The significance of hyperglycaemia and other comorbidities during the COVID-19 pandemic

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From the plethora of recently published world-wide papers, along with extensive media reporting, knowledge of diabetes as a major comorbidity for COVID-19 infection, particularly as a risk factor for poor prognosis, is now well recognised. The preliminary reports from China, cited in earlier *Practical Diabetes* editorial leaders,[1,2] identified diabetes as being linked with a two- to three-fold increase in adverse outcome for those critically ill with COVID-19 infection,[3,4] an association subsequently replicated across the world. In Italy 35.5% of patients dying from COVID-19 infection were reported to have diabetes;[5] in the USA 32% of those admitted to the ICU had diabetes.[6] While, within the UK, NHS England observes that across England one third of hospital deaths from COVID-19 occurred in people with diabetes,[7] a 3.5-fold increase in mortality risk for the 31.4% with type 2 diabetes (T2DM) and a 2.03 increase for the 1.5% with type 1 diabetes (T1DM) compared to those without diabetes.

At the time of our earlier editorial[2] three months into the COVID-19 pandemic, diabetes was registered simply as a significant association with adverse outcome to the infection, raising a number of uncertainties concerning which particular aspects of diabetes predispose to greater severity of risk. Since then much more detail has emerged, mostly in line with intuitive understanding as to what might seem reasonably predictable, but with some questions yet to be settled. A recently published review,[8] discussing the potential causes for poor outcome with COVID-19 infection in people with diabetes, reasonably comments on the multifactorial nature of diabetes, noting the presence of composite comorbidities, including obesity, hypertension, renal and vascular complications, and increasingly apparent, pro-inflammatory and pro-coagulative states, as part of the overall metabolic dysfunction with diabetes. In their review of 12 published articles (11 meta-analyses, one cohort study), it is interestingly observed that diabetes itself does not seem to increase the risk of COVID-19 occurring; rather in those with severe illness diabetes occurred more frequently, with a mortality risk varying from 1.49 up to 3.64. Neither is diabetes exceptional in respect of known age and gender consideration, a study[9] from Wuhan, China finding that among patients with diabetes, non-survivors from COVID-19 were older (76.0 vs 63.0 years) and most were males (71.0% vs 29.0%).

Hyperglycaemia predicts adverse outcome

It is perhaps surprising that the role of glycaemic control in those with known diabetes prior to hospital admission is still unclear. A French multi-centre observational study of 1317 people with diabetes hospitalised with COVID-19 between 10–31 March 2020 (the CORONADO study[10]) found no significant association between HbA1c, an indicator of preceding glycaemic control, and the primary outcomes of ITU ventilation and/or death. In contrast, the English cohort study[11] reported an independent association between the level of admission HbA1c, and COVID-19 related mortality, with an adjusted hazard ratio (HR) of 2.19 for T1DM and of 1.62 for T2DM with HbA1c >86mmol/mol compared to HbA1c 48–53mmol/mol. Risk was progressively higher in those with an HbA1c >58mmol/mol.

Even if the contribution of preceding glycaemic control remains uncertain, the level of plasma glucose at admission has clearly been identified as a significant predictor of adverse outcome with COVID-19 infection. A study[12] from Jinan University Hospital, Guangzhou, China observed that an elevated fasting blood glucose (FBG) on admission was an important risk factor for critical illness and poor outcome with COVID-19, an FBG value of >6.23mmol/L being an optimal cut-off for poor prognosis within 30 days of admission. Patients with a poor outcome had a higher FBG level (mean 9.91mmol/L) compared to those with favourable outcome (mean 5.92mmol/L). In another study,[13] critically ill patients, of whom 82.9% had no previous history of diabetes, recorded significantly higher FBG at 7.4mmol/L (6.5–11.9) than non-critical patients at 5.7mmol/L (5.0–6.9). The admission FBG level was also noted to positively correlate with inflammatory biomarkers and negatively with immune status. Another retrospective analysis from Wuhan of 605 hospitalised patients, all without a previous diagnosis of diabetes, found that an FBG >7.0mmol/L independently predicted 28-day mortality (HR 2.30).[14]

Glycaemic control during illness and new diabetes

It follows that mitigation of hyperglycaemia is an important therapeutic consideration in clinical management during the illness. A US study[15] of 1122 patients in 88 hospitals observed that patients with poorly controlled hyperglycaemia during admission had significantly longer length of stay and a four-fold higher mortality rate. Similarly, a multi-centre study[16] from Hubei Province, China of 952 pre-existing T2DM patients with COVID-19 infection found that, during hospitalisation, well-controlled blood glucose (BG) levels (glycaemic variability 3.9–10.0mmol/L) were associated with markedly lower mortality compared to individuals with poorly controlled BG (glycaemic variability exceeding 10mmol/L). In the CORONADO study,[10] despite the lack of association with preceding HbA1c, the admission plasma glucose was significantly associated with need for mechanical ventilation and/or with death within seven days.

