Commentary

Type 1 diabetes triggered by covid-19 pandemic: A potential outbreak?

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The global concern is currently focused on the novel coronavirus, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was isolated in China in January 2020. This virus is responsible for an outbreak of pneumonia, defined as coronavirus disease 2019 (COVID-19), which appeared in Hubei province (China) at the end of 2019 and later spread worldwide [1].

Although the disease supposedly originated from a zoonotic virus transmission by live wild animals, it became a person-to-person transmitted infection: the virus is mostly carried by asymptomatic or mild symptomatic people. In the majority of patients, the immune system can successfully defeat the infection. However, the clinical severity of COVID-19 is strictly related to coexisting conditions, which could determine a dysfunctional immune/inflammatory response to environmental factors [1,2].

Diabetes mellitus (DM) has been identified as one of the most common comorbidities associated with COVID-19: people with DM, especially type 2 diabetes, infected with SARS-CoV-2 are susceptible of worse clinical outcomes (higher hospitalization rate and mortality) [3]. Similarly, a major risk of hospitalization and Intensive Care Unit (ICU) admission was described in people with diabetes in 2010, during Influenza A (H1N1) pandemic, confirming the frailty of these patients due to the impaired immune response [4].

On the other hand, viral infections have been widely associated with type 1 diabetes (T1DM) pathogenesis. T1DM is an autoimmune disease characterized by progressive pancreatic

β-cells destruction and insulin deficiency. In the past 30 years, T1DM incidence increased due to the exposure to both environmental and lifestyle factors which promote the generation of an autoimmune process against β-cells responsible for islet destruction and insulin depletion, resulting in hyperglycemia. Specific T1DM autoantibodies can be detected months/years after their effective production in affected individuals. Moreover, T1DM onset can be further delayed, leading to a difficult recognition of the trigger factor [5].

An important evidence of the relationship between coronavirus and diabetes dates back to the SARS-CoV pandemic of 2003: hyperglycemia was described as an independent predictor of morbidity and mortality, in both diabetic and non-diabetic patients. Hyperglycemia was found in patients with mild respiratory symptoms, even in those not treated with glucocorticoids, reinforcing hence the hypothesis of β-cells acute damage as a consequence of the virus replicative cycle in endocrine pancreas [6].

Moreover, prospective studies of genetically predisposed individuals have reported an intriguing connection between viral infections and T1DM. In 2017, TEDDY study reported an increased risk of β-cell autoimmunity in a group of 87,327 patients with a recent respiratory infection, involving both the upper and the lower respiratory tract. Overall, the 5.8% of enrolled patients developed persistent pancreatic islet autoimmunity, with single or multiple T1DM autoantibodies at seroconversion after 9 months from the respiratory infection. Autoantibodies were more commonly detected in patients with severe respiratory disease, although mild symptomatic infections were also associated with autoimmunity. Interestingly, coronaviruses were identified among the different pathogens involved [7]. In 2018, a cohort study investigated the relationship between T1DM and both pandemic and seasonal influenza infections: although a clear association was not demonstrated, a twofold excess of incident T1DM was found among the 76,173 patients with pandemic H1N1 infection diagnosed by laboratory or specialist healthcare [8].

Autoimmune insulitis and pancreatic β-cell destruction could be triggered by viral infections through several mechanisms. The loss of β-cells may directly result from virus amplification cycle and/or viral antigens diffusion through the circulation. This mechanism determines an aggressive immune response, which also involves surrounding exocrine pancreatic cells, leading frequently to fulminant T1DM [9,10]. Moreover, β-cell damage may determine the release of sequestered islet antigens which consequently are expressed by antigen-presenting cells in the regional lymphnodes. Especially during chronic infections, the overexpression of the major histocompatibility complex class I proteins could be responsible for a prolonged presentation of β-cell epitopes to the immune system, increasing the risk of autoantibodies generation. Furthermore, viral epitopes sharing homologies with aminoacid sequences of autoantigens could lead to the production of cross-reactive antibodies against β-cells, even after the viral infection is cleared (molecular mimicry hypothesis). Finally, viral infection can contribute to a faster development of T1DM through cytokines release and T cells activation in individuals genetically predisposed to autoimmunity [10].

Since SARS-Cov-2 infection has been declared by the World Health Organization as a global health emergency, several studies are ongoing worldwide to clarify pathogenic aspects and discover therapies. Similarly to the SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 infects both the upper and the lower respiratory tract cells, causing an aggressive inflammatory response induced by virus replicative cycle which hesitates in pulmonary cells' death. This phenomenon, along with viruses' emission from cells, induces a local immune response, with recruitment of macrophages/monocytes and lymphocytes and cytokines release. Moreover, SARS-CoV-2 uses a spike protein binding the angiotensin converting enzyme (ACE2) to enter the cells, so that ACE2 downregulation resulting from the virus' bond determines enhanced inflammation and increased vascular permeability in the respiratory tract [2,11]. COVID-19 clinical features include: asymptomatic course, upper respiratory tract symptoms, acute pneumonia and death [2]. The severity of the pulmonary involvement, with secondary respiratory failure, has required major hospitalization and/or admission to ICU.

As a result of the COVID-19 pandemic, health organizations and scientists are focused on the early diagnosis of the affected patients, the isolation of the healthy carriers and the development of effective therapies for more than 4 million people infected with SARS-CoV-2. These efforts will not be probably attenuated until a vaccine becomes available. However, the massive spread of the infection arouses concerns about the heavy health consequences we may deal with in the future, including virus-induced diseases. Given that T1DM pathogenesis has already been related to coronavirus respiratory infections [7,8], it is reasonable to suppose that an increasing incidence of T1DM may be triggered by this pandemic, with a worrisome T1DM outbreak in COVID-19 patients for the next months/years.

In conclusion, awaiting for the availability of pharmacological preventive approaches, future studies are warranted to investigate the existence of a pathogenetic role of COVID-19 pandemic on T1DM onset. In the meantime, clinical practitioners should be aware of this contingency, giving more attention to individuals predisposed to autoimmunity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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