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 health care 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. Copyright © 2021 John Wiley & Sons.

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Key words

diabetes; COVID-19; pathophysiology; clinical management; blood glucose management

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 health care 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 may 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 HbA_{1c} impair macrophage and neutrophil function, as well as lymphocyte proliferation to diminish the response to bacterial and viral infection.[5–7] 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

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hyperglycaemia. However, some argue that hyperglycaemia may be a 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 and 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 diabetic ketoacidosis (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 beta 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 three 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 parallel 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, while 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 (HbA_{1c}) suffered the highest mortality. In patients with T1D the association became statistically significant with an HbA_{1c} >85mmol/mol (10.0%) whereas in those with T2D the association became apparent when HbA_{1c} was >58mmol/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 25–30kg/m^2. The presence of chronic kidney disease and COVID-19 related death in England increased 2-fold with an estimated glomerular filtration rate (eGFR) of 30–40ml/min/1.73m^2 and was significantly higher in those with an eGFR <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]

Hyperglycaemia

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 4-fold increase in mortality rate.[20–23]

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.

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Day-to-day management

Due to concerns about possible restricted access to usual health care 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] Health care 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 regimens 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 HbA_{1c}. Blood glucose (BG) targets of 4.0–8.0mmol/L and HbA_{1c} <53mmol/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 4–10mmol/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 health care 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. Patients on specific glucose-lowering agents such as sulphonylureas or insulin therapy were encouraged to self-monitor BG 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 3.9mmol/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 RAs). 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 (SGLT2) inhibitors. 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 have been 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 GLP-1 RAs and SGLT2 inhibitors.

Management of cardiovascular risk factors

The majority of patients with T2D have associated comorbidity 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 antihypertensive agents.[26,32]

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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 may be 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 12.0mmol/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. Particular cautions have been recommended around fluid resuscitation given the risk of ARDS with COVID-19 disease. These concerns led to the development of subcutaneous regimens 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] While use of these regimens is not always necessary, it is important that clinicians working in diabetes are familiar with their use.

Variable/characteristic	Value
Total number of patients with COVID-19	110
Number having diabetes – no. (%)	19/110 (17%)
Type of diabetes: type 1/type 2 – no.	1/18
Gender: male/female – no.	9/10
Age (years) – Mean (SD) – Median	 76.3 (8.9) 77
Duration of diabetes (years) – median	5–9
HbA_{1c} (mmol/mol) – mean (SD)	54.9 (15.3)
eGFR (ml/min/1.73m^2) – mean (SD)	56 (21.5)
Length of admission (days) – median	15–20
Survival to discharge – no. (%)	11/19 (58%)

Table 1. Demographic and clinical characteristics of patients with diabetes and COVID-19 admitted to Singleton Hospital during the first wave of the pandemic

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 of BG in patients treated with dexamethasone.[37] Important recommendations to monitor BG at least every 6 hours while on dexamethasone 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 reduce to once-daily BG monitoring at 5–6pm provided BG values were all below 10.0mmol/L. Should BG exceed 12.0mmol/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 while 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, while 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

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and the 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) show that during the first wave, 110 patients with confirmed COVID-19 were admitted to Singleton Hospital, 17% (19/110) of these patients having underlying diabetes. Over 90% of patients admitted to Singleton Hospital had T2D. Of the 19 patients with diabetes, nine were male and 10 were female, with a median age of 77 years. The median duration of diabetes pre-admission was between five and nine years and mean (SD) HbA_{1c} 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.

KEY POINTS

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

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 comorbidity 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 promotes hyperglycaemia such as dexamethasone when BG should be measured at least every 6 hours, ideally pre-meal while 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 5–6pm if all BG values are below 10.0mmol/L.

Declaration of interests

There are no conflicts of interest declared.

References

References are available in *Practical Diabetes* online at https://wchh.onlinelibrary.wiley.com.

