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Clinical Paper

Diabetes and Covid-19: Clinical implications and novel management strategies

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Abstract

From the outset of the Covid-19 pandemic, diabetes has been identified as attracting higher rates of severe infection and associated mortality. Our understanding of the mechanisms behind these observations continue to develop but it is clear that the comorbidities associated with diabetes play a key role. Here we provide a brief overview of the clinical implications relevant to Covid-19 infection in diabetes and outline the changes we have instituted to adapt the management of both acute hyperglycaemic emergencies and routine diabetes care during the current pandemic.

Introduction

Diabetes is associated with an increased risk for both bacterial and viral respiratory tract infections and this risk is moderated to some extent by glycaemic control. [1,2] In previous novel coronavirus outbreaks, such as the Middle East Respiratory Syndrome (MERS) epidemic, diabetes was associated with an increased risk of infection and an increased risk of mortality when compared to cases without diabetes. [3] Whilst understanding of the interplay between diabetes and Covid-19 continues to develop, it appears to present considerable morbidity and mortality in those affected.

Diabetes and risk of covid-19 infection

The relationship between diabetes and the risk of initial infection with Covid-19 remains unclear. Consideration must be given to the fact that most initial data pertains to hospitalised patients who represent the more severe end of the disease spectrum. An early meta-analysis from Chinese centres found an overall prevalence of 9.7% for diabetes among 1,576 confirmed Covid-19 cases, which is similar to the IDF reported diabetes prevalence for the region (10.9%).[4] Data from the United States however point towards a gross over-representation of diabetes among confirmed cases across all settings, with a prevalence of 30% among 1,320,488 laboratory confirmed Covid-19 cases.[5]

Clinical course in Covid-19 with diabetes

It is clear however, that diabetes has a profound impact on the clinical course for those infected with Covid-19. In a population wide study of 61 million individuals for Public Health England, a prior diagnosis of diabetes conferred an increased odds for in-hospital mortality.[6] Among 23,698 Covid-19 deaths, a third were among those with a prior diagnosis of diabetes, 31·4% in people with type 2 diabetes and 1·5% in those with type 1 diabetes. Compared to those without diabetes, the odds ratios for in-hospital Covid-19 death were 3·51 for type 1 diabetes and 2·03 for type 2 diabetes. A subsequent analysis on the same dataset highlights that overall glycaemic control was a significant modifier of risk.[7] Among patients with type 1 diabetes, for those with HbA1c ≥86mmol/mol, when compared to those with HbA1c 48-53mmol/mol, the mortality was two-fold higher (HR 2.23). A similar relationship was seen in type 2 diabetes (HR 1.61).

The greater severity of covid-19 infection among people with diabetes was also illustrated in the French multi-centre CORONADO study which followed the disease course among 1,317 patients hospitalised with covid-19, all of whom had diabetes.[8] A primary outcome of death or intubation for mechanical ventilation by day 7 was seen in 29% of patients. The mortality rate by day 7 was 10.6% and only 18% were fit to be discharged after 7 days.

The burden of diabetes in intensive care units is seen across multiple cohorts. As a proxy of disease severity, the prevalence of diabetes is greater among hospitalised adults with covid-19 (24%) than in the community (6%) and is greater still among intensive care unit admissions (32%).[9]

Overall, there is a clear picture that disease severity, the need for ICU admission and mortality are significantly higher among patients with diabetes.

The mechanisms which underpin these increased risks are complex. The co-morbidities associated with diabetes undoubtedly exert a significant influence as mediators of risk. The interaction between these factors confer a state of heightened mortality as illustrated in figure 1 below. Frequent concomitant factors such as obesity, hypertension, coagulopathy and acute hyperglycaemia are of particular importance in the pathophysiology of Covid-19.

