COVID-19 on pancreatic islets may also unmask latent type 2 diabetes (T2D) in people with COVID-19. Similarly, during the SARS-CoV-1 outbreak about 50% of non-diabetic patients developed diabetes, though following 3 years of follow up diabetes persisted in only 5% of these patients [12].

Morbidity and Mortality

The publication of COVID-19 data from NHS England demonstrated a dramatic increase in the overall mortality rates for patients with type 1 diabetes (T1D) and T2D between March and May 2020. The higher rates of death linked to COVID-19 in patients with diabetes parallels the increased mortality risk in people with diabetes in previous coronavirus epidemics including SARS-CoV-1 and MERS-CoV [18]. People with T1D had a 3.5 fold increased risk of death, whilst people with T2D had a 2-fold increased mortality rate compared to people without diabetes [19] Increased mortality was correlated with glycaemic control and those patients with highest glycated haemoglobin (HbA1c) suffered the highest mortality. In patients with T1D the association became statistically significant with an HbA1c greater than 85 mmol/mol (10.0%) whereas in those with T2D the association became apparent when HbA1c was greater than 58 mmol/mol (7.5%) [18]. Apart from hyperglycaemia, obesity was also

identified as an independent risk factor for mortality. Mortality from COVID-19 correlates with increasing body mass index (BMI) and the lowest risk observed in those with BMI 25-30 kg/m^2. The presence of chronic kidney disease (CKD) and COVID-19 related death in England increased 2-fold with an estimated glomerular filtration rate (eGFR) 30-40 ml/min/1.73 m^2 and was significantly higher in those with an eGFR less than 15ml/min/1.73m^2 [18].

The impact of comorbidities such as coronary artery disease, congestive cardiac failure, cerebrovascular disease, hypertension or renal impairment typically seen in people with diabetes impacts their physiological reserve and may also cause increased mortality. Further independent risk factors associated with adverse outcomes include increasing age, male sex, ethnic origin, lower socioeconomic status and history of smoking [18].

Clinical management

Given the recognised association of hyperglycaemia with adverse outcomes and increased mortality in COVID-19 disease, early optimisation of glycaemic control is essential. As the hyperglycaemic effect of diabetes is relatively asymptomatic, it is imperative to proactively mitigate hyperglycaemia. Intensification of glycaemic therapies upon admission to hospital remains crucial as data from China and the USA both identified a strong association between increasing admission plasma glucose and adverse outcomes with COVID-19 resulting in up to four-fold increase in mortality rate [20, 21, 22, 23].

Practical considerations

General advice includes handwashing guidance, social distancing measures, and facial coverings, especially in those with diabetes and other serious comorbidities. Patients with diabetes were identified as clinically vulnerable and of moderate increased risk from

coronavirus by the UK Government and NHS England. Although not in the high risk (clinically extremely vulnerable) category who were advised to shield, individuals with diabetes were advised to minimise unnecessary contact, and to work from home whenever possible.

Day to day management

Due to concerns about possible restricted access to usual healthcare services, patients were advised to ensure they had adequate supplies of insulin, glucose monitoring equipment, ketone testing, sensors, pump supplies, and back-up insulin pens [24]. Healthcare professionals have been urged to reiterate patient education for sick day management rules, and how to transition from continuous subcutaneous insulin infusions (CSII) to multiple daily injection (MDI) insulin regimes in the event of delayed access to supplies or replacement equipment [25].

Clinical management

Type 1 Diabetes

Both acute and chronic hyperglycaemia are important risk factors for severe COVID-19 disease. Therefore, measures to optimise glycaemic control are critical, especially in those with T1D and elevated HbA1c. Blood glucose (BG) targets of 4.0-8.0 mmol/l and HbA1c less than 53 mmol/mol (7%) are recommended. Also, with the use of technology such as Libre sensors or real-time continuous glucose monitoring (RT-CGM) the time in range of 4-10 mmol/l of 70% or more with minimal hypoglycaemia continues to be advocated [26]. Patients should be given sick day rule advice, including ketone monitoring equipment and clear advice on when to seek medical help [27]. Early in the pandemic there was a reduction in hospital admissions and some concern patients would fail to seek help for non-COVID related illness leading to increased hyperglycaemia-related illness such as DKA. Thus, making patients aware of such complications and early healthcare professional support is crucial.

Type 2 Diabetes

Similar management recommendations to ensure adequate access to medication, glucose monitoring and strategies to seeking help if unwell are supported in this patient group. For patients on specific glucose-lowering agents such as sulphonylureas or insulin therapy were encouraged to self-monitor blood glucose more regularly [28, 29]. For the majority of patients with T2D who may not be self-monitoring BG, an awareness of symptoms of hyperglycaemia such as thirst, malaise and increased frequency of urination and advice to seek medical attention should they develop, needs to be reiterated. Should patients become unwell with reduced appetite, fever or dehydration, advice was issued for frequently used hypoglycaemic agents, to prevent complications from developing and aggravating their infective illness [26,28,29].

