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Caso Clínico

A Case Series of Follow-ups in COVID-Related Diabetes: Could the Damage in Beta Cells be Recovered?

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A B S T R A C T

SARS-CoV-2 infection may be related to new-onset diabetes and diabetic ketoacidosis (DKA). We describe a long-term follow-up of 3 cases presented in the Emergency Department with DKA and COVID-19. In 2 of them, the clinical course permitted withdrawal of insulin therapy during follow-up. The third case, a more serious one with pulmonary thromboembolism, continued to require bedtime insulin during the follow-up period. Such cases demonstrate that insulin treatment can control glucotoxicity and help beta cells recover after an acute insult such as COVID-19.

Palavras-chave:
Cetoacidose Diabética;
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Uma Série de Casos de Seguimento de Diabetes Relacionada à COVID: Pode o Dano na Célula Beta ser Recuperado?

R E S U M O

A infecção por SARS-CoV-2 pode estar relacionada a diabetes de início recente e cetoacidose diabética (CAD). Descrevemos o seguimento a longo prazo de 3 casos apresentados no Serviço de Urgência com CAD e COVID-19. A evolução clínica em 2 deles permitiu a suspensão de insulinoterapia durante o seguimento. O terceiro caso, mais grave que teve tromboembolismo pulmonar, ainda necessitou de insulina basal ao deitar durante o seguimento. Esses casos demonstram que o tratamento com insulina pode controlar a glicotoxicidade e auxiliar na recuperação das células beta após um insulto agudo como a COVID-19.

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Introduction

The World Health Organization declared the new coronavirus a pandemic at the beginning of 2020. Several cases of diabetes have been recorded as a result of this viral infection. The SARS-CoV-2 virus is thought to increase insulin resistance in peripheral tissues due to cytokines storm, produce beta cell apoptosis resulting in insulinopenia, which predisposes to diabetic ketoacidosis (DKA) even in type 2 diabetes.[1,2] Data and long-term follow-up of these patients are lacking, particularly regarding recovery of beta cell function after virus infection.

Therefore, we aim to describe 3 cases of COVID-related diabetes presenting with DKA, with a longer follow-up than in previous reports.

Case Report

Case 1

A 44-year-old man presented to the Emergency Department (ED) in Abril 2020 referring fever, myalgia, and cough in the past week. He had no comorbidities, no symptom of insulinopenia and no family history of diabetes. On physical examination, he had an oxygen saturation of 80% on room air, a respiratory rate of 40 cpm, and a BMI of 27 kg/m^2. SARS-CoV-2 was confirmed using real-time PCR. Admission test exams revealed hyperglycemia, associated with a high anion gap metabolic acidosis (Table 1) and ketonuria, fulfilling diagnostic criteria for DKA. He received subcutaneous (SC) regular insulin, IV fluids, replacement of electrolytes, oxygen supplementation, and awake prone position; he did not receive corticosteroids since the RECOVERY trial was only published in the end of 2020.[3] Islet cell and glutamic acid decarboxylase antibodies were negative. HbA1c was 12%, with low C peptide value of 0.9 ng/dL (concurrent glucose of 208 mg/dL). His DKA resolved the following day, and he was discharged home after 2 weeks on room air, with SC NPH basal insulin and premeal regular insulin (total daily dose of 0.2 IU/kg). At this time, the diabetes type was still in debate, and type 1B diabetes was one of the differentials proposed.

After one year of follow-up with a low daily insulin dose, his HbA1c decreased to 6.5% with no hypoglycemia. We collected a new C-peptide of 2.4 ng/dL (glucose 189 mg/dL) and switched insulin therapy to metformin 2 g/day due to type 2 diabetes. His HbA1c was maintained in 6.5%.

Case 2

In September 2020, a 44-year-old man presented to the ED with flu-like symptoms for the past week. His mother and sister had a history of type 2 diabetes. He had Down syndrome with no other medical condition. Upon admission, he had an oxygen saturation of 87% on room air, a respiratory rate of 17 cpm, and a BMI of 28 kg/m^2. He also had hyperglycemia associated with a high anion gap metabolic acidosis (Table 1) and ketonuria. Mild DKA was resolved the next day and was managed in the intensive care unit. Real-time PCR for SARS-CoV-2 was positive, his HbA1c was 11.2%, with a C-peptide of 1 ng/dL (glucose 203 mg/dL), and negative type 1A diabetes antibodies (islet cell and glutamic acid decarboxylase antibodies).

This patient did receive dexamethasone for COVID-19 infection. Unfortunately, his condition deteriorated dramatically: he was intubated and submitted to thrombolysis due to an acute pulmonary embolism with severe hypotension.

