Treatment of a Severe Form of Euglycemic Ketoacidosis in a Patient Treated with SGLT-2 Inhibitors with the Aid of Somatostatin

Nefrologo in corsia

Aristide Torre[1], Nicola Bisogno[1], Carmine Botta[1], Antonella Caiazza[1], Francesca D'Angelo[1], Luigi Del Giudice[1], Pio Fiorentini[1], Luigi Marzano[1], Rita Nigro[1], Dario Sassone[1], Paola Torre[1], Daniela Vicedomini[1]

1 U.O.C. di Nefrologia e Dialisi, Ospedale Umberto I°, Nocera Inferiore (SA)


Aristide Torre

Corresponding author:
Aristide Torre
U.O.C. of Nephrology and Dialysis
Hospital Umberto I° of Nocera Inferiore
Via Alfonso De Nicola 1 84014 Nocera Inferiore (SA), Italia
Tel/Fax 06.3382973073
E-mail: aristidetorre@gmail.com

ABSTRACT
Currently, the use of SGLT2 inhibitors is becoming more widespread, both for their role in controlling diabetes, and for their pleiotropic effects on glomerular hyperfiltration and heart failure. Along with their positive effects, these drugs can lead to various complications, the most severe being euglycemic ketoacidosis. The clinical case we have reported precisely describes this potentially serious complication which occurred in a 47-year-old patient who had been on SGLT2 inhibitor therapy for 5 years. In the resolution of this case we used, in addition to standard therapy, the continuous infusion of somatostatin, resulting in a rapid resolution of ketoacidosis and an improvement in the clinical condition.

KEYWORDS: SGLT-2, somatostatin, euglycemic ketoacidosis

Ogni riproduzione del presente documento, anche parziale, è vietata senza la preventiva autorizzazione della Società Italiana di Nefrologia ai sensi della L. n.633/1941

Introduction

Euglycemic ketoacidosis was first described by Munro in 1973 [1]. It differs from classical DKA due to glycaemic levels below 200 mg/dl [2].

In their genesis, these forms may present an exogenous and/or endogenous insulin deficiency, associated with a reduction in caloric intake and fluids, inducing the increase of insulin counter-regulatory hormones (cortisol, glucagon, catecholamines, etc.). Glucagon promotes glycogenolysis but in the absence of glycogen deposits, it stimulates adipocytes to lipolysis, achieving an increase in free fatty acids that promote ketogenesis in the liver. SGLT2 inhibitors (SGLT2i) are also able to stimulate, in addition to the release of glucagon, the resorption of ketones in the renal tubules to further increase the concentration of ketone bodies [3]. For this reason, even in the presence of normoglycemia in subjects who use these drugs and who have symptoms compatible with a state of acidosis (lack of appetite, nausea, vomiting, tachypnoea, and mental confusion), it seems appropriate to look for the presence of ketones in the urine. In the 1980s, to counteract this effect, a therapy aimed at reducing hyperglycaemic levels through the administration of somatostatin [4] was hypothesized. In fact, the drug was indicated as an adjuvant to the treatment of diabetic ketoacidosis. The most marked benefits seemed to be realized in those forms of DKA where a kind of vicious circle amplified the effects of the glucagon [5]. Over the years, its use became less frequent, both for the improvement of insulin therapies and for the early diagnosis of diabetic disease.

Mechanism of euglycemic ketoacidosis with SGLT2i and Somatostatin action

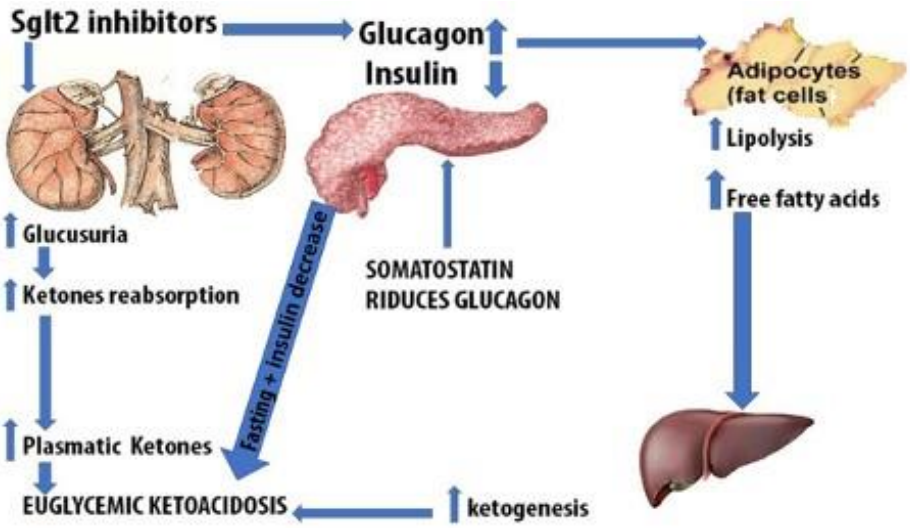

Figure 1. Organs and pathological mechanisms involved in euglycemic ketoacidosis.