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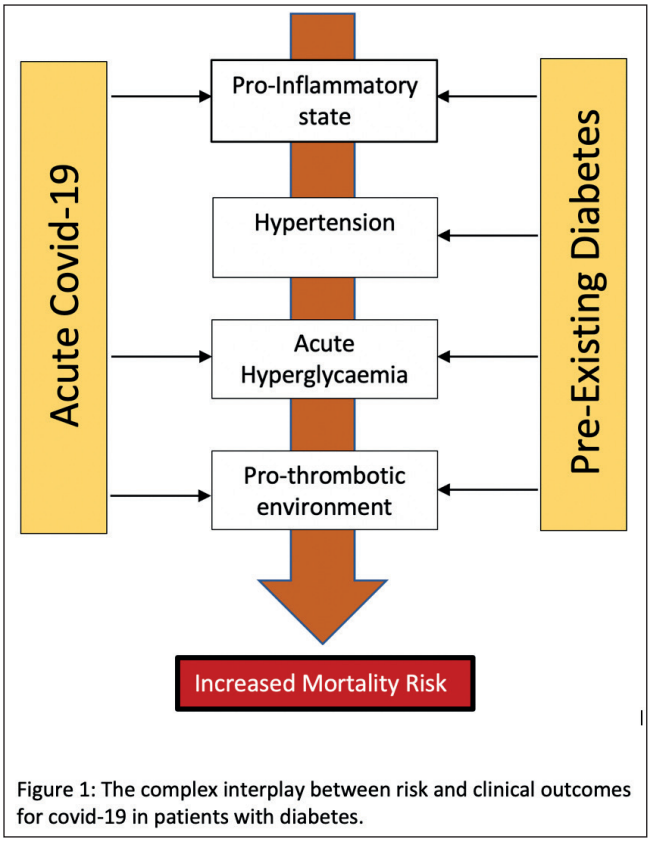

Figure 1: The complex interplay between risk and clinical outcomes for covid-19 in patients with diabetes.

Obesity

Obesity has been shown to be an independent risk for covid-19 severity and mortality. Obesity presents not only mechanical ventilatory constraints but also alters cytokine expression and exerts a pro-inflammatory effect, which may exacerbate the cytokine storm seen in severe covid-19 pneumonitis. Similar to diabetes, there is a high prevalence of obesity among patients requiring intubation and mechanical ventilation. [10] It is also an independent predictor of mortality and the requirement for hospitalisation.[11] One large primary care analysis demonstrates clearly a trend for rising mortality with increasing BMI, reaching a hazard ratio of 1.92 for BMI ≥40kg/m^2.[12]

Hypertension

Hypertension emerged early in reports of covid-19 as a prevalent comorbidity and as having particular association with more severe disease. Early data from China identified hypertension as the most common comorbidity (21.1%) and when present, the odds of severe disease were more than doubled (OR 2.36).[4] A similar picture was highlighted in large European and North American observational studies, principally that a diagnosis of hypertension is more common among positive cases than controls and that the odds of severe covid-19 infection were increased.[13,14] Given that SARS-CoV2 exploits the ACE2 receptor for cell entry, concern quickly arose as to the whether use of renin-angiotensin-inhibitors, frequently used in patients with diabetes, might pose a risk by up-regulating ACE2 receptors and facilitating increased viral entry potential. However, these concerns appear unfounded. Systematic reviews suggest that the prior use of ACE-inhibitors (ACEi) and Angiotensin Receptor Antagonists (ARB) does not increase the odds of infection nor of severe disease.[15,16] There is no evidence to support the withdrawal of ACEi or ARB in patients with covid-19 unless otherwise indicated, with one large retrospective analysis in Chinese centres actually suggesting a reduction in 28-day mortality in patients who continued ACEi or ARB when compared with other anti-hypertensive agents (HR 0.31 vs 0.49).[17]

