The impact of diabetes on COVID-19 infection

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Within the relatively short time scale since the emergence of this current novel coronavirus pandemic (SARS-CoV-2/ COVID-19) from Wuhan, China, it has become rapidly apparent that those with known preceding comorbidities are much more likely to develop life-threatening complications of pneumonia and acute respiratory distress syndrome. Not unexpectedly, diabetes has been identified as posing a particular adverse risk, along with chronic renal and coronary heart disease, and such surrogate risk indicators as obesity and hypertension.

Actual susceptibility to infection with diabetes may be argued, but infection once acquired is likely to be more severe and prolonged, determined by a number of factors, including duration of diabetes, the presence of diabetes-related complications and the level of glycaemic control. Sub-optimal blood glucose levels, compounded by the adverse vicious cycle of response to infection, increase vulnerability and adverse outcome. For a comprehensive review as to how the immune system may be disturbed with diabetes, the relevant chapter, 'Infection and Diabetes', in *Joslin's Diabetes Mellitus*[1] is to be recommended. For example, studies are described reporting defects of cell-mediated immunity and diminished lymphocyte transformation response in people with poorly-controlled diabetes, while impaired leucocyte function, the first line of defence against secondary bacterial infection, can be demonstrated from observation of reduced phagocytic activity with increasing levels of blood glucose.[2] Such disturbances of immune function are very likely to have significant impact on the outcome of COVID-19 infection complicated by diabetes. Furthermore, it has been suggested that increased glucose concentrations in airway secretions may expose pulmonary epithelial cells to greater viral replication and consequent pneumonitis.[3]

Reports from China

Although criticism has been levelled concerning the transparency of the early coronavirus epidemic experience in China, several preliminary clinical and epidemiological papers, summarised in a recent *Practical Diabetes* editorial,[4] have achieved rapid publication[5–7] primarily listing diabetes simply as an adverse comorbidity, more prevalent in severe cases and with non-survivors. These early reports of COVID-19 infection included observations of 52 critically ill adult patients with coronavirus pneumonia admitted to the ICU at the Wuhan Jin Yin-tan hospital, where diabetes was found in twice the number of individuals who died compared to those who survived (22% vs 10%).[5]

This outcome has since been replicated on a wider scale from 552 hospitals across China[6] where, in a total of 1099 patients with established COVID-19 infection, diabetes was present in 7.4% cases overall, but recorded in a significantly greater proportion of those with severe compared to non-severe disease (16.2% vs 5.7%). A small sample analysis of 26 fatalities reported diabetes in 42.3% of cases.[7]

Further reports from Wuhan have since been published, with continued indication of diabetes as a risk factor for the progression and prognosis of COVID-19 infection. One study[8] has observed that 14% of cases had diabetes without any other comorbidities, but nonetheless these individuals were at much higher risk of developing severe pneumonia, excessive release of inflammatory bio-markers and increased hypercoagulability. This 'inflammatory storm' was associated with a more rapid deterioration of illness and a significantly higher mortality rate.

From analysis[9] of 150 patients, predictors of fatal outcome included older age, the presence of other underlying diseases, the onset of secondary infection and elevated inflammatory markers. In 68 fatal cases, five (7%) patients died with myocardial damage, described as 'fulminant myocarditis' consequent to the 'cytokine storm'. Working in central London as a junior doctor during the 1969 Hong Kong Flu pandemic, one recollects that deaths in young individuals were often attributed to viral myocarditis. It is a salutary reflection as to how diabetes has exploded in this modern age, barely recognised as a clinical issue 50 years ago.

Global impact and previous pandemic experience

In the western world, the University Hospital of Padua, at the epicentre of the outbreak in Italy,[10] reports that 35.5% of patients dying from COVID-19 infection had diabetes, compared to a matched population prevalence of 20.3%, while in preliminary estimates from the USA,[11] based on data from 122,653 persons with confirmed COVID-19 disease, diabetes proved to be the most significant medical comorbidity: 10.9% of total; 24% of those hospitalised and 32% of those admitted to the ICU.

So far data for the UK are limited. However, the Office of National Statistics has reported[12] that in England and Wales 91% of those dying from COVID-19 infection had at least one pre-existing condition, including diabetes. More specifically, statistics from NHS England[13] for the period 31 March to 12 May 2020 record that of 22,332 COVID-19 deaths in hospital, 5873 (26%) had diabetes, a comparable proportion to New York City, with diabetes identified in 25% of patients hospitalised with COVID-19 infection.[14]

Parallels have been drawn between this current coronavirus pandemic and the global Spanish Influenza pandemic of 100 years ago, but the concept of managing comorbidities, other than post-war malnutrition, would not have been foremost in mind at that time. Diabetes was, however, very much a consideration with the Swine Flu pandemic of 2009, when contingency planning and management guidelines were issued.[15,16] Even then it was recognised that people with diabetes were potentially six times more likely to require hospitalisation during an influenza epidemic.[17]

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However, circumstances are different now, with no natural innate COVID-19 immunity in the population and a preventative vaccination programme yet to be developed. Recognising that some people may be more seriously vulnerable to infection, the UK government identified certain groups, primarily those with potential immune deficiency or with severe respiratory conditions, and advised that they self-isolate at home for 12 weeks. Although diabetes was not included in this list, people with diabetes have nonetheless been encouraged to take particular care with precautionary measures such as social distancing and relative self-isolation.

