Should we expect a wave of type 1 diabetes following SARS-CoV-2 pandemic?

1 | INTRODUCTION

From December 2019 SARS-CoV-2 has affected almost all countries in the world, causing a pandemic emergency. Over 260 million confirmed infection and over 5.2 million deaths have been recorded till this moment (28 November 2021, WHO Emergency dashboard, www.who.int). Health efforts were initially aimed at containing the victims and the spread of the infection but now 2 years later, as cases continue to grow, the need to understand the long-term sequelae of the infection is underway. More and more evidences showed that SARS-CoV-2 has tropism for various tissue and organs and that long-lasting effects of COVID-19 exist. Recently, it has been described that glucose homeostasis may be impaired during acute COVID-19 and long after the recovery, with an increased insulin resistance and β-cell damage which may last up to 6 months. These glycometabolic abnormalities are foremost important as hyperglycemia worse outcomes of COVID-19. However, the clinical phenotype of this metabolic abnormalities appeared assimilable to type 2 diabetes or post-stress diabetes. Interestingly, the impact that SARS-CoV-2 pandemic could have on a potential increased incidence of type 1 diabetes in the near future is at present an unexplored topic. However, because effects of the infections on the immune system are being reported as well, this should be an area of investigation.

2 | EFFECTS OF COVID-19 ON IMMUNE SYSTEM

In the complex pathophysiology of autoimmune diseases, viral infections are among the most important environmental triggers, particularly in individuals with genetic susceptibility. Different mechanisms are involved, including epitope spreading, cross-reaction or molecular mimicry and presentation of cryptic antigens. Moreover, SARS-CoV-2 may lead to a hyper-inflammatory state sometimes resulting in a proneness to autoimmune reactions. In patients admitted to intensive care units with COVID-19, a moderated increase in the levels of some peripheral cytokytogens (i.e.; IL-1β, IL-2, IL-7, IL-10, TNF-α, GCSF, MIP-1A IP-10, MCP-1 and IFN-γ) was found. This may stimulate a T helper 1 immune response and may initiate the cytokine storm. Furthermore, some authors described a variety of effects of SARS-CoV-2 on peripheral lymphocyte subsets, including a decline in suppressor, regulatory and memory T cells and an increase in naïve helper T cells. Those alterations are similar and partially overlapped to those observed in other hyper inflammatory conditions such as cytokine release syndrome due to graft-versus-host disease or during chimaeric antigen receptor T cell therapies, acute respiratory distress syndrome and haemophagocytic lymphohistiocytosis induced by respiratory viruses. A recent study showed as alteration in cytokine profile that persist also after resolution of the acute phase of COVID-19 and resemble a sort of immune weakness. These alterations can be reverted by PD-1 blockade that is of interest for the onset and cure of autoimmune diabetes. The cytokine storm and the immune imbalance can possibly lead to autoimmune reactions similarly to what has been observed in the multisystem inflammatory syndrome in children (MIS-C), with Kawasaki-like disease during COVID-19. This is not the only autoimmune disease suspected to be associated with COVID-19, but also Guillain-Barre syndrome, immune thrombocytopenic purpura and autoimmune haemolytic anaemia. Several autoantibodies have been detected in COVID-19 patients such as antinuclear antibodies, lupus anticoagulant, anti-β2glycoprotein 1, and anticardiolipin antibody. As concerns the endocrine system, an increased prevalence of autoimmune thyroid diseases has been observed. It is well known that an association between type 1 diabetes onset and viral infections such as coxsackievirus, cytomegalovirus and enteroviruses exist. Moreover respiratory viral infections, including infections by coronaviruses, increased the risk of autoimmune diabetes. At present time a possible association among Sars-CoV-2 and type 1 diabetes has not yet been reported and specific autoantibodies have been found only in isolated case reports, but not in cohort of people affected or recovering from COVID-19. Anyway, considering the delay among the spread peak of COVID-19 and the observation of related autoimmune disease such as MIS-C or Kawasaki disease, it is not possible to exclude a future rise in the number of cases of type 1 diabetes (Table 1).

3 | EFFECTS OF COVID-19 ON β-CELL FUNCTION

A direct and indirect effect of SARS-CoV-2 on β-cell should be evaluated. SARS-CoV-2 can infect pancreas through angiotensin converting enzyme receptor 2 (ACE2) expressed in pancreatic β-cells and to a lesser extent in islet microvasculature and pancreatic α-cell. Moreover SARS-CoV-2 also induces a cytokine storm that establishes a systemic pro inflammatory milieu which may play a role...
in facilitating glucose metabolism alterations.\(^4\) In a cohort of 551 patients admitted to hospital for COVID-19 a high prevalence of new onset hyperglycemia was evident.\(^5\) Continuous glucose monitoring and an intravenous arginine stimulation showed hidden hormonal/metabolic abnormalities that persist up to 6 months from the discharge from the hospital. This is accompanied by increased insulin resistance and β-cell hyper stimulation, progressively lead to β-cell exhaustion.\(^2\) Although, it is getting clear that a damage of endocrine pancreas exists, it is difficult to quantify the β-cell mass damaged, the risk factors predisposing to such effect after viral infection and not even if this could lead to insulin-dependent diabetes through traditional pathogenetic mechanism or through new pathways (Table 1).

