



Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report

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Here we report a case where the manifestations of insulin-dependent diabetes occurred following SARS-CoV-2 infection in a young individual in the absence of autoantibodies typical for type 1 diabetes mellitus. Specifically, a 19-year-old white male presented at our emergency department with diabetic ketoacidosis, C-peptide level of 0.62 $\mu\text{g l}^{-1}$, blood glucose concentration of 30.6 mmol l^{-1} (552 mg dl^{-1}) and haemoglobin A1c of 16.8%. The patient's case history revealed probable COVID-19 infection 5–7 weeks before admission, based on a positive test for antibodies against SARS-CoV-2 proteins as determined by enzyme-linked immunosorbent assay. Interestingly, the patient carried a human leukocyte antigen genotype (HLA DR1-DR3-DQ2) considered to provide only a slightly elevated risk of developing autoimmune type 1 diabetes mellitus. However, as noted, no serum autoantibodies were observed against islet cells, glutamic acid decarboxylase, tyrosine phosphatase, insulin and zinc-transporter 8. Although our report cannot fully establish causality between COVID-19 and the development of diabetes in this patient, considering that SARS-CoV-2 entry receptors, including angiotensin-converting enzyme 2, are expressed on pancreatic β -cells and, given the circumstances of this case, we suggest that SARS-CoV-2 infection, or COVID-19, might negatively affect pancreatic function, perhaps through direct cytolytic effects of the virus on β -cells.

The recent COVID-19 pandemic caused by the SARS-CoV-2 virus represents a worldwide health crisis causing severe illness and death, especially in people with cardiovascular and metabolic abnormalities^{1,2}. SARS-CoV-2 enters human cells via angiotensin-converting enzyme 2 (ACE2)³, a transmembrane glycoprotein with proteolytic activity also found in human pancreatic β -cells⁴, suggesting that SARS-CoV-2 might alter pancreatic β -cell function and impair insulin secretion. Several recently published studies indicate a link between COVID-19 and diabetes: for example, acute hyperglycaemia has been observed in a large number of individuals infected with SARS-CoV-2, regardless of any past medical history of diabetes^{5–8}. In another study in Asia, patients were reported

with acute diabetic ketoacidosis (DKA) associated with COVID-19 disease⁹. The exact time course, causal relationship and presence or absence of autoantibodies were, however, not provided. Furthermore, a marked increase in DKA was observed in German children and adolescents during the COVID-19 pandemic¹⁰, suggesting a relationship between COVID-19 and new-onset type 1 diabetes mellitus (T1DM). Therefore, we recommended careful management of patients with diabetes and monitoring for new-onset diabetes during the pandemic¹¹.

Here we present the case of a 19-year-old white male patient admitted to our emergency department with abnormal fatigue, exhaustion and 12-kg weight loss over several weeks. A detailed timeline of events before presentation at our emergency ward is presented in Fig. 1. He exhibited increased polydipsia of $\sim 6\text{ l d}^{-1}$, nycturia (2–3 times per night) and an intermittent postprandial left-sided flank pain. Neither fever episodes nor typical chest pain was reported. Laboratory testing in our emergency department revealed DKA with blood pH 7.1, blood glucose 30.6 mmol l^{-1} (552 mg dl^{-1}), a reduced serum C-peptide level of 0.62 $\mu\text{g l}^{-1}$ (normal range, 1.1–4.4 $\mu\text{g l}^{-1}$) and haemoglobin A1c (HbA1c) 16.8%, as well as positive urinary ketones and glucosuria. Type 1 diabetes mellitus was assumed. The family history revealed a maternal cousin with autoantibody-positive T1DM and a maternal grandmother with type 2 diabetes. Human leukocyte antigen (HLA) genotyping revealed that the patient had no high-risk HLA genotype but a DR1-DR3-DQ2 genotype, which is associated with a slightly elevated risk of developing autoimmune T1DM (around 1.7-fold higher compared with the general population)^{12,13}. However, immunological examination yielded an absence of serum autoantibodies against islet cells (IC-Ab), glutamic acid decarboxylase (GAD65-Ab), tyrosine phosphatase (IA-2-Ab), insulin (I-Ab) and zinc-transporter 8 (ZnT8-Ab) in the affected patient (Table 1), suggesting a type 1B diabetes mellitus subtype¹⁴.

