Type 1 diabetes mellitus post-COVID-19: a trigger or a coincidence? A case report

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Case report

Abstract

Introduction:

Diabetes mellitus is proven to be one of the highest risks of developing severe illness in people infected with COVID-19, particularly in type 1 diabetes mellitus. Several research works have been done to study the relationship between COVID-19 and new-onset of type 1 diabetes mellitus.

Case presentation:

We are reporting a case of 25 years old Arabic male who had a mild COVID-19 infection and presented with type 1 diabetes mellitus with low C-peptide and positive anti-GAD two months after the infection.

Conclusions:

In conclusion, our case highlights a possible exacerbation of autoimmunity due to COVID-19 that induced or accelerated development of type 1 diabetes mellitus.

Our case highlights a possible exacerbation of autoimmunity due to COVID-19 that induced or accelerated development of T1DM. Therefore, clinicians should always keep in mind the possibility of new-onset T1DM following a COVID-19 infection

Introduction

Diabetes mellitus (DM) is proven to be one of the highest risks of developing severe illness in people infected with COVID-19, particularly in type 1 diabetes mellitus (T1DM), primarily due to poorer glycemic control. One study estimated that 50% of patients with T1DM who were infected with COVID-19 presented with hyperglycemia, and one-third presented with diabetic ketoacidosis (DKA).[1]

Several research works have been done to study the relationship between COVID-19 and new-onset of T1DM; one mechanism is that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can enter the islets cells of the pancreas through the angiotensin-converting enzyme-2 (ACE-2) receptors and lead to beta-cell damage.[2] Another theory suggests the islets autoimmunity, as shown in the TEDDY study.[3]

We are presenting a case of a 25-year-old male with previous normoglycemia. After two months of being infected with COVID-19, he presented with symptomatic hyperglycemia and was found to have laboratory evidence of T1DM. There were few similar case reports found in the literature. One case was reported in France of a 29 years old woman who was diagnosed as a case of T1DM with low C-peptide and positive anti-glutamic acid decarboxylase-65 (anti-GAD) autoantibodies one month after her first symptoms of COVID-19.[4] Another case was reported in Germany of an eight years old boy who was hospitalized as a newly diagnosed T1DM presenting with DKA and was found to have positive COVID-19 infection.[5]

Case Presentation

In July 2021, a 25-year-old Arabic male presented with fatigue and elevated random glucose of 11.4 mmol/L. He was recently diagnosed with DM – with no confirmation of type yet – and was taking Sitagliptin/Metformin 100/2000 mg daily along with Gliclazide 30 mg daily. At the time of presentation, type-confirmatory results were out and showed T1DM with low C-peptide of 0.91 ng/mL, low normal insulin of 4.3 microunit/mL, and positive anti-GAD of > 2000 IU/mL. The patient was informed about his diagnosis, started on a small dose of Glargine insulin six units daily and Aspart insulin four units three times daily. He was referred to endocrinology to get a continuous glucose monitoring sensor. Oral medications were stopped.

One month before, the patient presented with two weeks of fatigue, polydipsia, polyuria with weight loss of eight kilograms (Table 1). Past medical history included subclinical hypothyroidism; managed conservatively without medications, vitamin D deficiency, and rosacea. The patient had no past surgical history, but family history showed DM in parents. Laboratory tests showed random glucose of 15.1 mmol/L, hemoglobin A1c (HbA1c) of 11.8%, urine glucose A+++, urine ketones A++ (Table 2). The patient was given ten units of Aspart insulin and sent to the ED where his venous blood gases did not show DKA; PH: 7.375 - PCO2: 55 mmHg - potassium: 3.6 mmol/L - glucose: 8.3 mmol/L - HCO3: 32.2 mmol/L (Table 3). He was discharged on the same day as a case of newly diagnosed DM, with laboratory tests ordered to confirm the type, and started on Sitagliptin/Metformin and Gliclazide while waiting for other results.

