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## Commentary

# The contribution of diabetic micro-angiopathy to adverse outcomes in COVID-19



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## ABSTRACT

Increasing evidence points to endothelial cell dysfunction as a key pathophysiological factor in severe coronavirus disease-19 (COVID-19), manifested by platelet aggregation, microthrombi and altered vasomotor tone. This may be driven by direct endothelial cell entry by the virus, or indirectly by activated inflammatory cascade. Major risk groups identified for adverse outcomes in COVID-19 are diabetes, and those from the Black, Asian and ethnic minority (BAME) populations. Hyperglycaemia (expressed as glycated haemoglobin or mean hospital glucose) correlates with worse outcomes in COVID-19. It is not known whether hyperglycaemia is causative or is a surrogate marker - persistent hyperglycaemia is well known as an aetiological agent in microangiopathy. In this article, we propose that pre-existing endothelial dysfunction of microangiopathy, more commonly evident in diabetes and BAME groups, makes an individual vulnerable to the subsequent 'endothelitis' of COVID-19 infection.

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There is emerging understanding that coronavirus disease-19 (COVID-19) induced respiratory complications appear to have a distinct pattern that differs from typical adult respiratory distress syndrome (ARDS). It is characterised by a dissociation between relatively well-preserved lung mechanics and the severity of hypoxemia [1]. A possible explanation for the severe hypoxemia occurring in compliant lungs, is the loss of lung perfusion regulation and hypoxic vasoconstriction. Coagulation dysfunction also appears to be common in severe COVID-19 [2,3], with fatal cases exhibiting diffuse microvascular thrombosis, suggesting a thrombotic microangiopathy [4].

It is becoming increasingly recognised, therefore, that endothelial damage and pulmonary microvascular thrombosis are central to the clinical severity of COVID-19 [1,2,4]. Endothelial access by the virus is mediated via the protein angiotensin-converting enzyme 2 (ACE2), which is highly expressed on vascular tissue. Replication of virus within the host cell can cause direct cellular damage and release of pro-inflammatory signals. Angiotensin converting enzyme-2 (ACE-2) consumption by viral entry would be predicted to increase local angiotensin-II concentration, contributing to vasoconstriction, endothelial activation, and pro-inflammatory cytokine release - inducing further alveolar epithelial and vascular endothelial cell damage [2,3].

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Endothelial cell involvement may then spread across vascular beds of different organs [4].

Both diabetes and ethnicity appear to be additional risk factors emerging in clinical sequelae of the COVID-19 pandemic. Within the hospitalised COVID-19 population, individuals with diabetes are over-represented [5,6]. A systematic review reported a significant association between diabetes and COVID-19 infection severity (Odds ratio 2.67, 95% CI 1.91–3.74) [7]. Subsequent data from China estimated mortality rates near 10% in diabetes, from a sample of 72,314 confirmed cases [8]. The most recent publication, comprising 7336 patients, showed the risk of fatal outcome from COVID-19 was up to 50% higher in patients with diabetes [6]. Furthermore, well-controlled blood glucose was associated with lower hospital mortality than poorly controlled glucose (hazard ratio 0.14) [6].

Diabetes is characterised, not only by hyperglycaemia, but also endothelial dysfunction and microcirculatory impairment [9]. Microvascular disease (either retinopathy or nephropathy) is present in over one-third of newly-diagnosed patients with type-2 diabetes (T2D) [10]. The consequences of endothelial dysfunction include dysregulation of vasodilation, fibrinolysis, and anti-aggregation – classically leading to macrovascular disease – and may contribute to microvascular disease retinopathy, nephropathy and neuropathy [10]. However, evidence of microvascular dysfunction in one organ is a marker of systemic injury. It is increasingly recognised that there are microvascular pulmonary complications of diabetes (“diabetic lung”) [11]. It has been suggested that reduced pulmonary diffusing capacity for carbon monoxide ( $DL_{CO}$ ) [11,12] may be attributed to vascular injury of pulmonary capillaries related to diabetic microangiopathy [11,13]. Importantly, the functional impairment was directly related to the degree of glucose control (glycated haemoglobin -  $HbA_{1c}$ ) and the presence of diabetic microvascular complications including retinopathy, neuropathy, and microalbuminuria in a sex-specific manner [11]. The relationship of impaired gas exchange with diabetes was observed, even in those who had never smoked [11]. In these individuals, the pulmonary microvasculature may be poorly prepared to meet the challenge of COVID-19 infection.

The Black, Asian and minority ethnic (BAME) community have suffered disproportionately from COVID-19. BAME, although only 13% of the United Kingdom population and a younger age distribution [14], accounts for one third of all COVID-19 cases and 34% of critically-ill COVID-19 patients [15,16]. The mechanisms underlying the disproportionate effect of COVID-19 infection on BAME patients remain incompletely understood. However, BAME groups have a disproportionately high prevalence of T2D [17] and disparities have been observed in diabetes control, monitoring and presence of microvascular complications in the BAME, compared to white population [18]. In this context, dysglycaemia (both  $HbA_{1c}$  and mean glucose) associating with adverse outcomes in COVID-19, may be surrogates for the presence and severity of underlying microvascular disease [6]. The prevalence of prediabetes among adults is approximately 38% and 35%, in the United States [17] and United Kingdom [19] respectively. Prediabetes is also over-represented in BAME population. In the UK, the hazard ratio for prediabetes in South Asians was 1.67 (1.12–2.50) and for Blacks 1.45 (0.92–2.27), compared to the white

population [19]. Although it is alluring to think that people with prediabetes are protected from microvascular disease; early stages of retinopathy, nephropathy, and neuropathy have been reported in people with prediabetes, with a prevalence of up to 10% [10,20].

Microvascular disease and endothelial dysfunction may underlie adverse outcomes in COVID-19 and may represent the pathophysiological key missing link that identifies susceptible populations and may require specific treatment. Analyses of data on patients with COVID-19 should include details of diabetes complications and age, to untangle the complex interaction between ethnicity, diabetes and COVID-19 outcomes.

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## Declaration of Competing Interest

The authors declare no conflict of interest.

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