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Hyperosmolar hyperglycemic state and New Onset Diabetes Mellitus precipitated by COVID-19 Infection

Adishah Çerma[1], Pranvera Spahija[1], Gerond Husi[1], Marjeta Kërmaj[1], Klodiana Poshi[1], Adela Haxhiraj[1], Violeta Hoxha[1], AgronYlli

[1]*Hospital University Center "Mother Theresa", Tirana, Albania*

Abstract: **Background: Diabetes Mellitus is an important factor in COVID-19 patients, known as a risk factor for severe SARS-CoV-2 infection. SARS-CoV-2 infection actually causes acute diabetic complications such are DKA and HHS in known diabetic patients, and also some studies and case reports support the idea that COVID-19 could trigger New onset Diabetes. The incidence of DKA is higher than HHS in COVID-19 patients.**
Methods: The patient admitted with HHS, was diagnosed with COVID-19 on the bases of basis of Chest Computed Tomography, after a negative reverse transcription-polymerase chain reaction (RT-PCR) assay. Detailed medical history, physical examination and laboratory investigations were obtained.
Case presentation: Here we present a 70 year-old patient, not known to have DM before, presented in ED with somnolence, reporting a 2 weeks history with fever, urinary tract infection signs, fatigue, polyuria-polydipsia syndrome, home treated with antibiotics, with no improvement. His lab results showed high blood glucose, high effective osmolarity, no ketonuria, diagnostic for HHS. He got hospitalized in Endocrinology and Diabetology Department and treated successfully with intravenous fluids and insulin as per HHS protocol. Besides his metabolic improvement his body temperature persisted and a COVID-19 Disease was suspected. So he underwent a Chest Computed Tomography which confirmed SARS-CoV-2 Pneumonia, despite the negative RT-PCR test. The patient refused the treatment in a COVID-19 Hospital and he was discharged home in a stable condition.
Conclusion: COVID-19 has a diabetogenic effect that is yet to be fully understood. Based on the reviewed cases, patients with newly onset diabetes and a recently aggravated symptomatology need a careful investigation regarding the presence of SARS-CoV-2 as a potential trigger.

Keywords: **HHS, diabetes, COVID-19, ACE2.**

Abbreviations: HHS: Hyperosmolar Hyperglycemic State; DKA: Diabetic Ketoacidosis; COVID-19: Corona Virus -19; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; ACE2: Angiotensin-Converting Enzyme 2; ED: Emergency Department; ICU: Intensive Care Unit

1. INTRODUCTION

SARS-CoV-2 is a novel coronavirus, first isolated in December 2019 in Wuhan China, in patients presented with severe viral pneumonia. Since then, there are 54.5 million cases, 35.1 million have recovered and 1.32 million reported deaths in the world (as of 20 November 2020, data taken from WHO). Known important risk factors for severe illness and mortality, among patients with COVID-19, are: Cardiovascular disease, Diabetes Mellitus, Hypertension, Obesity [1]. The relationship between COVID-19 and Diabetes is bidirectional. Diabetes is known as a risk factor of severe COVID-19, also in COVID-19 patients, new onset Diabetes and severe complications of preexisting diabetes, including ketoacidosis and hyperosmolarity, have been observed [2]. The manifestations of Diabetes pose challenges in clinical management and suggest a complex pathophysiology of COVID-19 related Diabetes [3]. Acute hyperglycemic crises such are DKA and HHS are serious acute metabolic complications of diabetes, commonly precipitated by severe infections. In a retrospective study from China 6.4 % of patients admitted with COVID-19 had ketosis, out of which 35.7 % had diabetes and 20% of them had DKA. A few cases of HHA in COVID-19 patients are reported [1].

2. METHODS

Demography, detailed medical history, physical examination, laboratory investigations, including real time RT-PCR-test, computed tomography, imaging studies, treatment given, clinical course and management outcomes were documented prospectively. Informed consent was obtained from the patient for the study. Hyperosmolar hyperglycemic state was defined as: plasma glucose > 600 mg/dl, Effective serum osmolality > 320 mosm/kg, profound dehydration up to an average of 9 l, serum PH <7.30, Bicarbonate concentration > 15 mEq/l, absent ketonemia, small ketonuria, some alterations in consciousness. (According to ADA criteria for HHS).

