COMMENTARY

A brief analysis and hypotheses about the risk of COVID-19 for people with type 1 and type 2 diabetes mellitus

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Abstract

COVID-19 is an infectious respiratory disease which firstly occurred in Wuhan, China and evolved rapidly around the globe. The causative pathogen is a novel coronavirus called SARS-CoV-2 with genomic similarities with SARS-CoV and MERS-CoV. The disease is transmitted among humans either through direct contact or via droplets from sneeze or cough. Most infected persons remain asymptomatic or mildly symptomatic, but some patients may develop severe clinical features, including pneumonia, respiratory failure, sepsis and even death. People of advanced age and/or with underlying diseases (including diabetes mellitus) are at greater risk. The innate and adaptive immune system are responsible for protecting the body against viral infection. Nevertheless, it is assumed that SARS-CoV-2 interferes with the immune system through immunomodulating mechanisms which intensify its pathogenesis. A delayed or reduced response of the innate immune system is critical for the development of pathogenesis of the virus. People with diabetes are more likely to develop severe symptoms of COVID-19. The present article speculates that special aspects of the immune dysfunction caused by chronic hyperglycaemia is the main reason for this susceptibility.

Keywords COVID-19 · Diabetes mellitus · Hyperglycaemia · Diabetic complications

Epidemiology of COVID-19

Coronavirus disease 2019 (COVID-19) is a respiratory infection which is caused by a novel virus belonging to the Coronaviridae family [1] and is officially named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). In humans, coronaviruses primarily target the respiratory system and have also caused outbreaks of respiratory disease in the past, mainly the severe acute respiratory syndrome (SARS-CoV) in 2003 and the Middle East respiratory syndrome (MERS-CoV) in 2012. They are a large family of positive-sense single-stranded RNA viruses (+ ssRNA) with a crown-like appearance under the electron microscope due to the presence of spike glycoproteins on the envelope [2]. These viruses derive from animal species (bats, rodents, birds) and can cross barriers between species, also infecting humans [3].

The transmission of SARS-CoV-2 among humans occurs mainly through direct contact or droplets spread by coughing or sneezing from an infected individual [4] . The incubation period in most individuals varies between 2 and 14 days [5] . On average, each person has the potential to spread the infection to 2.2–2.7 other people [6] . The majority of infected individuals (about 80%) remains asymptomatic or with mild symptoms, whilst the remainder suffer from severe or critical clinical features. The most common symptoms of COVID-19 include fever, cough, sore throat, malaise and dyspnoea. In severe cases, patients may develop pneumonia, acute respiratory distress syndrome, respiratory failure, septic shock and multi-organ failure which can lead to death [7] . The elderly and those with underlying diseases (such as hypertension, cardiovascular diseases, diabetes mellitus and chronic pulmonary diseases) are more at risk of adverse outcomes [8] .

The first cases of COVID-19 were detected in Wuhan, the largest metropolitan area in Hubei province, China. The spread of the disease evolved quickly to a pandemic. As of June 29, 2020, the number of COVID-19 infections globally has exceeded 10 million cases in 188 countries/regions causing more than 500,000 deaths [9] . Many issues still remain to be determined with regard to the epidemiological evolution of

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the disease, especially the de-escalation of its prevalence, possible seasonal fluctuations of its incidence and the risk for future widespread reoccurrences. Nevertheless, it is already known that the resulting outbreak of COVID-19 has had a detrimental effect on public health, causing numerous deaths and burdening tremendously the health systems worldwide. For this reason, states around the world have been taking measures to restrict the impact of the spread. At the moment, management strategies aim at reducing transmission in the community and supporting patients with severe clinical features. At the same time, researchers have been working intensively towards the establishment of novel diagnostic procedures, effective therapeutic regimens and prevention products.

Pathogenesis of SARS-CoV-2

Coronaviruses' entry into susceptible cells is a complex process that is mediated through binding of the viral surface-exposed spike (S) glycoprotein to the host cell receptor. This interaction promotes the fusion of the viral and cellular membranes. SARS-related coronaviruses interact directly with angiotensin-converting enzyme 2 (ACE2) via the domain B of the S glycoprotein to enter cells [10] . ACE2 is mainly expressed in type 2 alveolar cells in the lungs [11] .