The patient reported that he had had an asymptomatic SARS-CoV-2 infection 5–7 weeks previously when returning from vacation in Austria with his family. On 29 April 2020 he tested positive for IgG—but not IgM—antibodies against SARS-CoV-2

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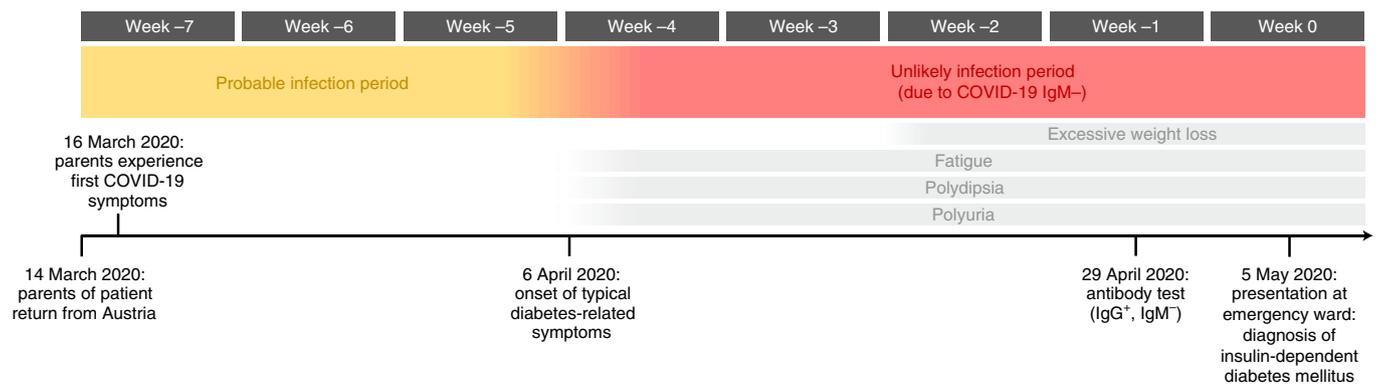


Fig. 1 | Timeline of events before diagnosis of insulin-dependent diabetes mellitus. On 14 March 2020, the patient's parents had returned from a vacation in Austria. Two days later, both parents started to develop COVID-19-typical symptoms (dry cough, shivering, fatigue, dyspnoea, joint pain and loss of smell and taste). No further PCR testing was performed because, at the time, official authorities did not invite them for testing despite both parents having reported their symptoms. On 6 April 2020, their 19-year-old son (the patient in this report) first noticed symptoms related to diabetes mellitus including fatigue, polydipsia and polyuria, which worsened over time. He did not show any typical COVID-19 symptoms. Around 20 April 2020, he further noticed excessive weight loss. In the meantime, both parents started to recover from their complaints. As they were suspected of having COVID-19, both parents and their two sons underwent a SARS-CoV-2 antibody test on 29 April 2020, which was positive (IgG⁺, IgM⁻) for both parents and the patient. The dizygotic sibling of the patient tested negative for SARS-CoV-2 antibodies and experienced neither COVID-19- nor diabetes-related symptoms. On 5 May 2020 the patient presented at our local emergency ward because his symptoms relating to diabetes mellitus had worsened. He was then diagnosed with insulin-dependent diabetes mellitus and received treatment according to international guidelines. Based on the information presented in this figure (adapted from reports on the patient and his parents, and from antibody test results), we assume that the possible infection period of the patient can be narrowed down to the last 2 weeks of March 2020 (yellow bar) while it is unlikely that the patient had COVID-19 in April 2020 (red bar). This is further supported by the absence of IgM antibodies detected in the patient's SARS-CoV-2 antibody test, which have previously been shown to persist for up to 4 weeks after infection with SARS-CoV-2 (ref. ¹⁵).

Table 1 | Immunity diagnostics

	Result (IU ml ⁻¹)	Reference range (IU ml ⁻¹)
GAD65-Ab	<5	<10
IA-2-Ab	<10	<10
IC-Ab	Negative	Negative
I-Ab	<0.1	<0.4
ZnT8-Ab	<10	<15
COVID-19 (SARS-CoV-2) IgG	Positive	Negative
COVID-19 (SARS-CoV-2) IgM	Negative	Negative

(Table 1), indicating that he had COVID-19 disease >4 weeks before antibody assessment¹⁵ (Fig. 1).

Acute pancreatitis was ruled out based on clinical assessment by experienced emergency room staff (no history of alcohol or drug abuse, no history of gallstones and no lipid disorders) and normal serum lipase of 19 U l⁻¹ (reference range, 13–60 U l⁻¹). Exocrine pancreatic function was not assessed because the patient did not complain of diarrhoea, increased stool volume and/or fatty stools.