3. CASE PRESENTATION

Our patient was 70-year old man, who presented with high temperature, weakness, polyuria –polydipsia, weight loss, and signs of urinary tract infection for 2 weeks, the last 2 days with somnolence. He had no clear history of contact with COVID-19 patients. He was initially treated at home with antibiotics for urinary tract infection for almost 2 weeks. The last 2 days his condition worsened and he presented to our emergency department with: somnolence, confusion, psychomotor agitation, body temperature 37.7 °C. He reported no respiratory symptoms or chest pain. He had no history of nausea, vomiting, diarrhea, abdominal pain. The patient reported no prior history of diabetes mellitus and no family history of diabetes mellitus. He was under medication just for Hypertension and recently urinary tract infection. Drugs taken: Corvitol, Aspirine, antibiotics.

Upon examination in the emergency room he was confused, he had difficulty in responding questions, looked dehydrated, respiratory rate 25/min, heart rate 120/min, blood pressure 120/70 mmHg, O2 saturation 96% on room air. Laboratory investigations were significant for hyperglycemia 1202 mg/dl , effective osmolality (344 mosm/kg). Urine and serum ketone bodies were not detected. ABGA on air room showed pH 7.39, HCO3- mmol/l, BEecf -5mmol/l.

The rest of his investigations showed the following:

- *Chest X-ray showed : dexter sub hilar opacity*
- *ECG: normal sinus rhythm*

	Patient's values	*Normal range*
1	BUN : 165 mg/dl	10-43 mg/dl
2	Creatinine : 2.3 mg/dl	0.5-1.2 mg/dl
3	AST : 24 UI/l	0-35 U/l
4	ALT : 45 UI/l	0-45 U/l
5	LDH : 287 UI/l	125-250
6	Total bilirubine 1.0 mg/dl	0.3-1.2 mg/dl
7	Natrium : 141 mmol/l	136-146 mmol/l
8	Kalium : 6.5 mmol/l	3.5-5.1 mmol/l
9	Chloride : 99 mmol/l	101-109 mmol/l
10	WBC : 15.2×10^3/L	4-10×10^3/L
11	Lymphocytes : 8.6 %	17-48 %
12	RBC : 6.15×10^3/L	4.2-6.1×10^6/L
13	Hgb : 18.0 g/dl	11.0-16.5g/dl
14	PLT : 429×10^3/L	150-400×10^3/L

Based on the laboratory results he was diagnosed with HHS and hospitalized in our department (Endocrinology and Diabetology). Treatment was provided with intravenous fluid, oral rehydration, regular insulin, empiric antibiotics and anticoagulants. Hyperglycemia and dehydration were promptly improved after proper management, but the body temperature persisted > 37 °C, so we suspected a COVID 19 Infection. The real time RT-PCR-test resulted Negative for SARS-CoV-2 and the patient underwent a chest computed tomography in day 3 of the treatment, which showed COVID -19 interstitial bilateral pneumonia. The patient refused to be hospitalized in a COVID specialized Hospital so he was discharged home in a stable condition under insulin therapy.