Table 1
Anthropometric measures

Measurements	At diagnosis	5 months before diagnosis
Height (cm)	168	168
Weight (Kg)	64	72
BMI (Kg/m^2)	22.67	25.51

Table 2
Laboratory investigation results

Test	At diagnosis	3 years before diagnosis
WBC (1000/microliter)	6.4	6
Hemoglobin (gm/dL)	15.6	15
Platelet (1000/microliter)	254	197
Creatinine (micromol/L)	76	86
Adjusted calcium (mmol/L)	2.41	2.42
Total Bilirubin (micromol/L)	20	11.8
Total Protein (gm/L)	75	69
Albumin (gm/L)	47	40
ALT (unit/L)	24	48
Random Glucose (mmol/L)	15.1	6.0
HbA1c (%)	11.8	5.4
Beta-Hydroxybutyrate (mmol/L)	0.66	
Lactic Acid (mmol/L)	1.4	
UA Glucose	A +++	
UA Ketones	A ++	
Insulin (microunit/mL)	4.3	
C-Peptide (ng/mL)	0.91	
Anti-GAD (IU/mL)	> 2000	
Anti-GAD (Interpretation)	Positive	
U MALB Ratio (ng/mmoL)	2.2	
Vitamin D (ng/mL)	16	12
TSH (mIU/L)	6.37	6.51
FT4 (pmol/L)	17.5	14.2
Anti-TPO (IU/mL)	262	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-GAD, anti-glutamic acid decarboxylase-65; Anti-TPO, anti-thyroid peroxidase; FT4, free thyroxine; HbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; UA, urinalysis; U MALB Ratio, urine microalbumin to creatinine ratio, WBC, white blood cells.

Test	At diagnosis	3 years before diagnosis
Anti-TPO (Interpretation)	Positive	
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-GAD, anti-glutamic acid decarboxylase-65; Anti-TPO, anti-thyroid peroxidase; FT4, free thyroxine; HbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; UA, urinalysis; U MALB Ratio, urine microalbumin to creatinine ratio, WBC, white blood cells.		

Table 3
Venous blood gases at diagnosis

pH	**7.375**
PCO2 (mmHg)	H 55
PO2 (mmHg)	25
Na (mmol/L)	141
K (mmol/L)	3.6
Cl (mmol/L)	99
BG Glucose (mmol/L)	H 8.3
BG Lactic Acid (mmol/L)	1.30
HCO3 (mmol/L)	H 32.2
TCO2 (mmol/L)	H 33.9
BE (mmol/L)	H 5.0
HCO3 (st) (mmol/L)	H 27.4
Abbreviations: BE, Base excess; BG, blood gases; Cl, chloride; HCO3, bicarbonate; HCO3 (st), standard bicarbonate; K, potassium; Na, sodium; PCO2, partial pressure of carbon dioxide; pH, potential of hydrogen; PO2: partial pressure of oxygen; TCO2, total carbon dioxide.	

In April 2021, the patient suffered a mild upper respiratory tract infection, and COVID-19 was proven by a nasopharyngeal swab with an average cycle threshold (CT) value of 15.65. The patient was stable and managed with home isolation and symptomatic treatment.

Three years ago, the patient had a checkup laboratory test that showed a normal HbA1c of 5.4% (Table 2).

At the 2-month follow-up after starting basal-bolus insulin therapy, HbA1c improved to 9.5%.

Throughout the diagnosis and follow-up period the patient was involved in the management plan and he agreed to the treatment prescribed.

Discussion

T1DM is characterized by autoimmune destruction of beta-cell of the pancreases causing absolute insulin deficiency. According to the American Diabetes Association (ADA), T1DM has three stages. In stage 1, there are only positive antibodies with normal glucose parameters. Impaired glucose parameters (i.e., prediabetes) develop in stage 2, and in stage 3, abnormal glucose testing meets the diagnostic criteria for DM.[6]

The COVID-19 pandemic has significantly impacted patients with DM in general. One systemic review conducted in the USA from fifteen studies including both adults and children concluded that the prevalence of T1DM in COVID-19 patients ranged from 0.15–28.98%, while the rate of COVID-19 in patients with T1DM ranged from 0–16.67%.[7] There is an ongoing registry project called COVIDIAB (https://covidiab.e-dendrite.com/) conducted by the King's College London and Monash University to collect data of all COVID-19 patients with new-onset DM and to study the association between the two conditions.

