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Case Report

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Euglycemic Diabetic Ketoacidosis in a Patient with SARS-COV-2 Infection, a Stress Induced Complication or a Coronavirus Related Complication?

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections have affected millions of persons around the globe since first described in December 2019. Coronavirus Disease (COVID-19) is primarily a respiratory tract infection and in severe cases may lead to pneumonia, acute respiratory distress syndrome and death. Diabetes mellitus comprises a serious comorbidity that has been associated with increased risk of adverse outcomes. In these patients, COVID-19 has been associated with increased risk of ketosis and ketoacidosis which is a life-threatening complication. Herein, we describe a case of a SARS-CoV-2 positive patient presenting with symptomatic euglycemic ketoacidosis soon after the initiation of a Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitor. Clinicians should be alert for diabetic ketoacidosis as a consequence of COVID-19 in the context of diabetes since early diagnosis and treatment may favorably affect outcome.

Keywords: COVID-19; SARS-COV-2; Ketoacidosis; Diabetes mellitus; Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitor

Abbreviations: COVID-19: Coronavirus Disease-19; DKA: Diabetic Ketoacidosis; SGLT-2: Sodium-Glucose Cotransporter-2; DM: Diabetes Mellitus

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections has transformed into pandemic after the first case of Coronavirus Disease (COVID-19) was identified in December 2019 in Wuhan [1]. COVID-19 poses a high risk of mortality and morbidity in specific groups of people, including those older than 65 years or people with underlying medical conditions like heart disease, lung disease, diabetes, and chronic kidney disease [2]. Diabetes comprises a serious comorbidity that increases the risk of adverse outcomes in patients with COVID-19. In these patients, clinicians should be alerted to identify and appropriate treat hyperglycemic complications, including Diabetic Ketoacidosis (DKA) and hyperosmolar status. DKA is characterized by elevated blood glucose levels greater than 250 mg/dl, arterial pH<7.30, and increased serum ketone levels (*i.e.* >3 mmol/L) [3]. On the other hand euglycemic ketoacidosis presents with near normal glucose levels (*i.e.* <250 mg/dl) and is considered a rare, but severe adverse event of Sodium-Glucose Co Transporter 2 (SGLT-2) inhibitors [4]. Herein, we report a case of SGLT-2 associated euglycemic ketoacidosis precipitated by SARS-COV-2 infection.

Case Report

An 83-year-old was transferred to the emergency department of our hospital due to a decline in the level of consciousness, drowsiness and reduced food and fluid intake. His medical history included a long-standing type 2 diabetes mellitus (>20 years), benign prostate hyperplasia, arterial hypertension, and new onset dementia. His medications included simvastatin 40 mg, valsartan 160 mg, amlodipine 5 mg, donepezil, metformin 1 gr bid, vildagliptin 100 mg qd, gliclazide 30 mg qd. Several days prior to admission, empagliflozin 25 mg qd was added to his medications. Upon admission, vital signs were as follows: blood pressure 137/70 mmHg, 78 beats per minute, SpO_2 90%, Temperature 36.2°C. Physical examination was unremarkable except for difficulty in naming his close relatives. An arterial blood gas analysis revealed metabolic acidosis with increased anion gap serum ketone levels were 5.7 mmol/L (Table 1); blood glucose was 180 mg/dL (10 mmol/L). Euglycemic DKA associated with an SGLT-2 inhibitor was a provisional diagnosis and treatment was started accordingly. Despite the absence of contact history, a RT-PCR for SARS-COV-2 was obtained which was positive, while a chest x-ray showed evidence of bilateral pulmonary infiltrates. He was transferred to the Infectious Diseases Unit and treatment protocols for COVID-19 and ketoacidosis were instituted. Of note, insulin autoantibodies were positive. The patient remained stable, without any need for supplemental oxygen. Mental status improved; acidosis gradually resolved. The patient was discharged home on day 15 of hospitalization.

Table 1: Laboratory data during patient's hospitalization.

	Day 1	Day 2	Day 3	Day 4	Day 8	Day 12	Day 15
pH	7.09	7.39	7.37	7.34	7.41	7.42	7.43
pCO2 mmHg	13	23	28	26	18	22	30
HCO3 (mmol/L)	8	17	18	17	16	18	21
pO2 mmHg	83	68	74	96	107	71	80
Lactate (mmol/L)	2.1	1.4	1.6	1.2	0.9	0.9	1.3
AG	23	7	7	9	9	9	10
Ketones (mmol/L)	5.9	1.2	0.6	-	-	-	-
WBC (/mm3)	15.73	10850	9410	7720	10360	11020	7480
Lymphocytes	1573	1160	1590	1500	1700	1740	1800
Urea (mg/dL)	80	78	63	38	10	27	28
Creatinine (mg/dL)	1.07	0.91	0.79	0.62	0.59	0.65	0.52
CRP (mg/dL)	99	67	57	28	24	11	11
Feritin (mg/dL)	307	519			295		
LDH (IU/dL)	266	317	618	313	355	292	211

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Table 2: Studies in patients with COVID-19 and DKA.