After nearly 2 months of hospitalization, he was discharged on NPH insulin plus regular insulin of approximately 0.7 IU/kg/day. After 6 months, HbA1c was reduced to 7.7% with no hypoglycemia and a C-peptide of 2.7 ng/dL (glucose 211 mg/dL). We switched to oral therapy and maintained only basal insulin. He achieved good glycemic control (HbA1c 7.1%) with a full dose of metformin, saxagliptin, gliclazide, and bedtime NPH 0.1 IU/kg/day.

Case 3

A 36-year-old man in May 2020 presented to the ED reporting polyuria, polyphagia, altered mental status, and cough in the past week. He had no relevant medical or family history. He was confused, with a Glasgow coma scale of 13, a BMI of 30 kg/m^2, and an oxygen saturation of 96% on room air. Admission exams demonstrated positive real-time PCR for SARS-CoV-2, hyperglycemia, and marked high anion gap metabolic acidosis (Table 1), and ketonuria.

DKA was resolved in 12 hours. He did not receive corticosteroids during hospital stay. The diabetes laboratory investigation revealed a HbA1c of 12.6%, negative islet cell and glutamic acid decarboxylase antibodies, and C-peptide of 4.1 ng/dL (glucose 226 mg/dL). He was initiated on NPH plus regular 0.45 IU/kg/day. After a 6-month follow-up, HbA1c was 6.1% (with no hypoglycemia, using only NPH 0.2 IU/kg/day), and C-peptide was

Table 1. Clinical and laboratory tests performed on patients during admission and follow-up.

	Case 1	Case 2	Case 3	Reference
Arterial pH	7.26	7.25	7	7.35-7.45
Bicarbonate (mmol/L)	15	15.4	7	20-24
pCO2 (mmHg)	33	32	29	35-45
Anion gap	22	17	24	8-12
Glucose (mg/dL)	307	460	980	<200
DKA classification	Mild	Mild	Severe	-
Arterial lactate (mg/dL)	15	8	7	4.5-14.4
Islet cells and glutamic acid decarboxylase antibodies	Negative	Negative	Negative	-
Initial C-peptide (ng/dL)*	0.9	1	4.1	1.1-4.4
Follow-up C-peptide (ng/dL)*	2.4	2.7	4	1.1-4.4
Admission HbA1c (%)	12	11.2	12.6	4%-5.6%
HbA1c after switch of diabetes drug therapy (%)	6.5	7.1	5.9	4%-5.6%
Total daily insulin dose prescribed after discharge (IU/kg/day)	0.2	0.7	0.45	-
Total daily insulin dose during follow-up (IU/kg/day)	-	0.1	-	-

* The glucose level was greater than 150 mg/dL at the time of sample collection.

4 ng/dL (glucose 177 mg/dL). Insulin therapy was withdrawn and the patient received a full dose of metformin with satisfactory glycemic control (HbA1c 5.9%).

Unfortunately, the Public Health System in Brazil does not provide GLP1 analogs, which would be an excellent choice for both diabetes and weight control. Moreover, our ED does not have capillary ketonemia and the DKA diagnosis in all cases was based on ketonuria. Other causes of high anion gap acidosis were ruled out for all presented cases: there was no history or clinical signs of exogenous intoxication, lactate was only mildly elevated in case 01 (Table 1) – probably due to the acute respiratory infection, and none of the patients had chronic kidney disease.

Discussion

Epidemiology studies comparing pre-pandemic versus first and second waves in COVID highlight an increase in admission to the ED for DKA, especially in type 2 diabetes.[4]

The mechanism responsible for hyperglycemia and DKA in COVID-19 is not well known and it is probably multifactorial. Theories include a possible previous undiagnosed diabetes, which could be triggered by lifestyle changes during the pandemic period (weight gain, self-isolation, decreased physical activity, and high-calorie diet).[5]

Stress-related hyperglycemia is another factor that influences glycemic levels. Even though hyperglycemia is not rare in acute ill-hospitalized patients, some evidence proposes that new-onset diabetes seems more prevalent due to COVID-19 rather than another acute event.[6]

Impairment in pancreatic function and insulin resistance may be caused by cytokine storm, in situ thrombosis leading to pancreatic cell ischemia, and direct viral replication.[7] The SARS-CoV-2 binds to ACE2 receptors expressed in the pancreatic beta cells, enters the cell for replication, diminishes pancreatic insulin levels, and can directly induce beta cell apoptosis.[1,8] All of these factors can lead to insulinopenia and increase the risk of DKA.

