



A Pediatric Case of Abrupt-Onset, Autoantibody-Negative Diabetes With Marked Insulin Resistance Concomitant With COVID-19

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By December 2020, coronavirus disease 2019 (COVID-19) had claimed the lives of more than 200,000 in the United States alone, with more than 10.8 million people infected (1). As the numbers grow, we continue to learn that this disease has wide-ranging outcomes of varying severity affecting multiple organs (2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel virus causing COVID-19, uses the ACE 2 receptor to enter human cells. This receptor is expressed in 15 different human organs (3). Moreover, it is avidly expressed in the pancreatic islets, but not on the exocrine pancreas, suggesting that the virus may directly affect β -cells (3).

The full effects of COVID-19 on diabetes are yet to be determined, but worse outcomes have been reported in adult patients with obesity, impaired glucose metabolism, and diabetes (4). Furthermore, new-onset diabetes, ketosis in people without diabetes, diabetic ketoacidosis (DKA), and worsening metabolic complications in patients with known diabetes have all been reported in adults with COVID-19 (5–7). Some experts have proposed a diabetogenic effect of COVID-19, perhaps presenting as a novel type of diabetes (8). Herein, we describe a case of new-onset, autoantibody-negative

diabetes presenting with DKA and marked insulin resistance in an otherwise healthy, nonobese adolescent.

Case Presentation

A 12-year-old previously healthy White Hispanic boy presented with a 1-week history of abrupt-onset polyuria, polydipsia, headache, and fatigue. He had no weight loss, fever, cough, anosmia, or diarrhea. Laboratory testing revealed DKA, with a blood pH of 7.04, glucose of 381 mg/dL, C-peptide level of 0.6 ng/mL, β -hydroxybutyrate level of 8.2 mmol/L, A1C of 11.3%, and a positive nasopharyngeal reverse transcription-PCR (RT-PCR) test for SARS-CoV-2. There was evidence of pancreatic inflammation (lipase 179 units/L [normal range 15–110]), but no elevation in systematic inflammatory markers, and all autoantibody tests for autoimmune diabetes were negative (Table 1). On exam, he was nonobese (BMI Z-score: -0.3), without acanthosis nigricans, and pubertal (Tanner 3). His medical and family histories were noncontributory; specifically, there was no family history of diabetes or neonatal hypoglycemia.

He was treated with intravenous (IV) insulin infusion at 0.1 units/kg/hour until DKA resolved within 24 hours. He appeared well, without signs of systemic inflammatory response and with no need for respiratory support or glucocorticoid use. He was then transitioned to a subcutaneous insulin regimen starting at 1 unit/kg/day but developed persistent hyperglycemia evidenced via continuous glucose monitoring, prompting an increase of insulin dosing and eventual resumption of IV insulin. His insulin requirements continued to increase consistently with marked insulin resistance (Supplementary Figure S1). Given his significantly elevated insulin requirements (>4 units/kg/day), metformin was initiated, and, 3 days later, his insulin requirements declined, allowing for discharge 9 days after initial diagnosis on an insulin regimen closer to 1.5 units/kg/day (Figure 1).

In the following days, the patient's insulin requirement continued to decrease. Metformin was discontinued 20 days after diagnosis without rebound hyperglycemia. Over the next weeks after discharge, his glycemic control continued to improve, as evidenced by A1C results of 8.8 and 5% at 4 and 12 weeks, respectively, with appropriate

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TABLE 1 Laboratory Tests on Admission

	Result	Reference Value
β-hydroxybutyrate, mmol/L	8.4	<0.3
Glucose, mg/dL	381	–
C-peptide, ng/mL	0.6	0.8–6.8
pH	7.04	7.25–7.35
Bicarbonate, mmol/L	<5	20–28
A1C, %	11.3	<5.7
Lipase, units/L	179	15–110
C-reactive protein, mg/dL	1.1	<1
Sedimentation rate, mm/hour	5	0–300
Ferritin, ng/mL	166	10–300
GAD autoantibody, units/mL	<5	<5
Insulin autoantibody, units/mL	<0.4	<0.4
Islet cell autoantigen 512 autoantibody, units/mL	<5.4	<5.4
Zinc transporter 8 autoantibody, units/mL	<10	<15
SARS-CoV-2 RT-PCR	Positive	–

insulin requirements for his age and pubertal status (0.86–0.9 units/kg/day). Furthermore, he had a C-peptide of 3.39 ng/mL at the time of euglycemia (102 mg/dL), which was consistent with recovery of β-cell function. His

insulin requirement continued to decline, and, by week 14, he was only on long-acting insulin at 0.2 units/kg/day with blood glucose levels ranging from 90 to 145 mg/dL. At week 23, long-acting insulin was discontinued

