Autoantibody-Negative Insulinopenic Diabetes Manifested After SARS-CoV-2 Infection: Two Cases With 9 Months of Follow-Up

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Case Presentation 1

A 53-year-old man (BMI 27.8 kg/m^2) presented in our clinic on 31 July 2020 with complaints of increased thirst and polyuria that had started 2 weeks earlier. He had had PCR-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with mild flu-like symptoms in March 2020. The SARS-CoV-2 IgG antibody test was positive on presentation in our clinic. In the 15-week interval between the SARS-CoV-2 infection and the onset of polyuria, the patient was free of symptoms and had an unimpaired general condition.

Laboratory testing on 31 July 2020 revealed elevated blood glucose (370 mg/dL), mild ketonuria without ketoacidosis (pH 7.40), and an A1C of 11.1% (98 mmol/mol). Fasting C-peptide was very low (0.01 ng/mL [range 0.80–4.20 ng/mL]), indicating absolute insulin deficiency, but autoantibodies against GAD65 (GAD65-Ab), tyrosine phosphatase (IA-2-Ab), zinc transporter 8 (ZnT8-Ab), and insulin (IA-Ab) were absent. Human leukocyte antigen genotyping revealed no type 1 diabetes risk locus (*HLA-DR3* and *HLA-DR4* negative).

Initially, a cumulative daily insulin dose of 50–70 units was required to achieve sufficient blood glucose control. Subsequently, his insulin requirement decreased, and, after about 4 weeks, the patient stopped taking basal insulin (glargine) and injected rapid-acting insulin (lispro) only occasionally to correct elevated glucose values.

In the 2 months leading up to the 39-week follow-up visit, insulin was stopped completely. His A1C gradually improved (Table 1) and was 6.9% (52 mmol/mol) in week 39. His C-peptide level became markedly higher (2.60 ng/mL) and remained in this range. Data from his 39-week follow-up are shown in Table 1.

Case Presentation 2

A 29-year-old woman (BMI 19.9 kg/m^2) presented in our department on 30 October 2020 with elevated fasting glucose levels first diagnosed in May 2020. The patient had suffered from coronavirus disease 2019 (COVID-19) in March 2020 (PCR-positive on 30 March, SARS-CoV-2 IgG antibody test positive). After the acute infection with moderate flu-like symptoms, recovery of her general condition was delayed.

Because of ongoing fatigue, laboratory testing was performed on 19 May 2020, revealing a fasting glucose of 116 mg/dL and an A1C of 6.1% (43 mmol/mol). Repeated self-measurements in the following weeks confirmed similar fasting glucose values. Further laboratory testing showed an A1C of 6.0% (42 mmol/mol) on 2 October 2020 and 5.9% (41 mmol/mol) on 30 October 2020 (Table 1). A 75-g oral glucose tolerance test performed on 13 November 2020 confirmed overt diabetes, with elevated glucose levels at 0 (115 mg/dL), 60 (251 mg/dL), and 120 minutes (245 mg/dL). The rise in insulin after the glucose load was inadequate and delayed (28.5 μU/mL at 60 minutes and 38.8 μU/mL at 120 minutes, with a fasting insulin of 4.1 μU/mL). Her fasting C-peptide level was low (1.07 ng/mL) but above the cut point, indicating absolute insulin deficiency (0.60 ng/mL), suggesting preserved β-cell reserve. The homeostasis model of insulin resistance indicated a normal insulin sensitivity (HOMA-IR 2.1). All autoantibodies (GAD65-Ab, IA-2-Ab, ZnT8-Ab, IA-Ab, and cytoplasmic islet cell antibodies [IC-Ab]) were undetectable. Human leukocyte antigen characterization revealed an increased risk for type 1 diabetes (*HLA-DR3* homozygous positive, *HLA-DR4* negative).