Coagulopathy

Diabetes is in itself a relatively prothrombotic state, with alterations in the coagulation cascade and fibrinolysis.[18] Severe covid-19 likewise is associated with widespread coagulopathic change and endothelial dysfunction culminating in diffuse microangiopathy and alveolar damage.[19] A retrospective review of Chinese patients with diabetes and Covid-19 found that those who ultimately died had significantly higher prothrombin time 15.2s vs 13.6s and D-Dimer 4.95 vs 0.41μg/mL on admission. [20] The combination of diabetes, obesity, and acute hyperglycaemia present a particular burden for thromboembolic disease in the setting of Covid-19. The precise role of anticoagulation in this setting and optimum therapeutic approaches have yet to be determined

Acute Hyperglycemia

The role of acute hyperglycaemia, as distinct from background glycaemic control referenced above, appears to bear particular relevance in patients with and without diabetes. In the CORONADO study, the plasma glucose on admission was found to have an association with both mortality and the requirement for intubation and ventilation, with the odds rising in line with plasma glucose.[8] Interestingly, this relationship was not found for HbA1c in this cohort. Similarly, a multi-centre study of 1,122 patients admitted to US hospitals with Covid-19 found that the overall mortality rate for patients without diabetes or uncontrolled hyperglycaemia (at least 2 glucose readings >10mmol/l) was 6.2%.[21] The mortality rate among those with prior diabetes was more than doubled at 14.8%. However, most strikingly, the mortality among those with uncontrolled hyperglycaemia, but no prior diagnosis of diabetes, was highest at 41.7%. These findings were replicated in a large Spanish registry analysis where acute hyperglycemia without prior diabetes was independently predictive of disease severity and overall mortality.[22] It is unclear to what extent acute hyperglycaemia per se exacerbates the clinical course or whether severe disease and the associated pro-inflammatory state is reflected in insulin resistance and hyperglycaemia. The ACE2 receptor is expressed on the pancreatic beta cell and acute hyperglycemia might therefore correlate with greater viral exposure and subsequent beta cell dysfunction. The role of acute glycaemic control and the most effective glucose targets in patients with Covid-19 have yet to be elucidated.

New Onset Diabetes

Some UK centres have reported an increase in presentations with new type 1 diabetes among children in comparison to the preceding five years along with an increase in presentations with severe ketoacidosis.[23] In contrast, results from a German multi-centre study found no overall increase in new presentations with type 1 diabetes[24] but another did find a significant rise in presentations with severe ketoacidosis.[25] However, it is clear that the sequelae of covid-19 infection present challenges to the management of diabetes particularly for those hyperglycaemic emergencies.

Hyperglycaemic Emergencies

Early in the course of the pandemic, many centres including those in the UK saw an increase in presentations with diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS).[26,27] In the setting of Covid-19 infection, there is an upregulation of pro-inflammatory cytokines culminating in reduced insulin output and often severe insulin resistance.[28] This response may be seen in those without prior diabetes but when coupled with the insulin resistant state of type 2 diabetes or the insulopenic state of type 1 diabetes, hyperglycaemic emergencies such as DKA or HHS may ensue rapidly. A review at one UK centre compared adult DKA attendances before and during the Covid-19 pandemic.[29] Although there was a downturn in medical admissions of one third, the absolute number of cases presenting with DKA remained similar between the two periods. The proportion of DKA among patients with type 2 diabetes however rose from 17% pre-pandemic to 37% in the observation period.

The propensity for insulin resistance and hyperglycaemic emergencies coupled with resource demands during covid-19 have required changes in the management of these emergencies. Our response locally has been to adapt existing protocols for DKA and HHS for use during the covid-19 pandemic. We have sought to highlight the tendency toward hyperglycaemic emergencies in patients with Covid-19 and its associated insulin resistance. Central to change in management was to rationalise fluid and electrolyte replacement in patients with severe pneumonitis, to mitigate the risk of fluid overload and third-space effect. The concomitant risk profile in these patients for severe disease and mortality was a critical consideration and early referral for intensive care unit management, where appropriate, is recommended.

