Distinguishing the real from the hyperglycaemia: does COVID-19 induce diabetes?

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Reports noting the deleterious impact of diabetes on people infected with SARS-CoV-2 arose in the earliest weeks of the COVID-19 pandemic.[1] Over time, obesity, hyperglycaemia, type 2 diabetes, and type 1 diabetes have each been reported to be associated with increased COVID-19 morbidity and mortality, as well as expanded therapeutic needs during hospital admission.[2] More controversial, however, has been the question of whether SARS-CoV-2 specifically is, in and of itself, capable of inducing diabetes; and, if so, in which of its forms.[3] Beyond this question, hypotheses abound as to whether such a disease-provoking activity (if it exists) is due to acceleration of an underlying and potentially pathogenic feature associated with traditional diabetes pathogenesis (ie, type 1 or type 2 diabetes), or incitement of a new variant of diabetes involving either acute β-cell destruction or impairment of insulin secretion.[4] What does seem clear is that SARS-CoV-2 infection, like many other infections, has the ability to induce hyperglycaemia in people without a previous diagnosis of diabetes, be it through diminished insulin secretion, enhanced release of counter-regulatory hormones, excessive hepatic glucose production, impaired glucose disposal, or a combination of these factors.[3,4]

Diabetes onset has been noted, in case reports, to occur simultaneously with acute SARS-CoV-2 infection or in the weeks to months following recovery from the infection.[5] However, findings from epidemiological studies have been conflicting: for example, work from the UK showed an increase in type 1 diabetes incidence during the COVID-19 pandemic,[6] whereas a larger study from Germany showed no such change,[7] although neither study confirmed COVID-19 diagnosis or accounted for viral load as a potential contributing factor. Recent summaries of the available scientific literature suggest that a causal association between COVID-19 and the onset of type 1 diabetes is unlikely, but there is need for further investigation.[4,8] Indeed, taken together, the available information provides a strong rationale for the recently formed CoviDiab Registry, which seeks to proactively address such questions.

Importantly, there is no consensus regarding which cells within the pancreas—and particularly whether the insulin-producing β cells—express the key viral receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), and additional factors or cofactors (eg, TMPRSS2, TMPRSS4, NRP-1, CD209L, and SR-B1) necessary for effective SARS-CoV-2 entry.[9] More than 150 human cell types reportedly express ACE2, with expression levels affected by various factors including age, sex, comorbidities, medications, inflammation, and constituents of the renin–angiotensin system.[10]

As with the epidemiological evidence, the reported data with respect to ACE2 expression in pancreatic cells are conflicting (panel). Studies of both isolated human islets and induced pluripotent stem cell (iPSC)-derived β cells suggest ACE2 expression in a limited subset of β cells or their insulin-producing surrogates, respectively. Whether isolated islets or iPSC-derived endocrine cells accurately mimic in-vivo infectivity is not known. By contrast, analyses of human pancreatic tissues from dozens of organ donors using immunohistochemistry did not identify

***Panel:* Summary of the published evidence for and against the expression of ACE2 in human pancreatic β cells**

Evidence for ACE2 expression

- Immunostaining of human pancreatic tissue sections*
- Immunofluorescence with isolated primary islets and iPSC-derived organelles†
- Immunofluorescence with isolated islets and pancreatic tissue sections from control patients and immunostaining of pancreatic tissue sections from COVID-19 patient autopsies‡

Evidence against ACE2 expression or suggesting limited expression

- Analysis of public scRNAseq datasets and immunostaining of control pancreas tissue sections§
- Analysis of public scRNAseq datasets and immunostaining of pancreas tissue sections from control organ donors and COVID-19 autopsies§

References for the panel are listed in the appendix. ACE2=angiotensin-converting enzyme 2. iPSC=induced pluripotent stem cell. *In one study that used this method, tissue was from a single donor and antibody clone was not identified; in a second study that used this method, there was observed preferential expression of the short, non-virus-binding ACE2 isoform. †Isolated islets or iPSC organelles might have different expression patterns. ‡Infection of human islet cells in vitro does not prove infection in vivo. §Three studies examined ACE2 localisation in human pancreatic tissue sections by immunostaining and analysed publicly available scRNAseq datasets, with the two approaches yielding the same takeaways regarding which cells express ACE2.

See Online for appendix

For the **CoviDiab Registry** see https://covidiab.e-dendrite.com

ACE2 expression on endocrine cells (including β cells), but rather showed clear ACE2 expression by ductal structures and microvasculature within islet and acinar regions of the pancreas (panel). Coexpression of ACE2 and required cofactors such as TMPRSS2 was also rarely observed in these tissues (as assessed by transcriptional profiling and immunostaining), reducing the likelihood that SARS-CoV-2 can infect islet endocrine cells in vivo (panel). Immunofluorescence staining of a small number of autopsy pancreases identified ACE2 and C-peptide colocalisation within islets, but the greatest ACE2 expression was within islet microvasculature (panel). The very small number of studies examining autopsy specimens from the pancreases of patients who died from complications associated with COVID-19 have not, as yet, provided clear answers (panel). Such studies are key to addressing the question of whether ACE2 or other entry factors could be induced in β cells or other cells within the pancreas as part of the tissue inflammation associated with SARS-CoV-2 infection. Although ACE2 and TMPRSS2 appear to be expressed in pancreatic ductal cells, histological evidence or clinical reports of pancreatitis have not been commonly reported (panel). Finally, we would expect ACE2 expression in β cells to be a key feature necessary for the virus to inflict their specific loss and promote diabetes development directly—an observation not reported to date.

The potential role of SARS-CoV-2 in inducing diabetes is likely to be more complex than the mere notion of pancreatic ACE2 expression and β-cell destruction.[4] As with many clinical scenarios, new-onset diabetes can result from several pathogenic processes involving factors that induce autoimmunity, β-cell stress, or insulin resistance in liver, skeletal muscle, and adipose tissues. Furthermore, β cells could be indirectly damaged as a result of local hypoxia and inflammation due to SARS-CoV-2 infection of the islet microvasculature. Proof of direct toxicity to β cells will require histological evidence of β-cell loss and the presence of SARS-CoV-2 within pancreatic islet cells of individuals infected with SARS-CoV-2. Many of the aforementioned questions will also require continued research to definitively determine whether SARS-CoV-2 (or emerging variants thereof) affect the pancreas and specifically induce diabetes.

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1 Banerjee A, Pasea L, Harris S, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020; **395:** 1715–25.
2 Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and coronavirus disease 2019. *Diabetes Care* 2020; **43:** 2339–44.
3 Accili D. Can COVID-19 cause diabetes? *Nat Metab* 2021; **3:** 123–25.
4 Drucker D. Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. *Cell Metab* 2021; **33:** 479–98.
5 Sathish T, Kapoor N, Cao Y, Tapp R, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. *Diabetes Obes Metab* 2020; **23:** 870–74.
6 Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. *Diabetes Care* 2020; **43:** e170–71.
7 Tittel SR, Rosenbauer J, Kamrath C, et al. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? *Diabetes Care* 2020; **43:** e172–73.
8 DiMeglio LA, Albanese-O'Neill A, Muñoz CE, Maahs DM. COVID-19 and children with diabetes—updates, unknowns, and next steps: first, do no extrapolation. *Diabetes Care* 2020; **43:** 2631–34.
9 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181:** 271–80.e8.
10 Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol* 2020; **16:** e9610.