Author	Type of study	Number of patients	Type of diabetes	SGLT-2 inhibitor use	Outcome	Reference
Croft, et al.	Case series	5	Type 2	no	1 deceased	[7]
Li, et al.	Retrospective cohort	658	Type 1 and type 2 and non-DM	-	9/42 ketosis patients deceased	[8]
Hollstein, et al.	Case report	1	No	no	Discharged	[9]
Pal, et al.	Systematic review	110	Type 2 (77%), new-onset((10%)	7/110	45% deceased	[10]
Smati, et al.	Case report	1	Gestational	no	Discharged	[11]
Batista, et al.	Case report	1	type 2 DM	yes	Discharged	[12]
Palermo, et al.	Case series	2	Type 2 (one) and new-onset(one)	yes (1)	Discharged	[13]
Oriot, et al.	Case report	1	Type 1	yes	Discharged	[14]
Fang, et al.	Case report	1	Type2	yes	Discharged	[15]
Tollard, et al.	Case report	1	New-onset diabetes along with acute pancreatitis	no	Deceased	[16]
Naguib, et al.	Case report	1	New-onset diabetes(8years of age)	no	Discharged	[17]

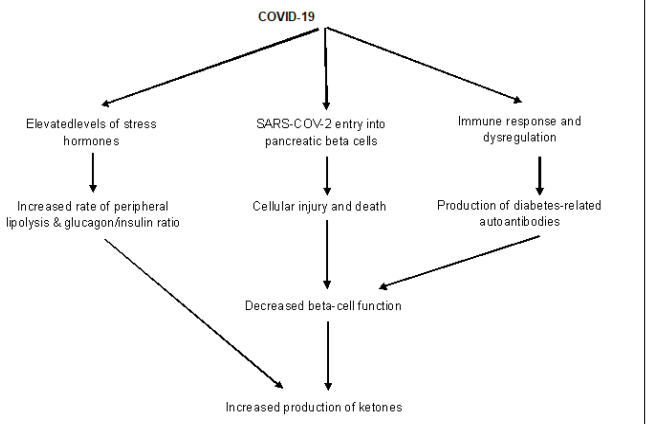

Figure 1: Underlying mechanisms of COVID-19-related ketosis.

Discussion

Diabetic ketoacidosis is a recognized and extremely rare complication of treatment with SGLT-2 inhibitors [5]. Common precipitating factors of SGLT2-associated DKA include fasting, dietary modifications, inter current illnesses (such as serious infections, pancreatitis, cerebrovascular accidents, acute coronary events), surgical stress, insulin insufficiency, inappropriate reduction of insulin dosing and inappropriate management of SGLT2 in the 'periprocedural period' (e.g. colonoscopy). It may present with elevated, normal or near-normal glucose levels, a condition called euglycemic DKA [6]. To our knowledge, this is the first reported case of empagliflozin-associated euglycemic DKA precipitated by SARS-COV-2 infection with positive anti-insulin autoantibodies. COVID-19 is notoriously known for its serious pulmonary manifestations including pneumonia and Acute Respiratory Distress Syndrome (ARDS) which are the main causes of morbidity and mortality in COVID-19 patients. Beside the lung predilection of SARS-COV-2, several extra pulmonary manifestations have been recognized. DKA has been described in patients with COVID-19 in various settings (Table 2). These include case reports denoting new onset DKA in patients with type 2 diabetes [7,8], absence of autoantibodies in insulin dependent diabetes [9] and increased mortality nearing 50% [10]. Of note, euglycemic ketoacidosis has been reported in a COVID-19 patient with gestational diabetes [11]. Euglycemic ketoacidosis in patients receiving SGLT-2 has also been recently described in various clinical settings [12-15]. Finally, DKA has been reported in a patient with acute pancreatitis due to SARS-COV-2 [16] and in a child with multisystem inflammatory syndrome precipitated by SARS-COV-2 infection [17]. Although not fully elucidated, the proposed underlying mechanisms of COVID-19-induced ketosis and ketoacidosis involve (Figure 1):

1. Production of stress hormones is intensified during COVID-19 due to cytokine storm" leading to increased peripheral lipolysis, a raised glucagon to insulin ratio and thus hepatic ketone production,

SARS-COV-2 enters human cells by spiked glycoprotein binding to the Angiotensin Converting Enzyme (ACE)-2 receptors on human cell membranes, in the lungs as well as in a number of extra pulmonary tissues, including pancreatic beta cells [18,19]. The latter has been proposed to cause cell injury and death, and consequently reduced function of beta cells on the islets of Langerhans. These factors may account for the development of ketoacidosis in patients with type 2 diabetes and the development of new onset diabetes mellitus in previously healthy persons.

Immune dysregulation and production of insulin dependent diabetes related autoantibodies could also play a role in the development of both new onset diabetes and diabetic ketoacidosis in patients with COVID-19. This could be the case in our patient who tested positive for anti-insulin autoantibodies.

All in all, COVID-19 has been associated with numerous extra pulmonary manifestations, including new onset diabetes as well as DKA in otherwise previously healthy or stable patients with type 2 diabetes. The presence of high anion gap metabolic acidosis in COVID-19 patients with diabetes mellitus type 1 or type 2 should alert physicians to emergency treatment. Prior treatment with a SGLT-2 inhibitor could be a precipitating factor of euglycemic DKA and should be discontinued.

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