### TABLE 1 Damage pathways and potential pathogenic mechanism of new-onset diabetes following COVID-19

| New-onset diabetes following COVID-19 | Pathogenic mechanism | Consequence |
|--------------------------------------|----------------------|-------------|
| Damage pathway | β-cell destruction | Autoimmune diabetes |
| | Insulin secretion decrease | Insulin deficient diabetes |
| | Insulin signalling alterations | New form diabetes? |
| Enhanced autoimmunity | β-cell destruction | Autoimmune diabetes |
| | Insulin secretion decrease | Insulin deficient diabetes |
| | β-cell exhaustion glycogenolysis, gluconeogenesis and glucose uptake alterations | Insulin resistant diabetes |
| | Insulin resistance increase | New form diabetes? |
| Pro-inflammatory cytokine and milieu | β-cell destruction | Autoimmune diabetes |
| | Insulin secretion decrease | Insulin deficient diabetes |
| | β-cell exhaustion glycogenolysis, gluconeogenesis and glucose uptake alterations | Insulin resistant diabetes |
| | Insulin resistance increase | New form diabetes? |
| Drugs | Insulin secretion decrease | Insulin deficient diabetes |
| | Insulin resistance increase | Insulin resistant diabetes |
| Lockdown lifestyle changes | Inactivity | Insulin resistant diabetes |
| | Weight gain | Obesity related diabetes |

Abbreviation: ACE, angiotensin converting enzyme.

4 | NEW ONSET OF TYPE 1 DIABETES DURING COVID-19 PANDEMIC

The first observation of a case of new onset of type 1 diabetes in a young woman just 1 month after SARS-CoV-2 infection supported the hypothesis that COVID-19 could favour the occurrence of type 1 diabetes.\(^11\) Anyway epidemiological preliminary observations show contrasting results. The Italian Society for Paediatric Endocrinology and Diabetes has conducted a survey to evaluate the changes in frequency of diabetic ketoacidosis in new-onset or established type 1 diabetes during the pandemic months February-April 2020 as compared to the same months of the previous year. Authors found a 23% reduction in the number of the new onsets of type 1 diabetes in 2020 as compared to 2019 but with more severe form of diabetic ketoacidosis presentation.\(^13\) This could be probably due to the delayed diagnosis, to the reduced access to the paediatric centres but also to a lower exposure to seasonal viruses known to be type 1 diabetes triggers as a result of social distancing. Opposite results have been registered in northwest London, UK, where some authors during the first 3 months of pandemic registered an increase of 12-15 new cases of type 1 diabetes representing almost an 80% more than previous years in the same region.\(^14\) Finally in Germany a population-based study showed a substantial stability in the number of type 1 diabetes cases registered but a significant increase in severe ketoacidosis in children and adolescents presenting with new-onset type 1 diabetes.\(^15\) More recently data from the United States showed a significant increase in diagnosis of diabetes among paediatric patients in the 30 days after COVID-19 infection versus patients <18 years old without COVID-19 (HR = 2.66, 95% CI = 1.98–3.56) and those with non-COVID-19 acute respiratory infection in the pre-pandemic period (HR = 2.16, 95% CI = 1.64–2.86).\(^15\) Unfortunately among those data it is not possible to distinguish type 1 or 2 diabetes patients but interestingly 48.5% of them had diabetic ketoacidosis at the diagnosis while only 13.6% of non-COVID patients.\(^16\) It is possible that different form of diabetes could be responsible of this increased incidence, such as autoimmune, insulin deficient, insulin resistant in predisposed individuals or even new form of diabetes. Those data have been also confirmed by another report from United States (San Diego) showing an increase of 57% in patients admitted with type 1 diabetes during the pandemic year versus the last 5 pre-pandemic years and an increase of 49.7% in patients with diabetic ketoacidosis in the same periods.\(^17\) Obviously result of those studies could be affected by the
limited number of cases observed and by the shortness of registration period. The social distancing could have influenced the epidemiological records and overall it is possible that a delay among SARS-CoV-2 infection and type 1 diabetes occurrence could exist. Finally children are generally less prone to COVID-19, have a milder disease course and there are important differences among their immune system and that of adult subjects.18 To better explore this link it would be necessary to have larger observation cohorts and longer observation periods during the pandemic progression.

5 | CONCLUSIONS
In conclusion, it is plausible that SARS-CoV-2 infection could have a role in promoting the complex pathogenesis of type 1 diabetes, however many questions at this time remains unsolved. Firstly, it would be interesting to explore how long the β-cell damage induced by COVID-19 lasts. Secondarily, the potential mechanism should be thoroughly acknowledged. To this purpose initiative such as global registry should be encouraged, as the COVID-19-related diabetes registry (covidien.e-dendrite.com), part of the CoviDIAB Project. However, considering the huge number of susceptible individuals exposed to SARS-CoV-2 worldwide, a rise in type 1 diabetes in the near future cannot be excluded. This is a very intriguingly and unexplored topic, and as pandemic evolves global efforts should deepen the comprehension of its physio-pathological mechanisms. In the meanwhile it would be advisable to increase surveillance strategies to avoid serious presentation which may parallel an increase in new onset type 1 diabetes.

KEYWORDS
beta-cell damage, COVID-19, pancreatic autoimmunity, type 1 diabetes

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CONFLICT OF INTEREST
The authors have no actual or potential conflict of interests.

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AUTHOR CONTRIBUTIONS
Laura Montefusco draughted the manuscript. Andrea Mario Bolla reviewed the manuscript. Paolo Fiorina conceived and finalised the manuscript.

DISCLOSURE
The authors have nothing to disclose.

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