These observations raise interesting questions in respect of the relationship between hyperglycaemia and COVID-19 infection, particularly without a previous history of diagnosed diabetes. Stress hyperglycaemia such as seen with various acute illness is a recognised

phenomenon and it is possible in many cases a latent susceptibility to diabetes may have been unmasked. A possible bi-directional relationship between COVID-19 and diabetes has also been postulated,[17] commenting that the virus (SARS-CoV-2) potentially may bind to ACE2 receptors expressed on pancreatic beta cells, thereby directly affecting beta cell function, with impairment of insulin secretion and development of new diabetes. In many of these reported studies, a relatively high incidence of diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome has been recorded, consistent with a particular destructive targeting of the virus on the pancreas.

These are complex issues, but this link between diabetes, whether previously or newly diagnosed, and observed adverse outcomes with COVID-19 infection, provides an evidence-based rationale for ensuring that optimal glycaemic control is attained from the immediate onset of illness and throughout hospital admission. Indeed, people with diabetes, not yet exposed to the virus, have been identified as at particular risk and encouraged to take as reasonable personal precaution as possible, including ensuring that their blood glucose control is as good as can be achieved. With this intended objective guidelines, supported by Diabetes UK, the Association of British Clinical Diabetologists and NHS England, for use by health care professionals have been made available to assist the provision of diabetes inpatient care during the COVID-19 pandemic.[18] In addition, as a collateral objective, an essential need is recognised that basic diabetes services should be protected at a time when diabetes specialist personnel might be re-deployed to provide general medical assistance with the management of acute COVID-19 inpatients.

From the data so far analysed, it is evident that hyperglycaemia alone is an independent risk factor, impairing immune responses and stimulating inflammatory and pro-coagulation states. In all probability, the degree of preceding glycaemic control, and certainly the level of FBG on admission are proportionally related to severity of illness and prospects of progression to ITU, mechanical ventilation and/or death. Optimising glucose control during admission makes clear clinical sense and has been shown to increase likelihood of a favourable outcome.

Composite comorbidities

Apart from hyperglycaemia, what is the role of other diabetes related comorbidities? In an earlier issue of *Practical Diabetes*, Hinchliffe *et al.*[19] reviewed the substantial evidence on *obesity* emerging as an unequivocal adverse risk factor, not just contributing to ventilatory difficulties, but also predisposing to inflammatory, immunity and coagulation dysfunction, and the intriguing implication that vitamin D deficiency might be involved in disease severity. Interestingly, the English cohort study[11] observed a U-shaped relationship between BMI and COVID-19 mortality, with a BMI of 20kg/m^2 at greater risk compared to a BMI of 25–29.9kg/m^2 (HR for T1DM 2.11; for T2DM 2.26). A BMI of >40kg/m^2 resulted in an HR of 2.15 for those with T1DM and of 1.46 for T2DM, a 'paradox' of less pronounced risk with morbid obesity also noted in the CORONADO study.[10]

A systematic review[20] of seven COVID-19 studies from multiple countries identified *hypertension* in 21% of severely ill cases, a 2.36-fold increase compared with non-severe patients. Examining the clinical characteristics and risk factors for mortality in COVID-19 patients with diabetes, the retrospective Wuhan analysis[9] found non-survivors were more likely to have underlying hypertension (83.9% vs 50.0%) and cardiovascular disease (45.2% vs 14.8%). Although frustratingly the precise definition of hypertension was not provided, it was concluded that comorbid hypertension was an important independent contribution to in-hospital death of patients with diabetes. However, when defining hypertension on the basis of prior prescription of antihypertensive medication, the English cohort study[11] found no statistically increased risk. In this context, theoretical concerns that blood pressure therapies with renin-angiotensin-aldosterone system blockers might facilitate viral entry to target cells via the ACE2 receptor have not been substantiated, with no evidence that either ACE inhibitors or ARBs affect risk of COVID-19.[21,22]

Closely linked to hypertension, *impaired renal function* adds yet further compromise. The prevalence of renal disease, both prior to admission and the added development of acute renal injury during hospitalisation in patients with COVID-19, is associated with a two-fold increased risk of in-hospital death.[23] In a large international registry[24] conducted in Europe and America, a high prevalence of kidney disease in hospitalised COVID-19 patients (8.5% with prior chronic kidney disease; 30% at admission) was associated with a three-fold higher in-hospital mortality rate. Although with diabetes specifically the independent risk factor of renal impairment has been generally noted as potentially influencing outcome to COVID-19 infection, robust information is still sparse. Once again, the English cohort[11] provides more detailed analysis, reporting that in people with T1DM and impaired renal function the relative risk of COVID-19 related death was double with eGFR of 30–40 and seven times greater with eGFR <15.

Finally, the predisposing risk of *cardiovascular disease*, both prior to COVID-19 infection and with secondary cardiac injury developing during the acute illness, has been reviewed by Miles Fisher in this issue of *Practical Diabetes*.[25] Perhaps one of the more fascinating reports published[26] is an article from Wuhan stating that use of statins may be associated with a reduced risk of mortality with COVID-19. Among 13,981 patients, mortality for statin users was 5.2% compared to 9.4% for non-users. Furthermore, statin users were twice as likely to have diabetes (34.0% vs 14.6%), suggesting an even more powerful beneficial statin effect, postulated as resulting from anti-inflammatory ± immunomodulatory benefits. Prospective studies and extended follow-up are now much needed[27] to clarify these ongoing issues.

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