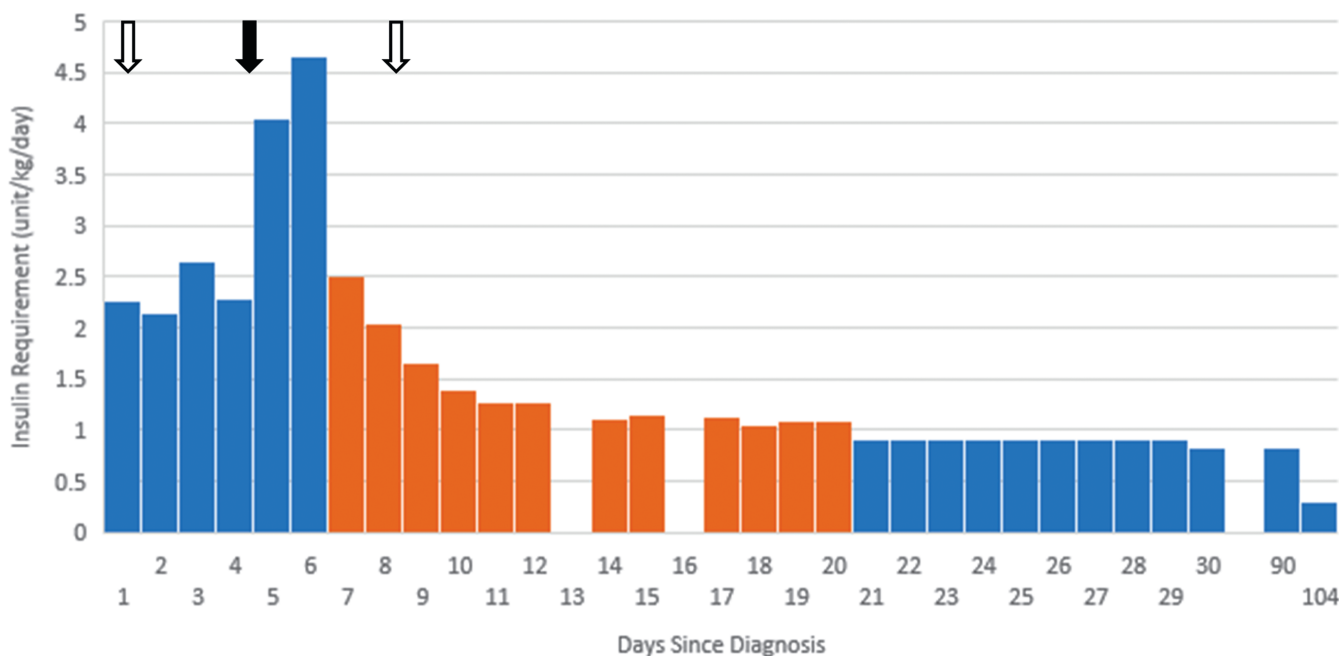


FIGURE 1 Insulin requirements from admission through follow-up. Arrows indicate the discontinuation (white) and resumption (black) of IV insulin. Orange bars indicate the concomitant use of metformin 1,000 mg/day and subcutaneous insulin. Data were unavailable for days 13 and 16. Insulin was discontinued altogether on day 162.

altogether. Finally, because of financial constraints and a very low probability of having maturity-onset diabetes of the young (~0.7%), molecular testing was not pursued (9).

Questions

1. Can SARS-CoV-2 directly target pancreatic β -cells, resulting in an abrupt-onset insulinopenic state?
2. Is there any association between insulin resistance and COVID-19 independent of the inflammatory response or severity of illness?
3. Could this form of nonautoimmune, insulin-dependent diabetes associated with COVID-19 be transient, similar to the insulin resistance displayed?

Commentary

The COVID-19 pandemic represents an unprecedented challenge for all health care providers globally, with its high rate of morbidity and mortality. As time passes, it is becoming more evident that the disease appears to have unique features not previously seen with similar pathogens. Early reports point not only to worsening of existing diabetes, but also increased incidence of new diagnoses of overt diabetes and impaired glucose metabolism (4–7).

Here, we report a novel case of new-onset, nonautoimmune diabetes in a nonobese child, with exceptional insulin resistance and evidence of pancreatic injury concomitant with COVID-19. The abrupt onset of disease, with severe metabolic derangement, insulinopenia, and no evidence of autoimmunity in the setting of a viral illness is reminiscent of the phenotype of fulminant type 1 diabetes, although the criteria for its diagnosis were not met (10). Additionally, that form of diabetes lacks features of insulin resistance.

Although the pathophysiology of this morbid condition remains obscure, we speculate that it could be mediated by a direct viral insult resulting in an insulinopenic state with insulin resistance. As in our case, pancreatic injury has been reported in 17% of adult patients with COVID-19 pneumonia, presenting with mean lipase levels of 71 ± 34 units/L (11). Additionally, two other cases of autoantibody-negative diabetes after COVID-19 in adolescents have been reported (5,12). However, the clinical course in both were fairly similar to that of other patients with newly diagnosed type 1 diabetes, and both lacked an abrupt onset and exceptional insulin resistance. Furthermore, in the case reported by Suwanwongse and Shabarek (5), evaluation for zinc-transporter-8 autoantibody was missing; thus, absolute exclusion of autoimmunity was

not possible. In the report by Hollstein et al. (12), the patient did not have evidence of pancreatic inflammation, although he presented more than 4 weeks after infection. Thus, its presence could not be clearly established. Our report may fill these gaps, supporting the hypothesis of nonautoimmune β -cell injury secondary to SARS-CoV-2 infection, as has been previously described with SARS-CoV-1 and Coxsackievirus-B4 (3,13).

