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Case Report

Empagliflozin-induced Myopathy

Sana Khan[1] **and Ashley Broce**[1]

[1]Freeman Health System, KCU-GME Consortium, Joplin, MO 64804, USA

Correspondence: Sana Khan, MD, Freeman Health System, KCU-GME Consortium, 1102 W. 32nd, St, Joplin, MO 64804, USA. Email: san.khan840@gmail.com, skhan3@freemanhealth.com.

Abstract

Sodium/glucose co-transporter 2 (SGLT2) inhibitors are a frequently used medication for patients with type 2 diabetes, congestive heart failure (CHF), and chronic kidney disease. We present a 47-year-old patient with past medical history of type 2 diabetes and CHF who was initiated on empagliflozin and subsequently developed muscle pain and weakness. Evaluation of patient and laboratory testing confirmed drug-induced myopathy with elevated creatinine kinase (CK). Symptoms of myopathy and elevated CK resolved after holding empagliflozin. There are no current adverse effects listed with SGLT2 inhibitors including myopathy or rhabdomyolysis with the exception of other case studies. Physicians should be aware of this rare but serious side effect when initiating SGLT2 inhibitors.

Key Words: myopathy, SGLT-2 inhibitors, diabetes

Introduction

Sodium/glucose co-transporter 2 (SGLT2) inhibitors are commonly used as adjuvant or alternative monotherapy for patients with diabetes in whom initial therapy with lifestyle intervention and metformin failed. SGLT2 inhibitors are also indicated in conditions like chronic kidney disease or congestive heart failure (CHF) due to their benefits such as improved mortality and reduced hospitalizations [1, 2]. There are known complications from SGLT2 inhibitors such as genitourinary bacterial and yeast infections and mild volume loss. Rare but serious side effects include diabetic ketoacidosis and necrotizing fasciitis to the perineum [1]. There is little information about SGLT2 inhibitors causing myopathy. Here we present a case of empagliflozin-induced myopathy in a patient taking this medication for diabetes and CHF.

Case Presentation

Our case is a 47-year-old male with a past medical history of type 2 diabetes, heart failure with preserved ejection fraction, and chronic obstructive pulmonary disease treated with insulin and dulaglutide for the management of diabetes. Of note, the patient was not on any statins and has been on evolocumab 140 mg/mL every 2 weeks for hyperlipidemia as he has a history of statin-induced rhabdomyolysis requiring hospitalization. He was recently started on empagliflozin 25 mg once daily by his endocrinologist due to its known renal and cardiovascular benefits along with need for glycemic control due to a most recent hemoglobin A1c of 8.42% (normal <5.7%). Within a week of initiating the SGLT2, the patient developed significant pain in his bilateral lower extremities. He described the pain as constant aching in his legs and thighs with no specific aggravating or alleviating factors. He also reported symptoms were similar to when he had myopathy from statins. He denied any recent trauma or fall and denied taking any other new medications or herbal supplements. The medication list was reviewed and did not reveal any common causes of myopathy. His home medications included insulin lispro, insulin glargine, dulaglutide, evolocumab, gabapentin, atenolol, bupropion, ziprasidone, rimegepant, galcanezumab, atenolol, and albuterol inhaler. His pain continued to get worse, and he sought care at the emergency department. The patient did not reveal any complaints of weight loss, change in urination, or feeling thirsty since starting empagliflozin.

His physical examination by the emergency room physician revealed vital signs within normal limits. The skin examination showed no erythema, subcutaneous edema, or lesions. No evidence of dehydration was noted clinically. The musculoskeletal examination revealed no joint effusions, and his range of motion was normal. Neurological examination indicated intact strength in both upper and lower extremities, with 5 out of 5 strength tests showing successful muscle activation against full resistance from the examiner. Both light and deep palpation along with resistance testing caused the patient discomfort and tenderness in the bilateral thighs and legs. Deep tendon reflexes were normal, and sensation was intact throughout. The remainder of the physical examination was unremarkable.

Diagnostic Assessment

Laboratory work was remarkable for elevated creatinine kinase (CK) of 958 U/L with the normal range being 39 to 308 U/L. Glucose was elevated at 206 mg/dL (11.43 mmol/L) (normal range 74-99 mg/dL, 3.9-5.5 mmol/L). Creatinine was at baseline 0.93 mg/dL (82.2 µmol/L), with estimated glomerular filtration rate >60 mL/min/1.73 m^2 (normal 0.67-1.17 mg/dL, 53-106 µmol/L). Magnesium was in range at 2.4 mg/dL (0.99 mmol/L) (normal 1.6-2.6 mg/dL, 0.65-1.05 mmol/L). Urinalysis was negative for blood or red blood cells. He had

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a mild elevation of liver enzymes, which was near the patient's baseline. His aspartate aminotransferase was 64 U/L, alanine aminotransferase 117 U/L (normal <40 U/L), and alkaline phosphatase 138 U/L (normal 40-129 U/L). Previous evaluation of this was consistent with metabolic dysfunction-associated steatotic liver disease with an ultrasound of the liver showing hepatomegaly with hepatic steatosis. Autoimmune workup for evaluation of myositis was unremarkable, including a negative antinuclear antibody and normal erythrocyte sedimentation rate of 21 mm/hr (normal 0-15 mm/hour).