The first-line defence against viral infection is the production of type I interferons (IFNs-α/β) which is an essential part of the innate immune system. In RNA viruses, such as the coronaviruses, the viral genome or the intermediates during viral replication are recognised by either endosomal RNA receptors or cytosolic RNA sensors in all nucleated cells of mammalians. This interaction leads to a downstream signalling cascade and an accompanying translocation of nuclear factors. This process results in expression of IFNs-α/β and other pro-inflammatory cytokines. These interferons act to neighbouring cells and via the JAK-STAT pathway stimulate the expression of antiviral proteins and induce other biological activities such as inhibition of cell proliferation, regulation of apoptosis and immunomodulation [12] .

A successful response of the IFNs-α/β-related innate immune system should be able to control viral replication and dispersion in the body at an early stage, at least to an extent. However, it is believed that SARS CoV-2 is able to subvert the host response through the action of structural and non-structural proteins. Due to the genomic sequence similarities with SARS-CoV (and secondarily with MERS-CoV), it is assumed that SARS-CoV-2 interferes with the relevant signalling processes of the host cells through degradation or inhibition of involved cellular molecules. Consequently, the delayed or vitiated INFs-α/β response compromises the early viral control, leading to escalation of the concentration of inflammatory neutrophils and monocytes and in turn to

overproduction of pro-inflammatory cytokines ('cytokine storm') that manifest the lung immunopathology of COVID-19 [13] .

The adaptive immunity response to SARS-CoV-2 has not yet been clarified. Presumably, antigens from invading pathogens (most probably the surface-exposed spike glycoprotein but perhaps also the membrane protein) are acquired by respiratory dendritic cells which become activated and present the processed antigen to circulating T cells. Activated CD4 + T cells promote the production of virus-specific antibodies by activating T-dependent B cells, whilst CD8 + T cells are cytotoxic and can kill infected cells. In addition, B cells produce specific antibodies which may neutralise the invading viruses [14] . If the pathogenesis in SARS applies to COVID-19, the upregulation of pro-inflammatory cytokines during the delayed innate immunity potentiates the occurrence of severe respiratory manifestations, whilst the progression to adaptive immunity is correlated with recovery [15] .

Susceptibility of patients with diabetes mellitus

Diabetes mellitus is a clinical syndrome of impaired glucose metabolism with inappropriate hyperglycaemia due to absolute or relative deficiency in insulin secretion, resistance to insulin action, or both [16] . The most common types of diabetes mellitus include type 1 and type 2 diabetes [17] . Although the clinical diagnosis of the type of diabetes is not always straightforward, type 1 and type 2 diabetes are heterogeneous diseases with considerably different pathophysiology. Type 1 diabetes is a catabolic disorder in which pancreatic β-cells fail to respond to all insulinogenic stimuli mainly due to immune-mediated and less frequently due to idiopathic destruction. [18, 19] . Type 2diabetes is characterised by various degrees of resistance to insulin action and insulin secretory defect and is associated with other metabolic disorders of the muscle tissue, liver, fat cells, gastrointestinal tract, pancreatic α-cells, kidneys, and brain [20] . The global prevalence of diabetes mellitus has risen dramatically over the past forty years and it is expected to grow further over the next decades. In 2019, it was approximately 9.3% (463 million people) and it is estimated to rise around to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [21] .

Chronic hyperglycaemia is associated with increased susceptibility to pathogens. Many common infections are more frequent and severe in individuals with diabetes mellitus, whilst some rare infections (e.g. rhinocerebral mucormycosis, emphysematous infections of the gallbladder and urinary tract, invasive otitis externa) affect almost exclusively the diabetic population [22] . Although the reasons for this vulnerability are not completely defined, it is believed that abnormalities in innate and adaptive immunity, diminished vascularisation,

and facilitation of colonisation and growth of a variety of organisms are critical factors [23] . In case of viral infections, it is assumed that impairments mainly in innate as well as in cell-mediated and humoral immunity could contribute to the increased susceptibility.

The existence of diabetes is strongly associated with an increased risk of developing severe COVID-19 in case of infection with SARS-CoV-2 [24, 25] . However, it is not clear how diabetes mellitus worsens the clinical presentation of COVID-19. Several suggestions can be made. The present article supports that heightened inflammatory processes constitute the main pathophysiologic factor for the severity of COVID-19 among patients with diabetes mellitus, whilst impairments in immune response and diabetic comorbidities contribute to the aggravated pathogenesis.