Advice and guidelines

The principles of diabetes management with infection remain relevant ('sick-day rules'). Under these circumstances people with diabetes may well feel anxious, with concerns about their diabetes control, availability of medical supplies and their access to expert advice. Guidance for people with diabetes has been made available online from organisations such as Diabetes UK[18] and JDRF,[19] and similarly for health care professionals from specialist bodies including the Association of British Clinical Diabetologists,[20] the US Endocrine Society jointly with the University of Leeds,[21] and an international perspective from the National Diabetes Foundation of India.[22] The latest (19 March 2020) clinical guide for the management of people with diabetes during the coronavirus pandemic has been issued jointly from the Royal College of Physicians, ABCD and the NHS,[23] while a National Diabetes Inpatient COVID Response Team has provided advice[24] on maintaining essential elements of the diabetes service, and collating shared experience to learn from these unprecedented circumstances.

Education programmes in self-management, especially what to do in the event of acute illness, should be returning the desired dividend, but specialist advice must continue to be available for people in difficulties with their diabetes control. For instance, immediate facility will need to be in place to initiate insulin therapy for those with type 2 diabetes previously bordering on the edge of acceptable control on maximum oral hypoglycaemic agents. With the Swine Flu pandemic a five- to 10-fold increase in new case insulin demand was anticipated, and it has to be assumed the same need will arise with this pandemic; important data to be analysed in due course.

Present uncertainties and lessons to be learnt

At the time of writing, the peak rate of those infected, the numbers hospitalised and sadly the case-fatalities in the UK has yet to be reached, with measures still in place to suppress virus transmission and lessen pressures on the NHS. Inevitably, questions concerning easing of current restrictions raise issues as to whether there is sufficient acquired immunity in the population – present indication is that still is a low proportion – or whether that can only be achieved once an effective vaccination programme has been developed. It is possible that countries where a speedier response was initiated at the outset of the epidemic, have been in a better position to see restrictions lifted. Having gained previous experience with the former SARS-CoV and MERS-CoV coronavirus pandemics, Singapore has been cited as an exemplary model of management, being well-prepared in terms of pre-planning and rapid implementation of control measures, quarantining of infected individuals and family, along with early school closure and workplace distancing.[25] Based on personal observation, as a visitor at the time, everyone on airport arrival and at entry to public buildings, was subject to infra-red thermal scanning and if febrile, individuals were immediately isolated with rigorous contact tracing. Seemingly an effective measure – was this a missed opportunity in the UK? Furthermore, the addition of extensive antigen testing for infected persons and in particular of asymptomatic contacts appeared crucial to early success in controlling the outbreak, thereby facilitating an earlier return to post-epidemic normality, albeit with a small secondary wave relapse attributed to returning nationals, since similarly reported in China.

At present uncertainty prevails, particularly for those in recognised vulnerable groups, such as diabetes. Without a reliable antibody test, many if not most people will be unsure as to their immune status, and indeed for those who have recovered from overt coronavirus infection, the degree and duration of immunity to further infection are uncertain. As yet, no specific data in respect of diabetes are available. Will the immune response to infection be different with diabetes? So many questions are at present waiting to be addressed. With diabetes itself being a potential composite comorbidity, to what extent is outcome determined by additional renal and cardiovascular considerations? How have differing levels of glycaemic control and medication influenced outcome? Were drugs such as metformin and SGLT2 inhibitors discontinued on hospitalisation as advised and, if so, with what consequence? What proportion of patients needed immediate conversion to insulin? Did statins improve the anti-inflammatory response or, like non-steroidals, possibly the reverse? Did ACE2 inhibitors adversely affect outcome or not? The answers will be awaited with considerable interest.

Meanwhile, as the pandemic takes its course, the focus moves towards an exit strategy from current restrictions, so far untested and almost impossible to configure without risking infection for those as yet unaffected by illness. By having taken extra precaution with those most vulnerable including diabetes, these individuals remain at risk, requiring a level of continued care probably until a safe and effective vaccine becomes available. Suggestions have been mooted of a differential phased release, but there is no easy answer, and much will be learnt from the experience. This pandemic will eventually settle, but it is unlikely to be the last. Knowledge gained should be used to prepare well in advance for such future contingency and, as ever, the extra burden of diabetes in the event of overwhelming contagious disease must be constantly addressed.

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