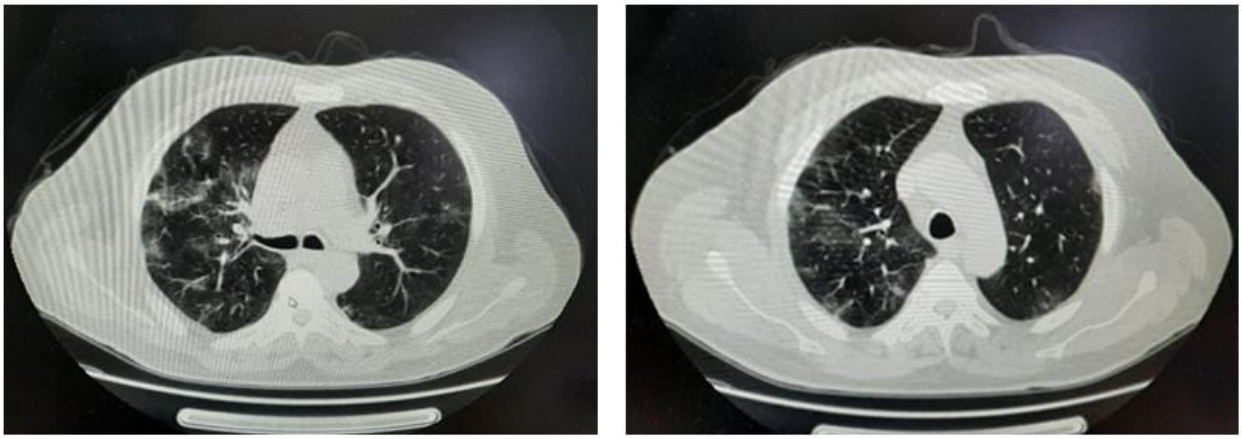

Fig: Axial pictures of CT showing bilateral ground-glass opacities

4. DISCUSSION

Hyperosmolar Hyperglycemic State (HHS) triggered by acute stress such as an infection, acute myocardial infarction or stroke. It's more common in older patients, especially those in nursing homes and not properly hydrated. Together with Diabetic Ketoacidosis (DKA), they pose challenges in clinical management due to the combination of severe hyperglycemia, electrolyte disturbances and additional comorbidities.

SARS-CoV2 pandemic has impacted the health system worldwide and raised various questions regarding the interaction between related medical conditions and the susceptibility to COVID-19 infection and the clinical outcome. The relationship between COVID-19 and diabetes appears to be bidirectional. On the one hand, diabetes is an important risk factor for COVID infection, poor clinical prognosis and death. In a large multicenter study in China, diabetes was a significant risk factor for complications in COVID-19 patients, presented in 26,9% of the patients in intensive care unit, mechanical ventilation and those with fatal outcome [4]. Similar data come from the Center for Disease Control (CDC), evaluating diabetes in 24% of non-ICU patients and 32% of ICU patients [5]. On the other hand, preexisting diabetes or new-onset diabetes associated with severe metabolic disturbances such as diabetic ketoacidosis and hyperosmolar hyperglycemic state have been observed in COVID-19 patients.

There are some previously reported cases of new-onset diabetes, with their first manifestation as DKA and HHS in recently COVID-19 patients. In a case-control study comparing diabetic emergencies presenting to a single center, from 21 patients (10 with DKA and 11 with HHS), 17 were COVID-19 positive on nasal/throat swabs (7 with DKA and 10 with HHS). 3 patients had new-onset diabetes (2 DKA and 1 HHS) [6]. Chee et al [2] reported the case of a 37 year-old previously healthy man who presented with DKA and COVID-19. In a case published by Heany et al [7], a 54 year-old comorbid male presented with new-onset diabetes, DKA and COVID-19 infection. Similar reports of DKA as first presentation of diabetes in COVID-19 patients come from Otair at al [8], Raddy at al [9], Suwanwongse and Shabarek [10]. These clinical observations support the idea of a diabetogenic effect of COVID-19 that goes beyond the recognized stress response associated with severe illness. The question is whether COVID-19 induces new-onset diabetes or just precipitates the clinical manifestation of a previously silent diabetes.

SARS-CoV-2 uses ACE-2 receptors to enter the targeted cells [11]. ACE2 receptors are located in various organs, including pancreas. In a 2009 article, Yang et al [12] reported that SARS coronavirus leads to diabetes via the direct injury of pancreatic islet cells in the infected patients. Moreover, the downregulation of ACE2 after viral entry causes unopposed angiotensin 2 action, which inhibits insulin secretion, eventually leading to enhanced counter-regulatory response. Another mechanism is the exaggerated activation of the pro-inflammatory pathways involving interleukin 6 (IL-6) [13]. The levels of IL-6, which is a very good predictor of disease severity and prognosis, were reported to be higher in diabetic patients [14].