SGLT2 inhibitors reduce blood sugar levels by increasing urinary glucose excretion, which in turn reduces insulin secretion from pancreatic beta cells. The decline of the circulating insulin levels results in a diminution of the anti-lipolytic activity of insulin and the consequent stimulation of the production of free fatty acids, which are converted into ketone bodies by β-oxidation in the liver (Figure 1) [3]. The decline of the circulating level of insulin promotes the production of ketone bodies. SGLT2 increase glucagon levels. It is unclear whether SGLT2 directly [6] affects glucagon secretion; the increase of glucagon is probably indirect, and it is mediated by the reduction of the secreted insulin while a direct stimulus on the alpha pancreatic cells has never been demonstrated [7].

Ogni riproduzione del presente documento, anche parziale, è vietata senza la preventiva autorizzazione della Società Italiana di Nefrologia ai sensi della L. n.633/1941

Clinical Case

A 47-year-old woman arrived in the emergency room with strong back pain and polypnea and said she already had it for two weeks with blood pressure of 125/70 mmHg and H.R. 96 b/min. The patient informed that she suffers from type 2 diabetes mellitus since the age of 30. During the anamnesis, she reports to be on treatment with Metformin 1000 mg x 2 and 7 U.I. of Insulin Deglutec to which, in the last 5 years, had been added dapagliflozin 10 mg. A few days before, she did blood chemistry tests, which revealed a 9% glycated haemoglobin. This value led the patient to reduce the caloric intake and dosage of Deglutec insulin from 7 to 3 units. The patient had not had fever, vomiting or diarrhea in the previous days. The tests carried out in the emergency room showed a blood sugar of 150 mg/dl and a normal renal function (Table 3 – exams at time T0), but performing an ABGA, it was found pH 6.9, HCO3 1 mmol/l, K+ 3.4 mmol/l, and lactates 1 mmol/L so that 15 ampoules of 10 meq/10 ml bicarbonate were administered. Presuming it was caused by metformin toxicity, the case was brought to the notice of the nephrology department which, comparing the pharmacological history to the normality level of lactates, quickly made the diagnosis of euglycemic DKA, with high Anion Gap (33.5), secondary to therapy with SGLT2i. An immediate urine test was carried out showing an off-scale glycosuria much higher than 2000 mg/dl, with ketonuria higher than 80 mg/dl. The nephrologist, after the suspension of dapagliflozin, added moisturizing therapy with physiological in glucose 10% and insulin in continuous infusion [8]. After about 10 hours in Emergency with a total infusion of about 2.5 l of liquids, the ABG showed a slight increase in serum bicarbonates, pH slightly above 7, and K+ of 2.9 mmol/l with an extension of QT. Two ampuls of KCL and one of magnesium sulfate were added. Numerous ABGs were repeated, showing a situation that could be superimposed on the previous one, with the continuation of a situation of severe polypnea and back pain.

pH	HCO3 mmol/l	Lactate mmol/l	Na mmol/l	K mmol/l	CL mmol/l	Glycemia mg/dl
6.9	1	1	141	4.3	111	177
7.1	2.8	3.3	144	4.2	111	166
7.009	1.8	2.0	144	3.6	112	160
7.039	1.9	1.9	144	3.5	113	143
7.04	2	1	134	2.9	113	86
7.08	1.4	1	139	3.5	113	104
7.09	4.6	1	135	3.2	113	101
7.08	3.7	1	135	2.9	112	99
7.05	2.5	1	138	3.0	109	170

Table 1. Serial EAB performed during hospitalization in the Emergency Department.