The patient needed treatment in the intensive care unit for 3 days for recompensating DKA, and was administered intravenous insulin therapy according to international guidelines. At day 4, he was transferred to the endocrine ward, and subcutaneous insulin therapy was initiated. Over the course of the next few days, blood glucose levels stabilized at 8.4–10.2 mmol l⁻¹ (reference range, 151–183 mg dl⁻¹). The patient received an educational programme according to guidelines for insulin-dependent diabetes mellitus management. He was discharged from hospital in good condition after 10 days.

It has been known for several years that corona-like viruses enter human cells via binding to membrane-bound proteases³. For example, the Middle East respiratory syndrome virus, responsible for an outbreak of acute respiratory syndrome, has been shown to use dipeptidylpeptidase-4, a protease known to be involved in the regulation of the incretin system¹⁶. Recently it has been demonstrated in a functional assay that ACE2 acts as the major binding partner for the SARS-CoV-2 spike glycoprotein, mediating host cell internalization¹⁷.

ACE2 is widely expressed in eukaryotic cell membranes, including those of pancreatic β -cells in mice^{18–20} and humans⁴. Using a high-fat diet mouse model, it was shown that β -cell de-differentiation is accompanied by reduction in ACE2 (ref. ²⁰). Deletion of ACE2 in non-obese diabetic mice resulted in hyperglycaemia, decreased β -cell insulin content and increased β -cell oxidative stress¹⁹. In addition, ACE2 deficiency reduced β -cell mass and impaired β -cell proliferation in obese C57BL/6 mice¹⁸, suggesting overall that this glycoprotein is important in β -cell homeostasis. Finally, it is currently under debate whether ACE2 is important in regard to intra-islet paracrine mechanisms in communication by α and β -cells¹⁹.

The hallmark in the pathology of classical T1DM is β -cell destruction caused by a complex autoimmune process²¹. Environmental factors are suspected to be responsible, involving activation of the immune system by reduction in gut microbiota, by the early introduction to fruit or cow's milk during childhood, by gluten, by toxins and, especially, by viruses²². Interestingly, besides the induction of autoimmunity, some viruses including enteroviruses might also exert direct cytolytic effects on pancreatic β -cells²³.

The patient reported here presented several weeks after a viral infection with severe DKA and profound loss of β -cell function. However, in contrast to the general idea that viral infections indirectly affect pancreatic β -cells by triggering autoimmunity, the absence of five typical antibodies in our patient might argue against classical autoimmune T1DM although autoantibody-negative

T1DM (type 1B subtype) is not a rare condition²⁴. Given the fact that ACE2 is expressed on human pancreatic β -cells⁴ and that it is the main receptor for SARS-CoV-2 internalization, we propose that, in this patient, direct cytolytic β -cell damage due to SARS-CoV-2 infection resulted in insulin-dependent diabetes with no classical autoimmune pathology evident. This assumption is supported by a recent mechanistic study demonstrating that adult human pancreatic α - and β -cells are permissive to SARS-CoV-2 pseudo-entry virus and SARS-CoV-2 virus infection²⁵. Furthermore, SARS-CoV-2 infection of pancreatic endocrine cells resulted in robust chemokine induction, as seen in patients with COVID-19 and upregulation of markers of cell death²⁵; in addition, SARS-CoV-1, the predecessor of SARS-CoV-2, has been shown to damage islet cells and cause diabetes in humans²⁶. Based on these findings, we hypothesize that COVID-19 might have caused T1DM in our patient.

Nonetheless, our case report has limitations. We are aware that the major limitation of this case report lies in the causality missing between SARS-CoV-2 infection and insulin-dependent diabetes. Future studies are warranted to investigate the direct cytotoxic effects of SARS-CoV-2 on pancreatic islet cells. Furthermore, one might argue that the high HbA1c level of our patient at the time of diagnosis does not support a recently developed T1DM due to COVID-19. However, although a high HbA1c level may suggest previous hyperglycaemia of several weeks' duration, diabetic ketoacidosis is reported with very high HbA1c levels irrespective of the duration of diabetes in several studies^{27,28}. There are also well-known variations in red blood cell survival that may cause variation in HbA1c levels for a given mean blood glucose²⁹. These studies indicate that the markedly elevated HbA1c level in our patient does not rule out an acute onset of T1DM within the reported time frame. This is supported by the reported onset of diabetes symptoms that occurred after the probable period of infection with SARS-CoV-2 (Fig. 1). The latter can be narrowed down to a time between mid-March and early April 2020, due to the positive IgG, but negative IgM, in the SARS-CoV-2 antibody test¹⁵.

