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COMMENTARY

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Diabetes, obesity and COVID-19: A complex interplay

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Abstract

With the accumulation of observational data showing an association of metabolic co-morbidities with adverse outcomes from COVID-19, there is a need to disentangle the contributions of pre-existing macro- and microvascular disease, obesity and glycaemia. This article outlines the complex mechanistic and clinical interplay between diabetes and COVID-19, the clinical and research questions which arise from this relationship, and the types of studies needed to answer those questions. The authors are clinicians and academics working in diabetes and obesity medicine, but the article is pitched to an audience of generalists with clinical experience of or interest in the management of COVID-19.

As the global COVID-19 pandemic has evolved, a surprising feature has been a transition in its perception from a condition of greatest risk to those with chronic obstructive pulmonary disease to one where the threat predominates in those with diabetes and metabolic dysfunction. In large case series, COPD was present in only 11% in China,[1] 5% in the United States[2] and 18% in the UK[3]; but, by contrast, diabetes was present in 8%,[1] 33.8%[2] and 21%[3] of cases, respectively. In addition, marked insulin resistance with ketosis has been reported,[4,5] even in those individuals with no preceding history of diabetes.[5,6]

These observations suggest an interplay between COVID-19 and diabetes, and a complex pathophysiology. Understanding how diabetes can lead to severe COVID-19 and, conversely, how COVID-19 can complicate diabetes pathophysiology or its outcomes, is an important priority for clinical practice and public health. To address this, a global registry (COVIDiab) has been launched to facilitate the study of the manifestations of COVID-19–related diabetes, its outcomes, and best treatment.[7]

Over the short duration of the COVID-19 pandemic, a wealth of data has emerged on this topic, but significant questions still need to be answered. Here, we review the existing literature on the interplay between COVID-19 and diabetes, and consider the priorities for future research.

1 | PREVALENCE OF DIABETES AMONG INDIVIDUALS WITH COVID-19

Epidemiological studies have shown that diabetes increases the risk of hospitalization,[8] admission to critical care[9] and mortality caused by COVID-19.[2,10–13] Individuals with diabetes have accounted for 7.8%-33% of all hospital deaths.[8,11,14] One early multicentre study from Wuhan reported that the risk of fatal outcome was up to 1.49-fold higher in patients with diabetes[14]; however, a report from the UK, which examined 23 804 COVID-19–related deaths, suggested that

the mortality risk could be up to 2-3 times greater in those with diabetes.[11] Other studies have reported a 2-fold increased risk for admission to critical care and an increased requirement for mechanical ventilation compared with those who did not have diabetes.[2,9,14] Pooled analyses from these early studies have indicated a prevalence rate of diabetes between 9.8% to 11.5%, after adjusting for heterogeneity.[15,16] Likewise, meta-analyses of early studies have suggested a 2- to 3-fold increase in the risk of severe forms of COVID-19 including critical admissions, and mortality in diabetes.[15,17–19] Diabetes may also predispose to co-morbidity in the context of COVID-19 infection, as has been reported for acute stroke.[20] There are, at present, limited data on the true case fatality rate in diabetes compared with other conditions and co-morbidities. This has left several unanswered questions, the first of which is: What is the generalizability of these reported data?

Most of the published data have been derived from hospital statistics, which can introduce selection bias. In many countries, communities outside of secondary-care centres had limited access to COVID-19 testing, resulting in diagnostic access bias, which may exaggerate overall severity and distort the case fatality rate. With this caveat, there seems to be worldwide consistency in the high prevalence of diabetes in hospitalized patients, as well as an association between severity of COVID-19 (variously defined as a requirement for critical care, invasive ventilation, or death) and diabetes. Although the type of diabetes is not always differentiated, severe COVID-19 has been reported for both type 1 and type 2 diabetes. Where reported separately, the relative risk appears to be greater for type 1 diabetes, but this may need to be interpreted with caution as overall case numbers are low.[21]