Alongside this upstroke in DKA/HHS there has also been a considerable burden of hyperglycaemia in non-diabetic patients with covid-19.[22] A number of reports describe marked insulin resistance in cases of severe Covid-19 with very high insulin requirements.[30] There appears to be some correlation between markers of cytokine release, disease severity and the resulting degree of insulin resistance.[28] Coupled with the now-widespread use of Dexamethasone[31] for covid-19, along with prolonged enteral feeding in intubated patients, there are marked demands on diabetes management resources for acute services. In response to this, a number of sites have been forced to implement DKA/HHS management using subcutaneous insulin where resources may be inadequate to meet the demands for typical intravenous insulin. Diabetes UK have subsequently published guidance on the management of DKA using of subcutaneous insulin for less severe cases of DKA in the UK.[26]

Likewise, existing guidance has been modified for the management of steroid-induced hyperglycemia and covid-19 related hyperglycaemia for use in hospital inpatients.[32]

Drug Management

Adjustments to diabetes medications are integral to the management of many hospitalised patients but there are particular concerns in the setting of covid-19. A summary is provided in table 1 below.

Metformin use should generally be suspended until the patient's renal function and clinical status are known. It is often withheld until the patient recovers, however recent observational evidence suggests a potential survival benefit in women.[33] Where renal function and clinical condition allow, Metformin may be continued.

SGLT2 inhibitors should be held owing to the risk of volume contraction, renal impairment and euglycemic ketoacidosis in the setting of covid-19.

DPP4 inhibitors and GLP-1 analogues are generally safe to continue though the latter may cause nausea in patients who are acutely unwell. Both classes have anti-inflammatory properties and DPP4 is also a target receptor for SARS-CoV2. Observational data suggest a survival benefit in patients supplemented with Sitagliptin with a two-fold reduction in mortality (HR 0.44) but randomised controlled trial data are lacking.[34]

Sulphonylureas do not pose particular risk or benefit but it is advisable to stop these drugs in patients unable to eat or drink. They may be useful in the setting of steroid induced hyperglycaemia, but their use may be limited where there is severe insulin resistance.

Drug Class	Advice
Metformin	Review renal function and clinical status. Continue where possible.
SGLT2 inhibitors	Hold for all acutely unwell patients until recovery.
DPP4 inhibitors	Safe to continue.
GLP1 Receptor Agonists	Safe to continue. May cause GI side effects in those unable to eat in the setting of acute illness.
Sulphonylurea	Hold initially in patients not eating. May be useful in milder cases of steroid-induced hyperglycaemia.

Table 1:
Diabetes medication advice in the setting of Covid-19

Outpatient Management

Addressing covid-19 has demanded significant restructuring of diabetes care delivery across Northern Ireland. Given the particular risks faced by patients with diabetes, maintaining care, support and education has been imperative. As has been the case in most settings, review consultations have been delivered virtually with face-to-face care restricted to emergencies-only across adult, transition and antenatal services. Direct patient contact has generally been reserved for high acuity situations such as new diagnoses of type 1 diabetes, diabetic emergencies, high risk pregnancies and active diabetic foot disease. There is concern, however, that the deferral of routine screening services for patients with diabetes will lead to an inevitable backlog of untreated complications in the post-Covid period.

The use of telemedicine has proved invaluable in delivering multidisciplinary education to patients. This has enabled us to continue routine diabetes monitoring as well as initiate new medications and diabetes technology remotely.

To facilitate patient access to specialist advice, a regional diabetes helpline and email address were established to offer specialist diabetes nursing support directly to patients 7 days per week.

Summary

Patients with diabetes face a more severe clinical course and significantly increased mortality when infected with Covid-19. The concomitant risk factors associated with diabetes appear to play a key role as mediators of this response. Increases in demand for diabetes services and the reconfigurations of secondary care have necessitated considerable adaptations in the provision of diabetes care and the institution of Covid-19 specific treatment approaches. Our understanding of how best to manage diabetes in this setting continues to develop.

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