Metformin

Patients were advised to ensure adequate oral intake, and to withhold metformin if not eating and drinking. If admitted to hospital, clinicians should check their urea and electrolytes and lactate to exclude lactic acidosis, and withhold in acute renal injury or advanced chronic kidney disease [26, 28, 29].

Sulphonylureas

Patients should continue if oral intake is adequate, and BG is elevated. However, if appetite is reduced due to illness patients should withhold due to risk of hypoglycaemia [28, 29]. If possible, patients should monitor BG when not eating to ensure BG remains above 3.9 mmol/l.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Drugs in this class represent a low risk of side effects in those with SARS-CoV-2 and advice is to continue these agents in acute COVID-19 illness [26].

Glucagon-like peptide-1 receptor analogues (GLP-1 RA)

These agents can lead to gastrointestinal side effects, particularly if patients are unwell. Therefore, general advice was to ensure adequate oral intake and hydration, and to withhold these medications if patients were not able to eat or drink adequately [26, 28].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

Medications in this class not only optimise glycaemic control they also confer substantial cardiovascular and renal benefits to people with T2D [30]. However, their use results in an enhanced diuresis and risk of dehydration. Moreover, their use can rarely result in metabolic decompensation leading to euglycaemic DKA, particularly in those who are systemically unwell such as with COVID-19. Therefore, in the event of COVID-19 patients should withhold these drugs pending resolution of illness. Renal function should be monitored due to risk of renal impairment [26, 28, 29].

In the event that glucose-lowering drugs were stopped there is a risk of developing hyperglycaemia as a consequence of this temporary withdrawal and the physiological stress of acute illness. In these circumstances the advice would be to consider starting insulin therapy to achieve glycaemic targets pending resolution of the illness, when usual therapy could resume [26, 29]. It is important that these agents do resume if safe to do so, given the recognised cardiovascular and renal benefits associated with the GLP1 RAs and SGLT2 inhibitors.

Management of CV risk factors

The majority of patients with T2D have associated co-morbidity such as hypertension, obesity or dyslipidaemia.

Hypertension

Particularly at the start of the 'first wave' of COVID-19 disease, there were concerns about the risk associated with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers (ARBs). This is because their use upregulates the ACE2 receptor and may therefore result in more severe infection [31]. However, a number of international consensus groups advised that the benefits would outweigh the theoretical risks associated with these medications. Subsequent studies confirmed that patients treated with these medications had better outcomes than those who were not. As such, it is strongly recommended to continue treatment with these anti-hypertensive agent [26, 32].

Dyslipidaemia

Due to its major role in the development of cardiovascular diseases, the recommendation was to continue to strive for excellent lipid control. The use of statins was thought to avoid the associated surge in interleukin (IL)-6 and IL-1β in COVID-19 disease and to prevent the 'cytokine storm'. There have also been some reports that suggest that statin therapy maybe protective in those with COVID-19 infections [26].

Hospitalisation

Typically, diabetes can be identified in 20-40% of patients admitted to hospitals in the UK. If admitted with COVID-19, it is important to consider a number of possibilities during this pandemic due to its effect on multi-organ systems. Patients admitted would typically be dyspnoeic and hypoxic which may reflect cardiorespiratory involvement. However, it is always important to consider the possibility of new onset diabetes or decompensation of known diabetes; where dyspnoea could reflect underlying metabolic acidosis or DKA? Are patients taking medications that could cause acute metabolic decompensation? Therefore, it is

imperative that all patients admitted to the hospital have their BG checked at the front door. In those with known diabetes or BG over 12.0 mmol/l, blood ketone levels should also be checked and medications reviewed [33].

In the first wave, there were also concerns around management of patients who may require intravenous fluids and intravenous insulin infusion for management of DKA or Hyperosmolar Hyperglycaemic State (HHS). Particular cautions have been recommended around fluid resuscitation given the risk of ARDS with COVID-19 disease. These concerns led to development of subcutaneous regimes for management of hyperglycaemia and some modification to DKA regimens to achieve individualised and finely targeted treatment for each patient and to prevent further sequelae of the infection [33, 34]. Whilst use of these regimes is not always necessary, it is important for clinicians working in diabetes are familiar with their use.

Dexamethasone

The RECOVERY trial reported the benefit of dexamethasone use in hospitalised patients with COVID-19 requiring oxygen therapy [35, 36]. However, there was concern about the impact of dexamethasone in people with diabetes and the risk of hyperglycaemia and precipitation of DKA. A helpful national expert consensus document was published which provided guidance on the management blood glucose in patients treated with Dexamethasone [37]. Important recommendations to monitor BG at least every 6 hours whilst on dexamethasone were made were made for patients with diabetes. For those without diabetes similar recommendations to monitor BG 6 hourly for at least 48 hours were also made with the option to then reduced to once daily BG monitoring at 5-6 pm provided BG values were all below 10.0 mmol/l. Should BG exceed 12.0 mmol/l the clinician should consider introducing insulin therapy on the basis

of possible impaired beta cell function, even in those not known to have diabetes. The document also provided practical guidance for corrective insulin doses and initiation of basal insulin whilst on steroid therapy to optimise BG control [37].