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TABLE 1 Clinical Course of Patients in Case Presentations 1 and 2

	Case 1: 53-Year-Old Man				Case 2: 29-Year-Old Woman					
Date	7/31/2020	10/28/2020	12/1/2020	1/19/2021	4/27/2021	5/19/2020	10/2/2020	11/13/2020	04/06/2021	04/29/2021
Week*	0	13	18	25	39	0	20	26	47	50
Glucose, mg/dL (mmol/L)	370 (20.5)	—	—	—		116 (6.4)	—	115 (6.4)	109 (6.1)	101 (5.6)
Average glucose, mg/dL (mmol/L)	—	—	154 (8.5)†	142 (7.9)†	141 (7.8)†	—	—	—	—	102 (5.7)‡
A1C, % (mmol/mol)	11.1 (98)	7.6 (60)	7.0 (53)	6.6 (49)	6.9 (52)	6.1 (43)	6.0 (42)	5.9 (41)	5.8 (40)	5.6 (38)
C-peptide, ng/mL	0.01	—	2.60	—	2.63	—	—	1.07	1.26	1.61
GAD65-Ab, units/mL	n.d.	—	n.d.	—	—	—	n.d.	—	n.d.	—
IA-2-Ab, units/mL	n.d.	—	n.d.	—	—	—	n.d.	—	n.d.	—
ZnT8-Ab, units/mL	n.d.	—	n.d.	—	—	—	—	—	n.d.	—
IC-Ab, units/mL	—	—	—	—	—	—	n.d.	—	—	—
IA-Ab, units/mL	—	—	n.d.	—	—	—	—	—	n.d.	—
eGFR, mL/min/1.73 m^2	98	99	98	99	94	110	106	—	98	91
UACR, mg/g	—	—	—	—	3.22	—	< 0.3	—	< 0.3	—
Triglycerides, mg/dL	—	—	—	—	100	102	—	—	60	—
LDL cholesterol, mg/dL	—	—	—	—	149	126	—	—	102	—
HDL cholesterol, mg/dL	—	—	—	—	47	86	—	—	95	—

*Time since diagnosis of impaired glucose tolerance. †Average glucose measured by FreeStyle Libre 2 continuous glucose monitoring system during the last 21 days. ‡Average glucose was available for the last 7 days. eGFR, estimated glomerular filtration rate; n.d., not detectable; UACR, urinary albumin-to-creatinine ratio.

Observing occasional postprandial increases in glucose, the patient intermittently used insulin lispro for carbohydrate-rich meals. In the weeks leading up to her week 50 follow-up, she was no longer using insulin because her postprandial glucose values were lower. Also, lower fasting glucose values of ∼100 mg/dL were measured. The autoantibodies remained undetectable during follow-up.

Both of these patients were of Caucasian origin and physically fit, and neither suffered from other medical conditions or took any medications before their diagnosis with diabetes. They had no clinical signs of exocrine pancreas or other organ dysfunction, and their lipase values were in the normal range. The mother of the patient in Case 1 was treated with oral antidiabetic medication for type 2 diabetes (diagnosed at >70 years of age), but there were no other cases of type 2 or type 1 diabetes in first- or second-degree relatives in his family. The 29-year-old patient had no first- or second-degree relatives with any type of diabetes.

Questions

1. Was the SARS-CoV-2 infection causative for the diabetes manifestation in these cases?
2. Was the insulinopenic diabetes autoimmune-mediated or related to other mechanisms?
3. What is the course of diabetes manifested after SARS-CoV-2 infection?
4. What are the risk factors for new-onset diabetes after SARS-CoV-2 infection?

Commentary

Increasing evidence indicates a link between SARS-CoV-2 infection and diabetes. Research has mostly focused on diabetes as a risk factor for a severe course of COVID-19. However, conversely, acute SARS-CoV-2 infection may also work to deteriorate glycemic control in patients with diabetes or cause increased glucose values in patients without known diabetes (1–3). Furthermore, several reports suggest that COVID-19 may precede the manifestation of insulinopenic diabetes (4–9). Here, we report two cases of insulinopenic diabetes after SARS-CoV-2 infection.

Epidemiological data regarding an increase in diabetes manifestation possibly linked to SARS-CoV-2 are as yet inconsistent. Although a higher incidence of type 1 diabetes during the COVID-19 pandemic was observed in children in some centers in the United Kingdom (10), this observation was not confirmed in other populations (11,12).

Despite the increasing number of reports on SARS-CoV-2–associated diabetes, the phenotype remains ill defined. Interestingly, neither of our patients displayed markers of autoimmunity typical for type 1 diabetes. One of our patients displayed a genetic predisposition for type 1 diabetes but had a negative family history. The other patient showed no risk factors for type 1 diabetes.