After the administration of 40 ampoules of sodium bicarbonate and with abundant hydrating therapy, the hemodilution had reduced the urate to 2.1, the creatininemia to 0.47 and the Urea to 23 mg/dl (Table 3. Exams at time T1), but the pH (7.05) was still altered so that hydration alone seemed insufficient to resolve the complication. It was decided therefore to transfer the patient to the department of nephrology where the administration of Somatostatin with a dose of 500 mcg/h [9] was started. After starting the administration of Somatostatin, we find the following values in the EAB: While suspending the infusion of bicarbonates due to the presence of hypokalaemia, after about 12 hours from the beginning of the administration of somatostatin, a pH of 7.24 and bicarbonate of 13.4 mmol/l with the disappearance of back pain and polypnea was observed. Continuing somatostatin for the other 24 hours, the pH was 7.32 and HCO3 18.1 mmol/l. In all nine days of hospitalization, the patient continued to have glycosuria higher than 2000 mg/dl and ketonuria higher than 80 mg/dl [10] and reported on the third day the biochemical values highlighted in Table 3 at time T2. The patient was discharged with a pH of 7.34 and HCO3 of 24 mmol/l.

Ogni riproduzione del presente documento, anche parziale, è vietata senza la preventiva autorizzazione della Società Italiana di Nefrologia ai sensi della L. n.633/1941

pH	HCO3 mmol/l	Lactate mmol/l	Na mmol/l	K mmol/l	CL mmol/l	Glycemia mg/dl
7.17	4.7	0.5	133	3	110	139
7.18	8.2	0.5	135	3.2	111	166
7.21	7.7	0.5	135	3	112	170
7.24	13.4	0.5	135	2.8	112	173
7.32	18.1	0.5	134	3.3	110	201
7.34	24.1	0.5	138	3.6	110	162

Table 2. Serial EAB performed during hospitalization in Nephrology.

On discharge he had the biochemical values shown in Table 3 at time T3.

Timing	Creatinine 0.7 – 1.2	Azotemia v.n. 10 – 50	Hemoglobin 13 – 17	Ac. Uric v.n. 3.4 – 7
T0	0.74 mg/dl	23 mg/dl	14 g/dl	4 mg/dl
T1	0.59 mg/dl	18 mg/dl	11.4 g/dl	3.6 mg/dl
T2	0.47 mg/dl	16 mg/dl	11.1 g/dl	2.4 mg/dl
T3	0.33 mg/dl	24 mg/dl	11.1g/dl	1.8 mg/dl

Table 3. Biochemical values recorded in hospitalization timings.

Discussion

The euglycemic ketoacidosis achieved in this case report requires significant consideration, both regarding the selection of patients for whom SGLT2i treatment is appropriate, and the need to implement a therapeutic protocol for this complication that, in rare cases, can be fatal. The administration of Somatostatin with a dose of at least 500 mcg/h [9] in combination with the use of glucose, insulin, hydration, and KCL seems to be an excellent cure for treating this complication [3]. The use of bicarbonates, however, does not improve the clinical picture but promotes the appearance of hypokalaemia; therefore, it is recommended only in cases of pH lower than 7. The prolonged presence of ketonuria higher than 80 mg/dl highlights a prolonged effect of glucagon with the consequential advantage of the use of somatostatin in these forms of euglycemic DKA. The use of this drug has speeded up, in the reported case, the healing timing [11], reducing the ketogenic effects.

A temporary increase in AST/ALT from 24/27 to a maximum of 102/53 was observed during the hospitalization and it could be linked to the hepatic uptake of fatty acids produced by lipolysis. Moreover, anti-Gad antibody dosage and Peptide C with positive C-peptide of 0.02 have been practiced, and this supports the diagnosis of LADA type diabetes (Latent Autoimmune Diabetes in Adults). When prescribing SGLT2i, if there is a doubt between type 1 or type 2 diabetes, a screening with Peptide C should be carried out, combining the dosage of autoantibodies to rule out type 1 diabetes. The anamnesis of the contributory causes also shows how in this type of patient the excessive reduction of carbohydrates and insulin therapy [1] is one of the triggers of this complication even after years from the start of drug administration [12]. All patients with type 2 DM should be educated regarding sufficient hydration and adequate carbohydrate intake while using SGLT2i [3]. Clinicians should avoid using SGLT2i in patients who are unable to tolerate oral food intake or in those who have an excessive drop in body weight or follow a very low carbohydrate diet.