Treatment

With symptoms consistent with myopathy including lower extremity pain along with elevated CK, which began after the initiation of empagliflozin, the offending agent was discontinued. The patient was also given intravenous fluids in the emergency department to help prevent worsening symptoms and rhabdomyolysis.

Outcome and Follow-up

The patient was discharged home with instructions to follow up with his primary care physician. On follow-up at our resident clinic, he reported significant improvement in his muscle pain and weakness after stopping empagliflozin with complete resolution within 2 weeks. His repeat laboratory work showed CK was downtrending with a most recent level of 215 U/L. On physical examination, the patient's pain and strength had returned to normal in all extremities. With the resolution of his symptoms and negative screening inflammatory testing, further laboratory or imaging testing for autoimmune causes of myopathies were deferred.

Discussion

Many drugs are known to cause myopathies and rhabdomyolysis. These include statins, antimalarial medications (chloroquine/hydroxychloroquine), and glucocorticoids, among others [3]. Empagliflozin or dapagliflozin are not classically known to cause myopathy or rhabdomyolysis. Commonly known adverse reactions of empagliflozin are genital candidiasis (due to glycosuria), dyslipidemia, increased thirst, increased urinary tract infection frequency, skin rash, hypovolemia, and rarely ketoacidosis and necrotizing fasciitis [1]. SGLT2 inhibitors-induced myopathy/rhabdomyolysis is a rare adverse reaction. Literature reviews showed only a few case reports are available, reporting myopathy and rhabdomyolysis [4-6]. Symptoms of muscle-related adverse events can range from asymptomatic CK elevation to myalgia and severe rhabdomyolysis with acute renal failure. Risk factors for myopathy include concomitant use of steroids and statin use [3, 7]. Kabadi et al in their case report described a case of marked weight loss, muscle wasting, and fatigue on the administration of empagliflozin as early as within 2 weeks [5]. Gupta et al also discussed the accelerated loss of muscle mass and function and the potentiation of statin-induced myotoxicity in patients taking SGLT2 inhibitor agents [7]. Our patient had not experienced recent weight loss or symptomatic dehydration after starting the medication. However, our patient did have a history of a significant reaction to multiple statins in the past including rhabdomyolysis secondary to atorvastatin requiring hospitalization. Prior case reports have shown the myopathy to occur while patients were concurrently taking statin therapy, which may have predisposed symptoms to occur by affecting metabolism of medication [6].

A number of mechanisms for drug-induced myopathy have been delineated, including direct cell toxicity and immunologic or inflammatory myopathy. Most drug-induced myopathies occur due to direct toxic effect interfering with metabolic pathways on muscles, causing myocyte apoptosis. This muscle toxicity resolves after withdrawal of the medication [3, 7]. SGLT2 inhibitors lower blood glucose levels mainly by inhibiting glucose reabsorption from the proximal tubules. There is, however, a possibility that SGLT2 inhibitors could increase energy expenditure and hypoxia in the kidney medulla. A low-glucose environment and hypoxia can stimulate gluconeogenesis in the liver, resulting in lipolysis, which reduces body fat. Muscle atrophy in patients with diabetes mellitus type 2 caused by SGLT2 inhibitors may be linked to the fact that SGLT2 inhibitors activates gluconeogenesis, promotes lipolysis, and facilitates the breakdown of muscle proteins into amino acids, which are then utilized by the liver as substrates. However, the exact mechanism remains debatable [8]. It is also unclear if patients with history of myopathy remain at higher risk for future drug-induced myopathy, but it would be reasonable to educate patients to notify physicians of development of recurrent symptoms.

It is also recommended to consider other differentials and order necessary lab workup to rule out other possibilities. This patient did not have any evidence of autoimmune causes, and other medications were reviewed. Treatment of myopathy includes stopping the medication and using alternative agents. Symptoms usually improve within 2 to 6 weeks after stopping the offending medication.

In conclusion, we present the case of a patient with drug-induced myopathy secondary to empagliflozin. With the increasing use of SGLT2 inhibitors, physicians need to consider drug-induced myopathy in patients presenting with muscle pains and taking these agents, as early recognition and diagnosis can prevent further morbidity and complications.

Learning Points

- SGLT2 inhibitors are commonly used medications in patients with type 2 diabetes, CHF, and chronic kidney disease due to benefits such as reduced morbidity and mortality.
- The most common side effects of SGLT2 inhibitors include genitourinary bacterial and yeast infections and euglycemic diabetic ketoacidosis, and they may be a rare cause of drug-induced myopathy.
- Drug-induced myopathy should be suspected if symptoms of myalgia, fatigue, and muscle weakness can be temporally connected to use of a drug. Improvement or resolution of the symptoms after discontinuation of the drug helps confirm the diagnosis of drug myopathy. This can be associated with or without elevated CK.

Contributors

All authors made individual contributions to the authorship. A.B. was involved in the diagnosis and management of this patient along with manuscript preparation. S.K. was involved in the preparation of the manuscript and additional research. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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