Two previous publications described patients with insulin-dependent diabetes without autoantibodies after SARS-CoV-2 infection, one of whom was a 19-year-old man with undetectable GAD65-Ab, IA-2-Ab, ZnT8-Ab, IC-Ab, and IA-Ab but classical features of type 1 diabetes (4). The other report characterized three patients with negative GAD65-Ab, with no other autoantibodies measured (7).

The prevalence of autoantibody-negative type 1 diabetes depends on ethnicity, among other things, and was found to be 7% in a cohort in South Germany (13). The described cases of diabetes after COVID-19 had a relatively short interval between infection and diabetes manifestation, ranging from weeks to a few months. Although cases with a longer latency will probably be reported in the future, the reports available to date suggest that, in addition to the general inflammatory response and possible induction of autoimmunity during a SARS-CoV-2 infection, β-cell damage may also be directly mediated by SARS-CoV-2.

Angiotensin-converting enzyme 2 (ACE2) acts as a receptor for the coronavirus spike protein (14) and is expressed in multiple tissues besides the lung, including the pancreas and β-cells (1,15,16). An in vitro study demonstrated that β-cells are permissive to SARS-CoV-2 (17). Notably, SARS-CoV-2 is not the only coronavirus with affinity to ACE2. The human coronavirus HCoV-NL63 also targets the ACE2 receptor (18). Recent data demonstrate that SARS-CoV-2 uses the same ACE2 receptor as SARS-CoV-1 for host cell entry (14,19), and coronavirus-mediated islet cell damage has been reported during previous coronavirus epidemics (SARS and MERS) (12,20). Yang et al. (20) found that pancreatic islets are strongly immune-positive for ACE2, whereas exocrine tissues are only weakly positive.

However, data on direct β-cell tropism of SARS-CoV-2 are conflicting. On one hand, SARS-CoV-2 infected cultured human islet cells, with subsequent impairment of glucose-stimulated insulin secretion (21), and SARS-CoV-2 nucleocapsid protein was detectable

in exocrine pancreatic cells as well as in cells positive for β-cell markers in postmortem examinations of COVID-19 patients (21). On the other hand, another study demonstrated ACE2 protein expression in islet and exocrine tissue microvasculature but not specifically in β-cells (22), and a further study found expression of ACE2 in pancreatic ductal epithelium and microvasculature, but only to a lesser extent in endocrine cells (23).

Pancreata from individuals with COVID-19 demonstrated multiple thrombotic lesions with SARS-CoV-2 nucleocapsid protein expression (23). Thus, alternative mechanisms causing glucose deterioration apart from autoimmune mechanisms and direct β-cell damage, such as SARS-CoV-2–mediated pancreatitis and microthrombotic pancreatic lesions, have to be considered (24,25). Neither of our patients displayed clinical or laboratory signs of pancreatic or other organ damage. However, because of the mild course of their acute SARS-CoV-2 infections, neither patient was hospitalized and neither received laboratory testing at the time of their infection.

To date, there are very few data available concerning the course of diabetes manifested after SARS-CoV-2 infection. Kuchay et al. (7) reported short-term follow-up of three patients with insulin-dependent diabetes without GAD65-Ab after SARS-CoV-2 infection. Remarkably, all three patients were successfully switched to an oral antidiabetic medication within weeks, despite an initial presentation with diabetic ketoacidosis. Our 53-year-old patient's insulin requirement became very low within 4 weeks, despite his initially severely elevated blood glucose, extremely low C-peptide, and high required insulin dose.

The clinical course of our patients and the three patients described by Kuchay et al. (7) implies partial recovery of insulin secretion, which was confirmed by a substantial increase in C-peptide in our patients. Our 29-year-old patient displayed stable, mildly elevated fasting glucose values and a slight decline in A1C during follow-up. A longer follow-up in a larger number of patients will be necessary to determine whether this phenotype of diabetes after SARS-CoV-2 infection undergoes a longer partial remission than the so-called honeymoon period often seen after therapy initiation in type 1 diabetes, whether even complete recovery of β-cell function due to a higher β-cell reserve may occur, or whether deterioration of glycemic control follows a pattern similar to that of classical autoimmune-mediated type 1 diabetes.