Despite tremendous progress in biomedical research over the centuries, the complex immunopathology of T1DM is still not completely understood. Detailed understanding of the induction and progression of pancreatic β -cell failure, however, is crucial in the development of therapies to prevent and/or cure this important metabolic disease. In that regard, the detailed examination of patients developing β -cell failure and insulin-dependent diabetes after SARS-CoV-2 infection might yield new insights into the hitherto-unknown role of ACE2 in β -cell function, and also into the potential virus-induced cytolytic processes in T1DM development. Thus, a global registry has been launched to provide a systematic platform for collection and analysis of patients with new-onset diabetes³⁰. It will be critical to explore the frequency, severity and duration of these complications and to investigate more deeply the mechanisms involved in primary human tissue. Because our case may illustrate the systemic nature of COVID-19-related organ damage, we think that a population-representative assessment of endocrine syndromes post COVID-19 would be necessary. The recently launched COVIDOM study of University Hospital Schleswig-Holstein represents an epidemiological campaign with the scope of a 10-year follow up after SARS-CoV-2 infection to assess the long-term consequences of COVID-19 in a larger population.

As a conclusion, our report indicates that diabetologists should be aware of the possibility of insulin-dependent diabetes as an acute complication in patients infected with SARS-CoV-2.

Methods

Clinical study. The patient reported here was treated in both the intensive care unit and the Division of Endocrinology, Diabetes and Clinical Nutrition, Department of Medicine I at the University of Kiel, Germany. All authors were directly involved

in the treatment of the patient or analysis of the available biomaterial. The patient provided written informed consent for publication of the information presented in this case report. Patient care and research were conducted in compliance with case report guidelines and the Declaration of Helsinki.

Diagnostics. Blood and urine samples (including serum autoantibodies against islet cells, GAD65, IA-2, insulin and ZnT8) were analysed at the Department of Clinical Chemistry and Laboratory Medicine at the University of Kiel, Germany. Autoantibody tests for GAD65, IA-2 and ZnT8 were repeated in another laboratory (Helmholtz Institute, Munich, Germany) using internationally standardized and evaluated assays³¹. These included the 3-Screen enzyme-linked immunosorbent assay (ELISA) that measures antibodies against GAD65, IA-2 and ZnT8 (RSR)³², and radiobinding immunoprecipitation assays with [³⁵S]methionine-labelled recombinant human proteins measuring antibodies against GAD65, IA-2 and ZnT8 (refs. 33,34).

Antibodies against SARS-CoV-2 were determined by an external laboratory using the EDI Novel Coronavirus COVID-19 IgG ELISA Kit (Epitope Diagnostics). According to the manufacturer, this assay has a limit of detection of 5 U ml⁻¹, a diagnostic specificity of 100% and a diagnostic sensitivity of 100%.

Further information on the methods used in this manuscript can be found in the Reporting Summary in the Supplementary information.

Reporting Summary. Further information on research design is available in the Reporting Summary linked to this article.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper.

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References

- Tay, M. Z., Poh, C. M., Rénia, L., Macary, P. A. & Ng, L. F. P. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol.* **20**, 363–374 (2020).
- Velavan, T. P. & Meyer, C. G. The COVID-19 epidemic. *Trop. Med. Int. Health* **25**, 278–280 (2020).
- Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **181**, 271–280. (2020).
- Fignani, D. et al. SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 is expressed in human pancreatic islet β -cells and is upregulated by inflammatory stress. Preprint at *bioRxiv* <https://doi.org/10.1101/2020.07.23.208041> (2020).
- Chen, N. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* **395**, 507–513 (2020).
- Iacobellis, G., Penaherrera, C. A., Bermudez, L. E. & Bernal Mizrahi, E. Admission hyperglycemia and radiological findings of SARS-CoV-2 in patients with and without diabetes. *Diabetes Res. Clin. Pract.* **164**, 108185 (2020).
- Sardu, C. et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care* **43**, 1408–1415 (2020).
- Wu, J. et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. *BMJ Open Diabetes Res. Care* **8**, e001476 (2020).
- Chee, Y. J., Ng, S. J. H. & Yeoh, E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res. Clin. Pract.* **164**, 108166 (2020).
- Kamrath, C. et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA* **324**, 801–804 (2020).
- Bornstein, S. R. et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* **8**, 546–550 (2020).
- Sabbah, E. et al. Glutamic acid decarboxylase antibodies in relation to other autoantibodies and genetic risk markers in children with newly diagnosed insulin-dependent diabetes. Childhood Diabetes in Finland Study Group. *J. Clin. Endocrinol. Metab.* **81**, 2455–2459 (1996).
- Lambert, A. P. et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. *J. Clin. Endocrinol. Metab.* **89**, 4037–4043 (2004).
- Imagawa, A., Hanafusa, T., Miyagawa, J. & Matsuzawa, Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. *N. Engl. J. Med.* **342**, 301–307 (2000).

