Case Report

Euglycemic diabetic ketoacidosis - a rare side effect of sodium-glucose co-transporter-2 inhibitor in a patient of type 2 diabetes mellitus with left ventricular dysfunction: a case report

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ABSTRACT

A 42 year old female with type 2 diabetes mellitus (T2DM), presented with angina on exertion and left ventricular (LV) dysfunction (global LV ejection fraction (EF)=26%). Patient was subjected to coronary angiography which revealed triple vessel disease. Patient was started on usual standard of care heart failure (HF) medications, including sodium-glucose co-transporter-2 (SGLT-2) inhibitor dapagliflozin which is promising new class of drug for treating T2DM and HF. Patient was advised myocardial revascularization in form of percutaneous transluminal coronary angioplasty (PTCA). Post angioplasty patient developed metabolic acidosis (high anion gap with normal lactate and increased ketone levels). Patient was diagnosed as case of euglycemic diabetic ketoacidosis (DKA) and patient was treated by volume resuscitation and insulin infusion.

Keywords: Type 2 diabetes mellitus, Diabetic ketoacidosis, SGLT-2

INTRODUCTION

The risk of cardiovascular diseases, myocardial infarction (MI) and congestive heart failure (CHF) are increased 5 folds in individuals with type 2 diabetes mellitus (T2DM) as stated in the Framingham heart study. Novel glucose lowering therapy with sodium-glucose co-transporter-2 (SGLT-2) inhibitors have proven to lower cardiovascular mortality with an unprecedented 38% relative risk reduction. Lehrke et al.1 SGLT-2 inhibitors act on the proximal tubule in the kidney and inhibit glucose reabsorption, lower renal threshold for glucose and lead to increased urinary glucose excretion. Role in heart failure (HF) has been demonstrated by improved cardiomyocyte calcium handling, enhanced myocardial energetics and induced autophagy, Shruti et al.2 During intercurrent volume-depleting illnesses with other metabolic stressors, inhibition of SGLT-2 on the alpha cell may lead to increased glucagon secretion and liver production of glucose and ketones which may lead to euglycemic diabetic ketoacidosis (DKA).

CASE REPORT

A 42 year old female with type 2 diabetes, presented with complaint of chest pain and dyspnea on exertion. 2D echo revealed regional wall motion abnormalities (RWMA) (mid anterior and mid distal septum, apex and apical anterior wall, basal mid inferior wall, mid posterior wall and basal inferior septum akinetic) with left ventricular (LV) dysfunction and rEF=26% with type 3 diastolic dysfunction. After stabilization, patient was subjected to angiography which revealed Triple vessel disease. Myocardial revascularization was planned in form of
percutaneous transluminal coronary angioplasty (PTCA) to right coronary artery (RCA)/left anterior descending (LAD)/left circumflex (LCX) which was successfully achieved with multiple DES as a staged procedure. Post angioplasty, patient complained of shortness of breath, and nausea. On examination, her respiratory rate was 24 breaths/min with altered breathing pattern. A random blood glucose test showed 139 mg/dl. Arterial blood gas analysis revealed metabolic acidosis (pH=7.2) with an increased anion gap of 31 mmol/l, and bicarbonate 2.2 mmol/l. Serum lactate level was normal. A bicarbonate drip was started to correct severe acidemia. Because the patient had been using dapagliflozin in the recent perioperative period, screening for DKA was initiated. A urinalysis revealed sugar 4+ and ketones positive. Serum ketone levels were 6.9 mmol/l. A diagnosis of euglycemic diabetic ketoacidosis, presumably related to SGLT-2 inhibitor therapy, was made. The patient was started on treatment with fluid resuscitation and insulin infusion, leading to closure of the anion gap acidosis.

| Parameters                  | Baseline | During euglycemic DKA | Recovery phase |
|-----------------------------|----------|-----------------------|----------------|
| Hematocrit (%)              | 25.1     | 28.2                  | 22.1           |
| TLC                         | 9800     | 21400                 | 21200          |
| Sodium (mmol/l)             | 134.66   | 130                   | 132            |
| Potassium (mmol/l)          | 4.13     | 5.67                  | 5.05           |
| Chloride (mmol/l)           | 99.2     | 100.1                 | 102.5          |
| Blood urea nitrogen (mg/dl) | 11.4     | 11.9                  | 12.5           |
| Creatinine (mg/dl)          | 0.65     | 0.95                  | 0.72           |
| pH                          | 7.2      | 7.4                   |                |
| PCO2 (mmHg)                 | 5.7      | 24.4                  |                |
| Anion gap                   | 31       | 9.3                   |                |
| Lactate (mmol/l)            | 1.57     | 0.90                  |                |
| Serum ketones (mmol/l)      | 6.9      |                       |                |