In the available case reports, the severity of COVID-19 preceding diabetes manifestation varied from oligosymptomatic to severe and prolonged courses, indicating that an affection of β-cells is not restricted to severe COVID-19. Further, patients' characteristics were variable in terms of age, BMI, and comorbidities. The low number and the heterogeneity of the described cases preclude speculations about predisposing factors for diabetes manifestation after COVID-19.

Clinical Pearls

- Autoantibody-negative insulin-dependent diabetes may manifest in temporal context with SARS-CoV-2 infection.
- Clinicians need to be aware of a possible blood glucose deterioration after COVID-19.
- The underlying mechanism and susceptibility factors remain elusive. Long-term follow-up of cases with autoantibody-negative insulinopenic diabetes associated with SARS-CoV-2 will provide more insight into the phenotype and the potential of remission.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

All authors treated the described patients and collected the data. C.T. wrote the manuscript. I.F. and J.S. reviewed/edited the manuscript. C.T. is the guarantor of this work and, as such, had full access to all the data in case study and takes responsibility for the integrity of the data and its presentation.

REFERENCES

1. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546–550

2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–513

3. Iacobellis G, Penaherrera CA, Bermudez LE, Bernal Mizrachi E. Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes. Diabetes Res Clin Pract 2020;164:108185

4. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab 2020;2:1021–1024

5. Marchand L, Pecquet M, Luyton C. Type 1 diabetes onset triggered by COVID-19. Acta Diabetol 2020;57:1265–1266

6. Soliman A, Al-Amri M, Ellithy K, Alaaraj N, Hamed N, De Sanctis V. Newly-onset type 1 diabetes mellitus precipitated by COVID-19 in an 8-month-old infant. Acta Biomedica. Published online ahead of print on 13 July 2020 (doi: https://doi.org/10.23750/abm.v91i3.10074)

7. Kuchay MS, Reddy PK, Gagneja S, Mathew A, Mishra SK. Short term follow-up of patients presenting with acute onset diabetes and diabetic ketoacidosis during an episode of COVID-19. Diabetes Metab Syndr 2020;14:2039–2041

8. Reddy PK, Kuchay MS, Mehta Y, Mishra SK. Diabetic ketoacidosis precipitated by COVID-19: a report of two cases and review of literature. Diabetes Metab Syndr 2020;14:1459–1462

9. Alizadeh F, O'Halloran A, Alghamdi A, et al. Toddler with new onset diabetes and atypical hemolytic-uremic syndrome in the setting of COVID-19. Pediatrics 2021; 147:e2020016774

10. 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;143: e170–e171

11. Tittel SR, Rosenbauer J, Kamrath C, et al.; DPV Initiative. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? Diabetes Care 2020;43:e172–e173

12. Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr 2020;14:2211–2217

13. Warncke K, Krasmann M, Puff R, Dunstheimer D, Ziegler AG, Beyerlein A. Does diabetes appear in distinct phenotypes in young people? Results of the Diabetes Mellitus Incidence Cohort Registry (DiMelli). PLoS One 2013;8:e74339

14. 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;181:271–280.e8

15. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002;532: 107–110

16. Fignani D, Licata G, Brusco N, et al. SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β-cells and in the human pancreas microvasculature. Front Endocrinol (Lausanne) 2020;11:596898

17. Yang L, Han Y, Nilsson-Payant BE, 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 2020;27:125–136.e7

18. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450–454

19. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444–1448

20. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–199

21. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021;3:149–165

22. Coate KC, Cha J, Shrestha S, et al.; HPAP Consortium. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. Cell Metab 2020;32:1028–1040.e4

23. Kusmartseva I, Wu W, Syed F, et al. Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab 2020;32:1041–1051.e6

24. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with coronavirus disease 19 pneumonia. Gastroenterology 2020;159:367–370

25. Szatmary P, Arora A, Thomas Raraty MG, Joseph Dunne DF, Baron RD, Halloran CM. Emerging phenotype of severe acute respiratory syndrome-coronavirus 2–associated pancreatitis. Gastroenterology 2020;159: 1551–1554