15. Liu, X. et al. Patterns of IgG and IgM antibody response in COVID-19 patients. *Emerg. Microbes Infect.* **9**, 1269–1274 (2020).
16. Fleischer, B. CD26: a surface protease involved in T-cell activation. *Immunol. Today* **15**, 180–184 (1994).
17. Letko, M., Marzi, A. & Munster, V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat. Microbiol.* **5**, 562–569 (2020).
18. Shoemaker, R., Yiannikouris, F., Thatcher, S. & Cassis, L. ACE2 deficiency reduces β -cell mass and impairs β -cell proliferation in obese C57BL/6 mice. *Am. J. Physiol. Endocrinol. Metab.* **309**, E621–E631 (2015).
19. Roca-Ho, H. et al. Angiotensin-converting enzyme 2 influences pancreatic and renal function in diabetic mice. *Lab. Invest.* **100**, 1169–1183 (2020).
20. Xuan, X. et al. Activation of ACE2/angiotensin (1-7) attenuates pancreatic β cell dedifferentiation in a high-fat-diet mouse model. *Metabolism* **81**, 83–96 (2018).
21. Saberzadeh-Ardestani, B. et al. Type 1 diabetes mellitus: cellular and molecular pathophysiology at a glance. *Cell J.* **20**, 294–301 (2018).
22. Knip, M. & Simell, O. Environmental triggers of type 1 diabetes. *Cold Spring Harb. Perspect. Med.* **2**, a007690 (2012).
23. Rodriguez-Calvo, T., Sabouri, S., Anquetil, F. & von Herrath, M. G. The viral paradigm in type 1 diabetes: who are the main suspects? *Autoimmun. Rev.* **15**, 964–969 (2016).
24. Wang, J. et al. Prevalence of autoantibody-negative diabetes is not rare at all ages and increases with older age and obesity. *J. Clin. Endocrinol. Metab.* **92**, 88–92 (2007).
25. Yang, L. et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell* **27**, 125–136 (2020).
26. Yang, J.-K., Lin, S.-S., Ji, X.-J. & Guo, L.-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* **47**, 193–199 (2010).
27. Ekpebegh, C., Longo-Mbenza, B. & Blanco-Blanco, E. Glycosylated haemoglobin is markedly elevated in new and known diabetes patients with hyperglycaemic ketoacidosis. *Afr. Health Sci.* **14**, 526–532 (2014).
28. Henderson, D. C. et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J. Clin. Psychiatry* **68**, 533–541 (2007).
29. Cohen, R. M. et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. *Blood* **112**, 4284–4291 (2008).
30. Rubino, F. et al. New-onset diabetes in Covid-19. *N. Engl. J. Med.* **383**, 789–790 (2020).
31. Ziegler, A.-G. et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA* **323**, 339–351 (2020).
32. Amoroso, M. et al. 3 Screen islet cell autoantibody ELISA: a sensitive and specific ELISA for the combined measurement of autoantibodies to GAD65, to IA-2 and to ZnT8. *Clin. Chim. Acta* **462**, 60–64 (2016).
33. Achenbach, P. et al. Autoantibodies to zinc transporter 8 and SLC30A8 genotype stratify type 1 diabetes risk. *Diabetologia* **52**, 1881–1888 (2009).
34. Bonifacio, E. et al. Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for National Institute of Diabetes and Digestive and Kidney Diseases Consortia. *J. Clin. Endocrinol. Metab.* **95**, 3360–3367 (2010).

Author contributions

T.H. attended the patient on the ward and wrote the manuscript. D.M.S. attended the patient in the emergency room and wrote the manuscript. J.S. and A.G. attended the patient in the intensive care unit and edited the manuscript. M.W. and A.F. performed HLA genotyping and edited the manuscript. S.S. attended the patient in the emergency room and edited the manuscript. E.B., A.G.Z. and S.R.B. performed further antibody testing, critically reviewed the case and edited the manuscript. M.L. attended the patient on the ward and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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