Ogni riproduzione del presente documento, anche parziale, è vietata senza la preventiva autorizzazione della Società Italiana di Nefrologia ai sensi della L. n.633/1941

BIBLIOGRAFIA

1. Thawabi, Mohammad, e Sarah Studyvin. «Euglycemic Diabetic Ketoacidosis, a Misleading Presentation of Diabetic Ketoacidosis». *North American Journal of Medical Sciences* 7, fasc. 6 (giugno 2015): 291–94. https://doi.org/10.4103/1947-2714.157490.
2. Ogawa, Wataru, e Kazuhiko Sakaguchi. «Euglycemic Diabetic Ketoacidosis Induced by SGLT2 Inhibitors: Possible Mechanism and Contributing Factors». *Journal of Diabetes Investigation* 7, fasc. 2 (marzo 2016): 135–38. https://doi.org/10.1111/jdi.12401.
3. Barski, Leonid, Tamar Eshkoli, Evgenia Brandstaetter, e Alan Jotkowitz. «Euglycemic Diabetic Ketoacidosis». *European Journal of Internal Medicine* 63 (maggio 2019): 9–14. https://doi.org/10.1016/j.ejim.2019.03.014.
4. Harano, Y., S. Ohgaku, H. Hidaka, K. Takatsuki, e Y. Shigeta. «Efficacy of Combined Insulin and Somatostatin Infusion for the Treatment of Experimental Diabetic Ketoacidosis». *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme* 11, fasc. 5 (maggio 1979): 338–42. https://doi.org/10.1055/s-0028-1092734.
5. Fallucca, F., F. Barbetti, A. Maldonato, V. Spallone, L. Giangrande, e S. Gambardella. «Effects of Somatostatin on Established Induced Ketosis». *Hormone and Metabolic Research* 14, fasc. 10 (ottobre 1982): 512–15. https://doi.org/10.1055/s-2007-1019064.
6. Saponaro, C., F. Pattou, e C. Bonner. «SGLT2 Inhibition and Glucagon Secretion in Humans». *Diabetes & Metabolism* 44, fasc. 5 (novembre 2018): 383–85. https://doi.org/10.1016/j.diabet.2018.06.005.
7. Chae, Heeyoung, Robert Augustin, Eva Gatineau, Eric Mayoux, Mohammed Bensellam, Nancy Antoine, Firas Khattab, et al. «SGLT2 Is Not Expressed in Pancreatic α- and β-Cells, and Its Inhibition Does Not Directly Affect Glucagon and Insulin Secretion in Rodents and Humans». *Molecular Metabolism* 42 (dicembre 2020): 101071. https://doi.org/10.1016/j.molmet.2020.101071.
8. Gosmanov, Aidar R., Elvira O. Gosmanova, e Erika Dillard-Cannon. «Management of Adult Diabetic Ketoacidosis». *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 7 (2014): 255–64. https://doi.org/10.2147/DMSO.S50516.
9. Greco, A. V., G. Ghirlanda, L. Altomonte, R. Manna, A. G. Rebuzzi, e A. Bertoli. «Somatostatin and Insulin Infusion in the Management of Diabetic Ketoacidosis». *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme* 13, fasc. 6 (giugno 1981): 310–14. https://doi.org/10.1055/s-2007-1019254.
10. Kelmenson, Daniel A., Kelsey Burr, Yusra Azhar, Paul Reynolds, Chelsea A. Baker, e Neda Rasouli. «Euglycemic Diabetic Ketoacidosis With Prolonged Glucosuria Associated With the Sodium-Glucose Cotransporter-2 Canagliflozin». *Journal of Investigative Medicine High Impact Case Reports* 5, fasc. 2 (2017): 2324709617712736. https://doi.org/10.1177/2324709617712736.
11. Yun, Y. S., H. C. Lee, C. S. Park, K. H. Chang, C. H. Cho, Y. D. Song, S. K. Lim, K. R. Kim, e K. B. Huh. «Effects of Long-Acting Somatostatin Analogue (Sandostatin) on Manifest Diabetic Ketoacidosis». *Journal of Diabetes and Its Complications* 13, fasc. 5–6 (1999): 288–92. https://doi.org/10.1016/s1056-8727(99)00059-8.
12. Fadini, Gian Paolo, Benedetta Maria Bonora, e Angelo Avogaro. «SGLT2 Inhibitors and Diabetic Ketoacidosis: Data from the FDA Adverse Event Reporting System». *Diabetologia* 60, fasc. 8 (agosto 2017): 1385–89. https://doi.org/10.1007/s00125-017-4301-8.

Ogni riproduzione del presente documento, anche parziale, è vietata senza la preventiva autorizzazione della Società Italiana di Nefrologia ai sensi della L. n.633/1941