2 | MECHANISTIC INTERPLAY BETWEEN DIABETES AND COVID-19

If diabetes does influence the outcomes of COVID-19, is that through susceptibility to COVID-19 infection, or via the immune response? Myriad defects of the innate response have been reported in diabetes, including dysfunction of granulocytes, monocyte/macrophages, dendritic cells, natural killer (NK) cells, B cells, T cells and cytokine signalling.[22,23] Unsurprisingly, the risk of bacterial and fungal infections is increased among patients with diabetes.[24] However, aside from hepatitis virus C[25] and herpes zoster,[26] there is little evidence that diabetes, or the level of glycaemic control, predisposes to the chance of viral infection.[27] Data from outside the hospital setting, centred in primary care, are needed to determine whether the presence of diabetes (and/or degree of glycaemic control) affects the infection rate of COVID-19. In addition to this, there may be additional specific mechanisms for dysglycaemia in COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) may gain selective entry to pancreatic islets via the angiotensin-converting enzyme-2 (ACE-2) receptor and lead to local cytopathic effects, diminishing beta-cell function.[28] Furthermore, ACE-2 receptors are highly prevalent in other metabolic organs and tissues including adipose tissue, the liver and the small intestine, providing a plausible mechanistic explanation for the observed marked insulin resistance in COVID-19.[29]

3 | CLINICAL INTERPLAY BETWEEN DIABETES AND COVID-19

Critical illness is characterized by a neuro-endocrine response including sympathetic nervous system activity, hyperglucagonaemia, cortisol and growth hormone release.[30] These all have the effect of inducing resistance to insulin action in multiple tissues, resulting in hyperglycaemia. In critical care, glucose clamp studies show greater insulin resistance with more severe medical illness, as determined by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[31] Microthrombi, a hallmark of COVID-19 pathology,[32] may compound impaired glucose disposal from pre-existing diabetic microangiopathy.[33] Likewise, blood glucose concentration may be a surrogate marker for disease severity in COVID-19. To date, there are no data that correlate COVID-19 disease severity to blood glucose, and to do this there needs to be consensus on a robust measure of severity. At present, validated measures of COVID-19 severity are lacking. A small series, exploring the predictive value of established severity measures, suggested some superiority of the APACHE II scale over the Sequential Organ Failure Assessment (SOFA) score and CURB-65 score.[34] Further validation of these illness-severity scores are needed for COVID-19.

At a systemic level, attempts should be made to evaluate the potential role of complications and co-morbidities of diabetes in COVID-19 outcomes. These should include obesity, obstructive sleep apnoea, hypertension and macrovascular disease, all of which have figured prominently as risk factors,[1–3] but also microvascular disease. Measured microvascular dysfunction (such as nephropathy, retinopathy or neuropathy) in one organ may be a manifestation of more systemic involvement that could include the peri-alveolar microvasculature.[33,35] The dissociation between preserved lung mechanics and the severity of hypoxaemia has led to an observation that respiratory failure in COVID-19 is 'atypical',[36,37] characterized by a form of catastrophic microvascular injury syndrome mediated by activation of complement pathways alongside a procoagulant state.[38] Microthrombi and 'endothelitis'[32] may contribute further to the impediment of microvascular blood flow and gas transfer in the lung,[39] increasing disease severity. Microangiopathy of diabetes may be an independent risk factor for severity of COVID-19 and this requires further study.

4 | IMPACT OF GLYCAEMIC CONTROL ON OUTCOMES

Defining the prognostic value of metabolic alterations in acute COVID-19 is crucial to inform clinical practice. However, there are currently no data to assist us in such an assessment. Because diabetes increases the severity of COVID-19, it makes intuitive sense to aggressively treat this; it is not clear, however, what variables and parameters should guide the escalation of therapeutic options. Is it the HbA1c value, the admission glucose level, or the mean/variance of the in-hospital glucose level? In the CORONADO study,

undertaken on 1317 participants across 53 French centres admitted to hospital with diabetes and COVID-19, the most recent HbA1c pre-admission did not independently predict death or need for intubation.[10] In this study, as in the large UK cohort,[21] a single HbA1c value was used as an index of glycaemic control. Correction of observational data for HbA1c may result in residual confounding if HbA1c does not adequately capture diabetes 'severity'. A mean, or variance, of HbA1c value over the duration of diabetes may be superior and might be accessible through further analysis of the UK NHS cohort.[21]

5 | IMPACT OF ETHNICITY

Concerns have also been raised that individuals from black, Asian and minority ethnic (BAME) backgrounds are at a disproportionate risk of contracting the virus,[40] admission to critical care[3] and mortality from COVID-19.[41,42] In the UK cohort, a higher risk of death was noted in the black and Asian population for both type 1 and type 2 diabetes.[11] In the CORONADO study, 38.1% of all admissions with diabetes were from BAME backgrounds.[10] Potential confounders for ethnicity effect include the well-recognized higher prevalence of diabetes, obesity and hypertension in BAME populations and socio-economic deprivation, but factors such as disparities in glycaemic control and access to care may also contribute.[40,43]

6 | THE NEED FOR FOCUS IN FUTURE RESEARCH DIRECTIONS

The recognition of the association between diabetes and COVID-19 is only the beginning of our understanding of the interplay between these two conditions; work is needed to understand the mechanisms and directionality of that relationship.