The primary hypothesis is that chronic hyperglycaemia is involved in inflammatory processes which further activate monocytes and promote the synthesis of pro-inflammatory cytokines, thus aggravating inflammation and injury in the lung tissue and worsening clinical condition. In this mechanism, the excess of circulating glucose causes oxidative stress in which free radical O_2 reduces the availability of nitric oxide (NO) and activates a series of pro-inflammatory transcription factors leading to inflammation. Moreover, hyperglycaemia increases the expression of tumour necrosis factor-alpha (TNF-a) and inteleukin-6 (IL-6) which further exacerbate inflammation [26] . A higher propensity to infections due to the involvement of inflammatory processes was documented in studies involving other viruses [27] .

In type 1 diabetes, autoimmunity induces an inflammatory activity which leads to pancreatic β-cell damage. The resultant chronic hyperglycaemia causes oxidative stress, increases the secretion of TNF-α and IL-6 and impairs NO-mediated vasodilatation [28] . In type 2 diabetes, inflammation is also caused by systemic factors, mainly obesity and subsequently insulin resistance. Adipose tissue enhances the inflammation process through the action of activated macrophages and the production of pro-inflammatory cytokines (including TNF-a and IL-6) [29, 30] . Yet it remains unclear whether the innate immune response is vitally impaired in both types of diabetes mellitus and whether hyperglycaemia favours the initial virulence of SARS-CoV-2.

Diabetes is a chronic condition that can affect the body's immune response to pathogens [31] . Indeed, the proliferative response of lymphocytes is impaired in patients with diabetes, particularly among those with poor glycaemic control [32] , and low lymphocyte count is a predictor of severe prognosis in patients with COVID-19 [33] . With regard to the production of neutralising antibodies, it is possible that glycosylation may impair humoral immunity, especially in patients with high HbA_{1c} values [34] . Furthermore, patients with diabetes mellitus may present dysfunctional type IV (delayed)

hypersensitivity reaction and abnormal complement activation [35] which may hinder the immune response.

Apart from the defects in inflammatory and immune functions due to hyperglycaemia, complications of diabetes mellitus and treatment regimens may be involved in the vulnerability of these patients. Endothelial dysfunction, in particular, may enable SASR-CoV-2 to have an easier access to host cells [36] . In addition, associated diabetic comorbidities and/ or complications, such as hypertension, cardiovascular disease, and chronic kidney disease may act synergistically and further worsen the prognosis [37] . Especially persons, who are treated with ACE inhibitors or angiotensin 2 receptor blockers, have increased expression of ACE2 which could potentially facilitate the infection with SARS-CoV-2 [38] .

Implications for diabetes' care

COVID-19 has evolved to a public health crisis. Currently, there is a lack of specific treatments, and only general preventive strategies are available. Within this context, appropriate guidance of patients with diabetes should be a priority. Social distancing and practicing good hygiene are invaluable tools for diminishing the transmission of SARS-CoV-2. In case of extended periods of isolation, individuals with diabetes should secure access to medications and consumable supplies, such as insulin, glucose test strips, disinfectants, and ensure unimpeded communication with health care professionals, including the use of phone and video calls to minimise face-to-face contact [39] .

Although individuals with diabetes do not appear to contract SARS-CoV-2 at an increased rate compared to the general population [40] , poor control of diabetes is associated with a higher risk for adverse clinical outcomes. Therefore, it is important that persons with diabetes mellitus maintain an optimal glycaemic control during a SARS-CoV-2 outbreak. Regular monitoring of blood glucose levels (and urinary ketones when needed) and adherence to treatment are necessary for this purpose. Attention to proper nutrition and physical activity (such as indoor exercise and unescorted walking) are also important [41] .

Epilogue

The health crisis due to the COVID-19 pandemic has been a global challenge for states, care systems and individuals. SARS-CoV-2 has been exceptionally infectious and pathogenic for humans. Patients with diabetes mellitus need to be in the core of health care attention because of greater risk for severe clinical course and mortality. In addition, the global community should focus on the discovery and production of the medical means that will affectively protect populations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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