Answer to the reviewers

Konstantinos I. Papadopoulos
-all appear in the uploaded file. I suggest adding an expanded discussion in new diabetes appearance due to COVID-19.

Esteemed reviewer, we accounted for your suggestion and added a substantial paragraph on this sensitive topic in the manuscript. We also added all references that you mentioned, to better build on this discussion.

"Viral infections, in particular by enteroviruses and coronaviruses, have been widely associated with type 1 diabetes mellitus (T1DM) pathogenesis.[121] T1DM is characterized by an autoimmune pancreatic β-cells progressive destruction leading to insulin deficiency. Therefore, SARS-CoV2 could also act as an infectious trigger decompensating and precipitating diabetic ketoacidosis in patients with no history of diabetes as reported in few case reports,[122-124] and arising evidence highlight the ability of SARS-CoV2 to trigger autoimmune disorders.[125] Nonetheless, data remain conflictual on this point. Evidence from an italian cross-sectional study revealed 23% fewer new-onset cases, with more children with new-onset disease presenting in diabetic ketoacidosis during early months of pandemia compared to the same period in 2019 while a multicenter study from the UK described an 80% increase in new-onset T1DM in children.[126] From a German Diabetes-Prospective Follow-up registry, the rate of new-onset T1DM from March to May 2020 did not differ significantly from rates observed over the previous decade.[127] However, when this study was done, COVID-19 infection incidence rate was relatively low in Germany, and weak effect cannot be excluded. Thus, from these studies, no compelling evidence emerge for a causal role of SARS-CoV2 in a change of T1DM incidence. Furthermore, it was difficult to differentiate a viral secondary diabetes from a real T1DM as no assay for type 1 diabetes antibodies (GAD, IA2, ZNT8, ICA antibodies) has been performed in those series. More complexly, a few cases of insulin-dependent diabetes with negative antibodies start to emerge suggesting a T1bDM.[128] However, such form of diabetes is particularly widespread among Sub-Saharan African, African-Americans and Hispanic descendants and case reports concern Caucasian and Asian ethnicities suggesting a viral secondary diabetes more than a T1DM or T1bDM. Follow-up studies on the evolution of anti-diabetic therapy are needed to understand the pathophysiology of SARS-CoV2-induced diabetes.

In the end, the potential diabetogenic role of SARS-CoV-2 may be more complex than the simple beta cell hosts destruction by the virus through ACE2 expression. New-onset diabetes can result from several pathogenic processes involving pancreatic cell destruction (including exocrine and endocrine cells) through viral or autoimmunity

destruction and/or insulin resistance in liver, skeletal muscles, and adipose tissue through disturbance of ACE2/Ang(1-7) activity."

Anonymous

-Definition of diabetes and interaction in summary.

Esteemed reviewer, we are delighted that you found our review of grade A (priority publishing). We added better explanations and definitions over diabetes and its interactions in the Summary as follow:

"Diabetes, whether due to pancreatic beta cells insufficiency or peripheral resistance to insulin, has been suggested as a risk factor of developing severe acute respiratory disease coronavirus-2 (SARS-CoV-2) infections. This metabolic disease has been associated with a higher risk of infections and higher risk of developing severe forms of coronavirus disease 2019 (COVID-19) related pneumonia. Diabetic patients often present associated comorbidities such as obesity, hypertension and cardiovascular diseases, and complications of diabetes, including chronic kidney disease, vasculopathy and relative immune dysfunction, all of which make them more susceptible to infectious complications. (…)"