Whether the association of diabetes with poor outcomes is direct, or secondary to co-morbidities, needs clarification. Epidemiological studies must assess diabetes groups stratified with respect to ethnicity, diabetes complications and therapies to further understand susceptibility to primary infection and the risk of developing severe disease. Some striking findings have been noted in data already published; a strong association between diabetes and poor outcome has been noted in younger (aged <55 years) and less hypertensive individuals,[17] as well as those previously undiagnosed as having diabetes.[44] Given the latter finding, screening all admissions to hospital for hyperglycaemia and instituting early treatment where needed is important.[45]

The atypical presentation of diabetes—with ketosis and marked insulin resistance—in COVID-19 creates specific challenges in management. In recognition of this, specific guidance based on theoretical principles has emerged,[46,47] but evidence of the efficacy of management strategies is needed. Published guidance has raised theoretical concerns surrounding the safe use of sodium-glucose co-transporter-2 inhibitors and metformin,[48,49] although, as yet, there are no systematic studies exploring outcomes and impact. Human dipeptidyl dipeptidase-4 (DPP-4) is a coronavirus receptor, suggesting a potential role for DPP-4 inhibitors in COVID-19,[50] however, early evidence has shown no reduction in hospitalization with their use.[51]

Corroborative data are required for the observation of a lower risk of death (hazard ratio 0.14) in those patients with normoglycaemia in hospital,[14] as this will affect glucose targets. It may be that avoidance of marked hyperglycaemia, rather than attaining normoglycaemia (with associated risk of hypoglycaemia), should be the goal for in-hospital management. This issue has assumed particular importance following the finding that dexamethasone treatment significantly improved outcomes in oxygenated and ventilated patients with COVID-19 in the RECOVERY trial.[52] In light of this, utilization of corticosteroids will probably become standard practice in severe COVID-19, therefore, defining an acceptable glucose target range and diabetes management strategy for these patients will be of the utmost importance. Of note, one quarter of the RECOVERY study population had diabetes, and post hoc analyses are awaited as to whether individuals with diabetes had similar outcomes with steroid therapy to the wider population.

Accumulating data regarding the disproportionate risk to BAME populations with diabetes requires rigorous scrutiny, given the broader implications for public health and social equity.[53] Vaccine studies should also be designed to include people with diabetes and from BAME groups in sufficient numbers to allow evaluation within these high-risk groups.

Mechanistic studies are needed to determine the effect of COVID-19 on tissue-specific insulin resistance, the impact on pancreatic B-cell dysfunction, and lung diffusion and perfusion dynamics in the presence of hyperglycaemia. Clinical studies to evaluate therapeutic strategies to ameliorate the severity of an infection also need to assess potential drug interactions with diabetes therapies. Further characterization of the unusual properties of diabetes seen in COVID-19 is needed, and, for this purpose, a global registry (COVIDiab)[7] has been set up to define the characteristics of new-onset diabetes in affected individuals. Long-term observational follow-up of COVID-19 survivors is also required to determine if there is an increased risk of diabetes after COVID-19 (as with 2002 SARS), and whether it impacts on progression to insulin or worsening microvascular disease during late follow-up.

The impact of 'the lockdown' on glycaemic control care among individuals with diabetes will be of considerable interest to healthcare professionals, epidemiologists and policymakers. Changes in physical activity, weight gain, behaviours and social isolation[54] brought on by the lockdown will have important clinical ramifications. Studies investigating changes in glycaemic control during this period of an enforced sedentary lifestyle and the 'legacy effects' of lockdown are awaited. The landscape surrounding access to care also seems to have rapidly shifted with the adoption of various telehealth initiatives, which have yet to be properly validated to confirm their effectiveness in delivering diabetes care.[55] Detailed studies exploring these new models are urgently required as health systems prepare to embark on post-COVID-19 recovery plans. Such initiatives also support medical preparedness[56] should a second wave of the pandemic appear.

Given that COVID-19 will probably persist for the foreseeable future, and the high global prevalence of diabetes, it is imperative that

research in these areas is prioritized to provide support for optimized clinical management and health policy formulation.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualization and review and editing; writing of original draft: PV and MBW. MBW is the guarantor of this article.

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