Notably, the presenting A1C in our case did not seem to correlate with the abrupt onset of symptoms, arguing against the causality of COVID-19. Nonetheless, elevated A1C levels are seen in DKA regardless of the duration of diabetes, and similar findings have been reported (12). Another consideration is the time of onset of diabetes relative to the SARS-CoV-2 infection. Because the positive RT-PCR test does not allow for an estimation of time of infection and children seem to have a prolonged viral shedding, with a median time of 32 days to achieve RT-PCR negativity (14), our patient could have become infected weeks before onset of symptoms of hyperglycemia, allowing for an incremental change in A1C.

Glucocorticoids and a stress response to critical illness are known to result in insulin resistance. However, the lack of exposure to these drugs, normal inflammatory markers, and the patient's clinical appearance do not support this as the origin of such exceptionally high insulin requirements, raising the possibility that this may have been a viral-mediated process. Similar findings of new-onset diabetes with COVID-19 in individuals lacking severe illness have been reported in adults (5). Insulin resistance is closely associated with COVID-19 severity and mortality, with patients with higher insulin resistance presenting with higher levels of inflammatory markers. Notably, there was a discordance between the severity of illness and insulin resistance in this case. Our patient was on an insulin drip for a few hours preceding the measurement of inflammatory markers, and insulin has an anti-inflammatory effect (15), which could potentially have led to a decline in the inflammation cascade. Nonetheless, it would be unlikely for insulin to completely blunt an inflammatory response in such a short span of time, and, had it done so, the subsequent insulin resistance should have improved, rather than lingering for days in this case. The question remains: did the use of metformin help to ameliorate the insulin resistance in a matter of days, or was this a result of defervescing inflammation in a resolving illness?

Finally, whether this is a transient or permanent form of diabetes is yet to be determined. Our patient seems to have recovered some β -cell function. It is important to note that, of patients who have developed acute diabetes after

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SARS-CoV-1 infection, only half had persistent diabetes 3 years after diagnosis (3). More data and investigation are needed to draw further conclusions, and results from initiatives such as the global CoviDIAB Project (8) are eagerly awaited to shed light on the matter.

Clinical Pearls

- COVID-19 can predispose to new-onset, non-autoimmune insulinopenic diabetes reminiscent of fulminant diabetes, but with an idiopathic severe and transient form of insulin resistance not otherwise explained by individual or pharmacologic factors or severity of viral illness.
- It appears that pancreatic islets may be particularly susceptible to COVID-19, with a variety of effects on insulin secretion and action independent of autoimmune-mediated injury. Whether this could be a novel phenotype of diabetes related to SARS-CoV-2 infection remains to be determined.
- The insulin resistance concomitant with COVID-19 seems to be transient, but whether the state of insulin deficiency is transient or permanent remains to be determined.
- Metformin might be useful in curbing insulin resistance associated with COVID-19.

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DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

All authors were actively involved in the discussion and construction of this project. A.H.-M. drafted the initial manuscript. K.H., T.P., J.B., and Y.L. critically revised and edited it accordingly. A.H.-M. is the guarantor of this work and, as such, had full access to all the data in the case and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Centers for Disease Control and Prevention. COVID-19 data tracker: demographic trends of COVID-19 cases and deaths in the US reported to CDC. Available from <https://covid.cdc.gov/covid-data-tracker/#demographics>. Accessed 4 December 2020
2. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ* 2020;369:m1996
3. 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* 2010;47:193-199
4. Smith SM, Boppana A, Traupman JA, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* 2021;93:409-415
5. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. *J Med Virol* 2021;93:1150-1153
6. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020;22:1935-1941
7. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract* 2020;164:108166
8. Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in Covid-19. *N Engl J Med* 2020;383:789-790
9. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* 2012;55:1265-1272
10. Liu L, Zeng L, Sang D, Lu Z, Shen J. Recent findings on fulminant type 1 diabetes. *Diabetes Metab Res Rev*. Online ahead of print on 25 September 2017 [doi: 10.1002/dmrr.2928]
11. 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
12. 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
13. Yoon JW, Austin M, Onodera T, Notkins AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med* 1979;300:1173-1179
14. Bahar B, Jacquot C, Mo YD, DeBiasi RL, Campos J, Delaney M. Kinetics of viral clearance and antibody production across age groups in children with severe acute respiratory syndrome coronavirus 2 infection. *J Pediatr* 2020;227:31-37.e1
15. Sun Q, Li J, Gao F. New insights into insulin: the anti-inflammatory effect and its clinical relevance. *World J Diabetes* 2014;5:89-96