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KETOACIDOSIS GENERATED BY TREATMENT WITH SGLT-2 INHIBITORS – A CASE REPORT

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Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a relatively recent class of oral glucose lowering drugs used in treatment of type 2 diabetes mellitus. The benefits of treatment with SGLT-2 inhibitors are: significant reductions of HbA1c and plasma fasting glucose, low risk of hypoglycaemia, weight loss, reduction in blood pressure. There is strong emerging evidence suggesting that the class of SGLT-2 inhibitors have major cardioprotective effects. Adverse event of treatment are represented by the risk of developing urinary tract infections and genital infections, increase the risk of fractures and lower limb amputation, ketoacidosis. A 44-year old Caucasian women without family history of diabetes is admitted in 2019 to the National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest in the following context: diagnosed with type 2 diabetes mellitus in November 2018 for which he received treatment with SGLT-2 inhibitor 10 mg/day ;three months after starting treatment, she was diagnosed with severe euglycemic ketoacidosis and admitted to the hospital in United Kingdom. She was diagnosed with type 1 diabetes and received basal bolus insulin therapy. At admission to the National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, patient presented important glycemic imbalance, hypercholesterolemia, alteration of thyroid function and autoantibodies to glutamate acid decarboxylase in normal range. Measures for lifestyle optimization, continued basal bolus insulin therapy, hyperlipidemia treatment and endocrine evaluation for the initiation of synthetic anti-thyroids drugs were recommended. Euglycemic ketoacidosis was considered as a consequence of treatment with SLGT-2 inhibitor, the precipitating factor being hyperthyroidism. Prospective studies developed over a long period of time are necessary to establish the clear relationship between ketoacidosis and treatment with SGLT-2 inhibitors. It is important to identify predisposing and precipitating factors and adapt therapy in order to reduce the risk of ketoacidosis.

Key words*:* diabetes mellitus, sodium-glucose cotransporter-2 inhibitors, ketoacidosis.

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (SGLT-2i) are a relatively recent class of diabetes oral drugs used in treatment of type 2 diabetes (T2DM). SGLT-2 inhibitors inhibit renal reabsorption of glucose in the proximal convoluted tubules and increase glucose excretion in the urine[1,2]. The amount of glycosuria depends on the level of hyperglycemia and the glomerular filtration rate[3]. The main representatives of this therapeutic class are: canagliflozin, dapagliflozin and empagliflozin. Only dapagliflozin and empagliflozin are currently reimbursed and prescribed in Romania.

SGLT-2 inhibitors under administration as monotherapy or in association with other glucose-lowering drugs in T2DM subjects generated robust (and statistically significant) reductions of glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG)[3]. SGLT-2i treatment has a low risk of hypoglycemia since the level of glycosuria declines as the plasma glucose level decreases[4]. Treatment with SGLT-2i generated glycosuria associated with caloric elimination and weight loss[5, 6]. In addition, osmotic diuresis and natriuresis with reduction in blood pressure is induced by SGLT-2i[1].

There is strong emerging evidence suggesting that the class of SGLT-2 inhibitors has major cardio protective effects. The main underlying cardio protective effects could be explained by

improvements in cardiac metabolism and bioenergetics, amelioration of ventricular loading conditions, restoration of the equilibrium between the pro and ant-inflammatory adipokines, reduction of cardiac fibrosis and necrosis etc.[7]. This is why in 2019 the American Diabetes Association made the following recommendation: "*Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit" and "Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred"*[8].

The most frequent adverse effects of SGLT-2i treatment are represented by the increased risk of developing urinary tract infections and genital infections[9,10]. In addition, treatment with SGLT-2 inhibitors was reported to influence bone density and lead to an increase risk of fractures[11,12]. Increased risk of lower limb amputation was reported for canagliflozin[13,14]. Overall, SGLT-2i are associated with a slightly increased risk of ketoacidosis[15,16].

CASE REPORT

A 44-year old Caucasian women without a family history of diabetes was admitted in 2019 to the National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest in the following clinical context:

- diagnosed with T2DM in November 2018 for which she received treatment with SGLT-2 inhibitor 10 mg/day;
- three months after starting treatment (January 2019), she was diagnosed with severe euglycemic ketoacidosis (pH: 6.9, FPG level 240 mg/dl) and admitted to the hospital in United Kingdom. She was re-classified as a type 1 diabetes (T1DM) case and received basal bolus insulin therapy.

At admission in the National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, patient presented important glycemic imbalance (FPG 317 mg/dl, HbA1c: 9.3%), hypercholesterolemia (total cholesterol: 266 mg/dl, low-density lipoprotein-cholesterol: 185 mg/dl), alteration of thyroid function (thyroid–stimulating hormone – TSH: 0.005 µIU/ml and anti-thyroid peroxidase – ATPO: 293 UI/ml) and autoantibodies to glutamate acid decarboxylase – GADA <5 IE/ml.

Measures for lifestyle optimization, continued basal bolus insulin therapy, hyperlipidemia treatment and endocrine evaluation for the initiation of synthetic antithyroid drugs were recommended. Euglycemic ketoacidosis was considered as a consequence of treatment with SLGT-2 inhibitor, the precipitating factor being hyperthyroidism.

DISCUSSIONS AND CONCLUSION

In 2015, the "*Food and Drug Administration (FDA) Adverse Event Reporting System Database*" reported 20 DKA cases in SGLT-2i treated patients from March 2013 to June 2014. It is worth mentioning that ketoacidosis is not typically observed in patients with T2DM and case presentations had only mildly elevated glucose levels[17]. Ketoacidosis associated with SGLT-2i treatment is a rare adverse event and fatal episodes represented only 1.6% of total SGLT-2i associated DKA cases[18]. In a review published in 2017 in Diabetologia, Fadini GP *et al.* provide analysis of ketoacidosis reports associated with treatment with SGLT-2 inhibitors from the "*Food and Drug Administration Adverse Event Reporting System*" between 2014 and 2016; the 2397 ketoacidosis reports associated with treatment with SGLT-2 inhibitors revealed a predominance of women. In 37 patient ketoacidosis was fatal[19].

Biological mechanisms for the increased risk of DKA generated by SGLT-2i include increased glucagon levels, insulin deficiency and negative glucose balance. Precipitating factor such as dehydration, excess alcohol intake, infection or the acute medical conditions including hyperthyroidism, surgery can trigger acidosis in SGLT-2i treated subjects[18]. The number of cases of ketoacidosis associated with treatment with SGLT-2 inhibitors is expected to rise with the increasing use of this treatment. Limenta M *et al*, in a review published in 2018 about SGLT-2 inhibitors treatment and diabetic ketoacidosis, recommend paying special attention to this potentially severe side effect especially during the first 6 months of treatment and more in female patients[20]. Ketosis/ketoacidosis has been mentioned in diabetic patients with hyperthyroidism or acromegaly in treatment with SGLT-2 inhibitors[21,22].

Prospective studies developed over a long period of time are necessary to establish the clear relationship between ketoacidosis and treatment with SGLT-2 inhibitors. It is important to identify predisposing and precipitating factors and adapt therapy in order to reduce the risk of ketoacidosis.

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