Still there isn't a proven causal relation between COVID-19 and diabetes. In the reported cases of diabetic emergencies, HbA1c was either high or unmeasured (such as in our case). This is an indicator that the further abrupt damage of the pancreatic islet cells leads to a state of insulin deficiency, which together with installed comorbidities and other metabolic disturbances from COVID-19 may precipitate the clinical manifestation of an existing silent diabetes. Still there are

unanswered questions regarding the predisposition of developing diabetes among previously healthy individuals, the factors affecting DKA or HHS presentation of diabetes in infected patients and the further pathogenesis of diabetes after the resolution of COVID-19 infection.

5. CONCLUSION

In conclusion, COVID19 has a diabetogenic effect that is yet to be fully understood. There are a small number of reported cases, including ours where the infected patients develop severe forms of hyperglycemia manifestations such as HHS with an altered metabolic panel and clinical presentation. Since the prevalence of COVID19 in diabetic patients is significantly high, it is required a careful approach towards patients presenting with newly onset diabetes and a recently aggravated symptomatology which might suggest the role of SARS-CoV2 as a potential trigger.

REFERENCES

[1] Zhou F, Yu T, Du R, FanG, Liu Y, Liu Z, XiangJ, Wang Y, Song B, Gu X, GuanL, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factorsfor mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohortstudy. Lancet2020;395:1054-62.

[2] 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 April 24 (Epub ahead of print).

[3] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, vanGoor H. Tissue distribution of ACE2 protein,the functional re- ceptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol2004;203:631-7.

[4] Guan, W-J, Ni, Z-Y, Hu, Y, et al.; China Medical Treatment Expert Group. Clinical characteristics of coronavirus disease 2019 in China [published online ahead of print February 28, 2020]. N Engl J Med.doi:10.1056/NEJMoa2002032

[5] Centers for Disease Control and Prevention . Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12–March 28, 2020 [Internet]. Centers for Disease Control and Prevention; 2020.

[6] M. S. B. Huda S. Shaho B. Trivedi G. Fraterrigo L. Chandrarajan P. Zolfaghari T. M. Dovey C. G. Garrett T. A Chowdhury; Diabetic emergencies during the COVID-19 pandemic: A case–control study

[7] Heaney AI, Griffin GD, Simon EL. Newly diagnosed diabetes and diabetic ketoacidosis precipitated by COVID-19 infection. Am J Emerg Med. 2020. https://doi.org/10.1016/j.ajem.2020.05.114

[8] Hadil A A O, Eman S, Bashayer Zuhair A S, Anwar J. Diabetic Ketoacidosis and New Onset Diabetes Mellitus Precipitated by COVID-19 Infection. JOJ Case Stud. 2020; 11(3): 555815. DOI: 10.19080/JOJCS.2020.11.555815

[9] Pavan Kumar Reddy, Mohammad Shafi Kuchay, Yatin Mehta, Sunil Kumar Mishra,Diabetic ketoacidosis precipitated by COVID-19: A report of two cases and review of literature,Diabetes & Metabolic Syndrome: Clinical Research & Reviews, Volume 14, Issue 5,2020,Pages 1459-1462,ISSN 1871-4021 https://doi.org/10.1016/j.dsx.2020.07.050

[10] Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: Causality or coincidence? A report of three cases. J Med Virol. 2020;1–4. https://doi.org/10.1002/jmv.26339

[11] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052. Epub 2020 Mar 5. PMID: 32142651; PMCID: PMC7102627.

[12] 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(3):193e9.

[13] Sardu C, Gargiulo G, Esposito G, Paolisso G, Marfella R: Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020, 19:76. 10.1186/s12933-020-01047-y

[14] Guo W, Li M, Dong Y, et al.: Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020, 10.1002/dmrr.3319