The patient in our study had a mild COVID-19 infection that did not need hospitalization, and no laboratory tests were done during his illness to check his glycemic levels. Then after two months, he presented with full-blown symptomatic hyperglycemia that did not reach the level of DKA. Subsequent tests confirmed T1DM with low C-peptide and positive anti-GAD. Again, this case raised a question regarding the relationship between COVID-19 and T1DM.

While it is well established that genetics play a major role in T1DM, viral infections role – particularly enteroviruses such as coxsackievirus – as triggers for T1DM has been supported in human studies.[8] In addition, researcher of the TEDDY study found a temporal link between respiratory infections and islet cell autoantibody seroconversion, where 454 children seroconverted after 87,327 recorded infectious respiratory episodes. [9]

As regards COVID-19 relationship with T1DM, one theory suggests that SARS-CoV-2 can enter the islets cells of the pancreases through the ACE-2 receptors and lead to beta-cell damage.[2] (3) Fignani et al. detected ACE2 in human pancreatic islets, and it was expressed in beta-cells more than alpha-cells. ACE2 was also highly detected in pancreas microvasculature pericytes. They also found that pro-inflammatory cytokines increased the expression of ACE2 in the beta-cells.[10]

Is it the local microvasculature inflammation that leads to beta-cell destruction? Or is it just a coincidence, i.e., the stress response induced by an acute infection unmasks an already ongoing undiagnosed T1DM? Or is it SARS-CoV-2 that causes an exacerbation of immunity? Hollstein et al. reported a case of 19 years old man diagnosed with autoantibody-negative T1DM, 5–7 weeks following a COVID-19 infection, and suggested a cytolytic effect of COVID-19 on beta-cells.[11] Dehghani et al. also reported a 23 years old man who was found to have T1DM with an HbA1c of 12.2% at the time of having

COVID-19 infection.[12] However, in our patient, autoimmune T1DM was diagnosed two months after COVID-19 infection, which points more towards an exacerbation of immunity.

Another vital issue to mention, the patient had non-medically treated subclinical hypothyroidism in 2018 with a similar level of TSH in 2021 (6.51 mIU/L in 2018 and 6.37 mIU/L in 2021). Anti-thyroid peroxidase (Anti-TPO) was positive after COVID-19, but it was not measured before. So here, the relationship between COVID-19 and positive anti-TPO remains an open question that needs more research.

Conclusion

In conclusion, several theories have been proposed to investigate the relationship between COVID-19 and T1DM. Our case highlights a possible exacerbation of autoimmunity due to COVID-19 that induced or accelerated development of T1DM. Therefore, clinicians should always keep in mind the possibility of new-onset T1DM following a COVID-19 infection.

Abbreviations

(DM) Diabetes Mellitus

(T1DM) Type 1 Diabetes Mellitus

(DKA) Diabetic Ketoacidosis

(SARS-CoV-2) severe acute respiratory syndrome coronavirus-2

(ACE-2) Angiotensin-converting enzyme-2

(anti-GAD) Anti-glutamic acid decarboxylase-65

(CT) cycle threshold

(Anti-TPO) Anti-thyroid peroxidase

Declarations

- <u>Ethics approval and consent to participate:</u>

Approval taken from the Institutional Review Board (IRB) at Hamad Medical Corporation (HMC) and Medical Research Council (MRC), MRC-04-22-332, and consent to participate obtained

- <u>Consent for publication</u>

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this

journal.

- <u>Availability of data and material:</u>

 All available

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Dr Nashwan Zainl Deen (First Author):

- Acquisition, analysis, and interpretation of data
- Manuscript writing
- Obtaining patient consent
- Obtaining ethical approval

Dr Mohamed Hnish (Co-Author)

- Literature review
- Manuscript writing
- Corresponding author in journal submission process

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- Scientific review of the manuscript

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