Local experience

At the outset of the COVID 19 pandemic there was great uncertainty about how it would impact the delivery of usual clinical services. There was a concern that diabetes teams would all be redeployed to frontline clinical work and that diabetes specialist nurses (DSNs) would be recruited to general inpatient duties. Locally, whilst our medical teams all contributed to frontline COVID services as part of our role in general internal medicine, our DSNs were largely able to continue with their usual role in supporting outpatient and inpatient diabetes services from the diabetes unit.

Patients admitted to hospital during the first wave of COVID-19 peaked in mid-April 2020 at approximately 200 patients. This was similar in our neighbouring health boards and overall peak number of patients was less in more rural areas. Locally, we established a pre-hospital triage system which was to direct patients with suspected COVID 19 infection to either Singleton or Morriston hospital in line with provision of local services. Local audit data (table 1) shows that during the first wave, 110 patients with confirmed COVID 19 were admitted to Singleton hospital, 17% (19/110) of these patients having underling diabetes. Over 90% of patients admitted to Singleton Hospital had T2D. Of the 19 patients with diabetes, 9 were male and 10 were female, with a median age of 77 years. The median duration of diabetes pre-admission was between 5-9 years and mean (SD) HbA1c was 54.9 (15.3) mmol/mol and mean (SD) eGFR was 56 (21.5) ml/min/1.73m^2. The median duration of hospital admission was

between 15-20 days and of those admitted with diabetes, 11 (58%) survived to discharge, these figures are similar to other patients admitted with COVID-19 who did not have diabetes and national figures overall [38]. However, given the locally employed triage, patients admitted to Singleton hospital reflected an older and frailer cohort overall. These data have been submitted to the ongoing national ABCD COVID-19 audit. It is expected that data reported in this audit will provide a more complete picture of the impact of COVID-19 infection on people with diabetes in the UK.

The first wave was a very dynamic process during which we were learning and adapting throughout. As evidence emerged, clinical practice changed considerably with numerous new guidelines being published to support clinical management. Locally, we have adapted these national recommendations for everyday clinical use within our hospitals. There, was also evidence of good collaboration between colleagues locally, regionally and nationally to share experience and ensure consistent clinical practice as the pandemic spread across the UK. Major advances were made within a very short period of time as a result of these collaborative efforts.

Conclusion

Patients with diabetes mellitus have been disproportionately adversely impacted by COVID-19. It is more common in at-risk groups and overall outcomes have been worse than for those without diabetes probably due to a combination of impaired immunity, cardiovascular and other co-morbidity and the cellular effect of hyperglycaemia on SARS-CoV-2 infectivity. Both hyperglycaemia and higher BMI were identified as important and modifiable risk factors which should be a cardinal focus for management to improve outcomes associated with COVID-19.

Also, it is essential to remember that patients with diabetes admitted to hospital are at risk of metabolic decompensation and should have their diabetes treatment reviewed. Strategies for the early identification and management of hyperglycaemia and complications such as DKA must be in place. These are especially important if patients with diabetes receive treatment that promote hyperglycaemia such as dexamethasone when blood glucose should be measured at least every 6 hours, ideally pre-meal whilst on steroid treatment. Similarly, patients not known to have diabetes receiving steroid treatment should have 6 hourly BG monitoring for at least 48 hours. For patients without diabetes BG monitoring frequency can then be reduced to once daily at 5-6 pm if all BG values are below 10.0 mmol/l.

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Table 1. Demographic and clinical characteristics of patients with Diabetes and COVID-19

Mean, (SD), [Median]

	Number
Total number of patients with COVID-19	110
Number having Diabetes-no (%)	19/110 (17%)
Type of Diabetes (Type 1/Type 2)	1/18
Gender (Male/Female)	9/10
Mean Age (years)	76.3 (8.9)
Median Age [years]	77
Median duration of diabetes [years]	[5-9]
HbA1c (mmol/mol)	54.9 (15.3)
eGFR (ml/min/1.73m)	56 (21.5)
length of admission [days]	[15-20]
Survival to discharge-no (%)	11/19 (58%)

Key words

- Diabetes
- COVID 19
- Pathophysiology
- Clinical Management
- Blood glucose management

Key points

1. Patients with Diabetes are at increased risk of adverse outcomes from COVID 19 infection
2. Patients should follow standard precautions to reduce the risk of contracting COVID 19
3. Optimal glycaemic control can reduce the risk of adverse outcome with COVID 19
4. For patients with Diabetes infected with COVID 19 close monitoring of glucose and optimal management of diabetes is vital