After the publication of the RECOVERY trial, corticosteroids were used to decrease mortality in COVID-19.[3] Besides those complex mechanisms that induce hyperglycemia, the use of steroids became another risk factor as it delays the recovery of beta cell function and increases insulin resistance.[5]

The real impact on the future secretion of insulin is unknown, although cases 01 and 03 show that beta cells can be preserved, especially following intensive treatment to stop glucotoxicity. Interestingly, Weng *et al* demonstrated in 2008 that intensive insulin treatment in newly diagnosed type 2 diabetes could maintain beta cell function and achieve diabetes remission even after one year of insulin therapy discontinuation.[9]

A larger retrospective study with 1902 subjects with COVID-19 showed that 77 (13%) had newly diagnosed diabetes. Compared to the patients with pre-existing diabetes, they had lower glycemic values, were younger, had longer hospital stay and intensive care unit admission, and had higher inflammatory markers. Although 25 (39.1%) of them were discharged on insulin, after one year of follow-up 26 (40.6%) regressed to normoglycemia or pre-diabetes.[10] Authors suggested the term "newly diagnosed diabetes" over "new-onset diabetes", as it is unclear in many cases whether the diabetes is truly new-onset or merely newly recognized. In fact, in their study, almost 70% of the newly diagnosed diabetes group had HbA1c >6.5% at admission. Like our patients, HbA1c levels indicate that they most likely had undiagnosed type 2 diabetes prior to COVID-19 diagnosis.

Post-COVID syndrome or long COVID is defined by signs or symptoms that can be reminiscent after 12 weeks of the viral disease. Although causality cannot be established, a relationship in diabetes development post-COVID has been described.[11] Wander *et al*, in a retrospective cohort, found a 2.56-fold increase in diabetes incidence in veteran American men after viral infection.[12] A matched pair analysis of a German healthcare database also identified an increased incidence rate ratio of 1.28 in type 2 diabetes in infected patients.[13] Type 1 diabetes, on the other hand, did not appear to have increased in incidence.[14]

The SARS-CoV-2 infection intensifies the risks and accelerates the manifestation of diabetes among individuals at high risk of diabetes. According to Xie *et al*, even people at low risk of diabetes revealed an increased risk after COVID-19, compared to the control group. Therefore, they concluded that post-COVID care should include routine screening and management of diabetes.[15]

In conclusion, the purpose of these cases is to describe a longer follow-up in patients with COVID-related diabetes. Early insulin therapy should be considered since apparently there might be a chance to recover beta cell function. More studies are needed concerning longer follow-up after COVID-19 to investigate diabetes in this population.

Contributorship Statement / Declaração de Contribuição:

MAMS: Conceptualization, data collection, writing original draft, and final approval.
LPL: Writing original draft, review and final approval.
PK, MN, MLCCG, MERS: supervision, review and final approval.

Responsabilidades Éticas

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References / Referências

1. 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: 1150-53.
2. de Sá-Ferreira CO, da Costa CH, Guimarães JC, Sampaio NS, Silva LM, de Mascarenhas LP, et al. Diabetic ketoacidosis and COVID-19: what have we learned so far? Am J Physiol Endocrinol Metab. 2022; 322: E44-E53.
3. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384: 693-704.
4. Misra S, Barron E, Vamos E, Thomas S, Dhatariya K, Kar P, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. Lancet Diabetes Endocrinol. 2021; 9: 671-80.
5. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and New-Onset Diabetes. Diabetes Care. 2021; 44: 2645-55.
6. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Obes Metab. 2021; 23: 870-74.
7. Qadir MMF, Bhondeley M, Beatty W, Gaupp DD, Doyle-Meyers LA, Fischer T, et al. SARS-CoV-2 infection of the pancreas promotes thrombofibrosis and is associated with new-onset diabetes. JCI Insight. 2021; 6: e151551.
8. Wu CT, Lidsky PV, Xiao Y, Lee IT, Cheng R, Nakayama T, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. Cell Metab. 2021; 33: 1565-76
9. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet. 2008; 371: 1753-60.
10. Cromer SJ, Colling C, Schatoff D, Leary M, Stamou MI, Selen DJ, et al. Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: Associated factors, short-term outcomes, and long-term glycemic phenotypes. J Diabetes Complications. 2022; 36: 108145.
11. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021; 372:n693.
12. Wander PL, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, et al. The incidence of diabetes among 2,777,768 veterans with and without recent SARS-CoV-2 infection. Diabetes Care. 2022; 45: 782-88.
13. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. Diabetologia. 2022; 65: 949-54.
14. Kamrath C, Rosenbauer J, Tittel SR, Warncke K, Hirtz R, Denzer C, Dost A, Neu A, Pacaud D, Holl RW. Frequency of autoantibody-negative type 1 diabetes in children, adolescents, and young adults during the first wave of the COVID-19 pandemic in Germany. Diabetes Care. 2021; 44: 1540-46.
15. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol. 2022; 10: 311-21.