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References

1. Chen Y, *et al*. Effects of hypertension, diabetes and coronary heart disease on COVID 19 disease severity: a systematic review and meta analysis. *Med Rxiv* 2020. https://doi.org/10.1101/2020.03.25.20043133.
2. Hespanhol V, Bárbara C. Pneumonia mortality, comorbidities matter? *Pulmonology* 2020; 26(3):123–9.
3. Zou Q, *et al*. Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments. *Int J Infect Dis* 2020;92:208–13.
4. Memish ZA, *et al*. Middle East respiratory syndrome. *Lancet* 2020;395:1063–77.
5. Williams DM, *et al*. Diabetes and novel coronavirus infection: Implications for treatment. *Diabetes Ther* 2020;11(9):1915–24.
6. Sentochnik DE, Eliopoulos GM. Infection and Diabetes. In *Joslin's Diabetes Mellitus*, 14th edn. Lippincott Williams & Wilkins 2005; chapter 60: pp1017–33.
7. Pearson-Stuttard J, *et al*. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes Endocrinol* 2016;4(2):148–58.
8. Bagdade JD, *et al*. Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes* 1974;23(1):9–15.
9. Hoffman M, *et al*. SARS-CoV-2 cell entry depends on ACE 2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271–80.
10. Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. *Diabetes Res Clin Pract* 2020;163:108186.
11. Yang JK, *et al*. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010;47(3):193–9.
12. Imai Y, *et al*. Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Cell Mol Life Sci* 2007;64:2006–12.
13. Imai Y, *et al*. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; 436(7047):112–6.
14. Imai Y, *et al*. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Experimental Physiol* 2008;93(5):543–8.
15. Chee YJ, *et al*. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract* 2020;164:108166.
16. Li J, *et al*. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020;22(10): 1935–41.
17. Ren H, *et al*. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovasc Diabetol* 2020;19:58. https://doi.org/10.1186/s12933-020-01035-2.
18. Holman N, *et al*. Type 1 and type 2 diabetes and COVID-19 related mortality in England: a cohort study in people with diabetes. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3605226 [accessed 17 Dec 2020].
19. Barron E, *et al*. Type 1 and type 2 diabetes and COVID-19 related mortality in England: a whole population study. NHS England, 2020. https://doi.org/10.1016/S2213-8587(20)30272-2 [accessed 17 Dec 2020].
20. Zhang B, *et al*. Admission fasting blood glucose predicts 30-day poor outcome in patients hospitalised for COVID-19 pneumonia. *Diabetes Obes Metab* 2020;22(10):1955–7.
21. Liu Q, *et al*. Fasting blood glucose predicts the occurrence of critical illness in COVID-19 patients. *J Infect* 2020;81(3):e20–e23.
22. Wang S, *et al*. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia* 2020;63:2102–11.
23. Bode B, *et al*. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol* 2020;14(4): 813–21.
24. NHS London Clinical Networks. Sick day rules for patients on multiple daily injections (MDI): how to manage type 1 diabetes if you become unwell with coronavirus. 2020. https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/2.-Covid-19-Diabetes-Sick-Day-Rules-Type-1-MDI-06042020.pdf [accessed 17 Dec 2020].
25. NHS London Clinical Networks. Sick day rules for patients on an insulin pump: how to manage type 1 diabetes if you become unwell with coronavirus. https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/1.-Covid-19-Diabetes-Sick-Day-Rules-Crib-Sheet-Type-1-Pump-06042020.pdf [accessed 17 Dec 2020].
26. Borstein SR, *et al*. Practical recommendations for the management of diabetes in patients with COVID 19. *Lancet Diabetes Endocrinol* 2020;8:546–50.
27. TREND-UK. Type 1 Diabetes: What To Do When You Are Ill. 2020. https://trenddiabetes.online/wp-content/uploads/2020/03/A5_T1Illness_TREND_FINAL.pdf [accessed 17 Dec 2020].
28. NHS London Clinical Networks. Sick day rules: how to manage type 2 diabetes if you become unwell with coronavirus and what to do with your medication. 2020. 3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf (england.nhs.uk) [accessed 17 Dec 2020].
29. TREND-UK. Type 2 Diabetes: What To Do When You Are Ill. 2020. https://trenddiabetes.online/wp-content/uploads/2020/03/A5_T2Illness_TREND_FINAL.pdf [accessed 17 Dec 2020].
30. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 2018;61(10): 2108–17.
31. Fang L, *et al*. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; 8(4):e21.
32. De Simone G. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang [accessed 17 Dec 2020].
33. National Inpatient Diabetes Covid-19 Response Group. COncise adVice on Inpatient Diabetes (COVID:Diabetes): Front Door Guidance. 2020. https://abcd.care/sites/abcd.care/files/site_uploads/COvID_Front_Door_v2.0.pdf [accessed 17 Dec 2020].
34. National Inpatient Diabetes Covid-19 Response Group. COncise adVice on Inpatient Diabetes (COVID:Diabetes): Guideline For Managing DKA Using Subcutaneous Insulin (where intravenous insulin infusion is not possible). 2020. https://abcd.care/sites/abcd.care/files/resources/COvID_DKA_SC_v3.3.pdf [accessed 17 Dec 2020].
35. Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report. *N Engl J Med* 2020 Jul 17;NEJMoa2021436. doi: 10.1056/NEJMoa2021436 [accessed 17 Dec 2020].
36. Whitty C. Dexamethasone in the treatment of COVID-19: Implementation and management of supply for treatment in hospitals. London: Medicines and Healthcare Products Regulatory Agency. 2020.https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054 [accessed 17 Dec 2020].
37. National Inpatient Diabetes Covid-19 Response Group. COncise adVice on Inpatient Diabetes (COVID:Diabetes): Dexamethasone Therapy in Covid-19 Patients: Implications and Guidance for the Management of Blood Glucose in People With and Without Diabetes. 2020. https://www.diabetes.org.uk/resources-s3/public/2020-06/COvID_Dex_v1.4.pdf [accessed 17 Dec 2020].
38. Navaratnam AV, *et al*. Patient and temporal trends associated with COVID-19 in-hospital mortality in England: an observational study using administrative data. *Lancet Respir Med* Feb 15 2021. https://doi.org/10.1016/S2213-2600(20)30579-8.

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