**DISCUSSION**

Whereas DKA is defined by the triad of hyperglycemia, ketosis, and high anion gap metabolic acidosis, current definitions of euglycemic DKA include blood glucose level <250 mg/dl, which can result in delayed diagnosis and treatment. Causes associated with euglycemic DKA include therapy with SGLT-2 inhibitors, pregnancy, intercurrent illness decreased caloric intake, reduced insulin doses, dehydration, extensive exercise, surgery, heavy alcohol use, cocaine abuse, pancreatitis, sepsis and liver cirrhosis, Barski et al.³

Packer et al demonstrated the role of SGLT-2 inhibitors in heart failure.⁴ The drug has been shown to reduce oxidative stress, ameliorate mitochondrial dysfunction, and attenuate proinflammatory pathways to potentially promote autophagy and upregulate sirtuin-1 (SIRT1) which regulates cellular stress. The drugs maintain ionic homeostasis in the myocardium, improve myocardial contractility, reverse adverse cardiac remodelling, and have diuretic and antihypertensive effects, thus yielding important cardioprotective effects.

Docherty et al described that in diabetic patients with HF, the reductions in the risk of worsening HF and cardiovascular death with dapagliflozin is found and it is recommended as first-line monotherapy.⁵

The European Medicines Agency (EMA) announced on 12 June 2015 that the pharmacovigilance risk assessment committee has started a review of the approved SGLT-2 inhibitors to evaluate the risk of DKA, which claimed that as of May 2015 a total of 101 cases of DKA have been reported worldwide with an estimated exposure over 0.5 million patient-years, Rosenstock et al.⁶

Reported rates of euglycemic DKA during clinical trials have been rare: 0.76, 0.6 and 0.24 per 1,000 patient-years for canagliflozin, dapagliflozin and empagliflozin, Mosley et al.⁷ FDA issued a drug safety communication that warns of an increased risk of DKA with uncharacteristically mild to moderate glucose elevations (euglycemic DKA) associated with the use of all the approved SGLT-2 inhibitors, based on 20 clinical cases requiring hospitalization between March 2013 and June 2014 in the FDA adverse event reporting system database, Taylor et al.⁸

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**Mechanism of euglycemic DKA**

DKA results from relative or absolute Insulin Deficiency combined with counter regulatory hormone excess. Decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, through activation of enzyme carnitine palmitoyl transferase. At physiological pH ketone bodies exist as ketoacids, which are neutralized by bicarbonates. As bicarbonate stores are depleted, metabolic acidosis ensues. Increased lactic acid production also contributes to acidosis, Wang et al.⁹

**Laboratory abnormalities**

Patients present with increased anion gap metabolic acidosis with ketosis. Arterial pH is between 6.8 and 7.3 depending upon the severity of acidosis. Despite a total body potassium deficit, the serum levels may be mildly elevated, secondary to acidosis and volume depletion. Total body stores of serum sodium are reduced as a consequence of diuresis due to SGLT2 inhibitors.
of the hyperglycemia (1.6 mmol reduction for every 100 mg/dl rise in serum glucose). Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Leukocytosis is a common finding. In DKA, the ketone body beta hydroxy butyrate, is synthesized at a greater rate than acetoacetate which is detected in the serum. However acetoacetate is detected in urine by a nitroprusside reagent.

Treatment

Initial treatment is directed towards volume resuscitation with isotonic saline. Continuous intravenous insulin infusion at a rate of 0.02–0.05 units/kg/hour is started. Dextrose-containing fluids should be started along with the insulin infusion to avoid hypoglycemia, with a target serum glucose level of 150–200 mg/dl. Serum electrolytes and glucose levels should be monitored closely during the treatment course. Resolution of euglycemic DKA is identified by the presence of two of the following: a serum bicarbonate level ≥15 mmol/l, an anion gap ≤12 mmol/l, or a pH>7. Ramoz et al.10

Figure 1: Mechanism of euglycemic DKA.

CONCLUSION

Due to the promising cardioprotective effects of SGLT-2 inhibitors, these drugs are the recommended therapy in T2DM with HF. These drugs should be used cautiously in patients who are at risk for euglycemic DKA due to intercurrent volume-depleting illnesses, with other metabolic stressors. SGLT-2 inhibitors can be withheld in patients when precipitants for euglycemic DKA develop. From intervention cardiologist perspective, being aware of such side effect of the drug is important because post angioplasty metabolic acidosis is frequently associated with contrast induced nephropathy whose treatment is totally different. For hospitalized patients prescribed SGLT-2 inhibitors who develop high-anion-gap metabolic acidosis, despite euglycemic status, clinicians should maintain a high index of suspicion for euglycemic DKA so that appropriate therapy can be provided in a timely manner.

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