A CASE OF SEVERE INSULIN RESISTANCE IN A DIABETIC PATIENT BEING TREATED FOR ACUTE PROMYELOCYTIC LEUKEMIA WITH ARSENIC AND GLUCOCORTICOIDS

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OBJECTIVE

To present a case of severe insulin resistance in a patient with a new diagnosis of acute promyelocytic leukemia (APML) treated with all-trans retinoic acid (ATRA), arsenic, and high-dose glucocorticoids.

CASE PRESENTATION

A 32- year-old male with a past medical history of type 2 diabetes and a recent hemoglobin A1c (HgA1c) of 5.8% on no medications, hypertension, morbid obesity (Body Mass Index of 45.3 kg/m2), migraines, and chronic back pain presented to the emergency department after he was found to be thrombocytopenic on outpatient labs. Diabetes was diagnosed two years ago with an HgA1c of 12.1%, while periodically taking steroids for migraines and back pain. In the emergency department, he reported one month of bruising on his arms and legs, epistaxis occurring two to three times a day, bleeding gums at the dentist and night sweats. A blood smear confirmed a diagnosis of APML. Treatment for APML was urgently started with ATRA, 22.5 mg daily of arsenic trioxide and 10 mg twice a day of intravenous dexamethasone. His blood glucose gradually increased and by day three of treatment, his blood glucose was greater than 400 mg/dL, beta-hydroxybutyrate was 30 mg/dL (0.2-2.8 mg/dL) and anion gap was 25 mmol/L (4-16 mmol/L), consistent with diabetic ketoacidosis (DKA). An insulin drip was started with requirements up to 25 units/hr on day one, 300 units/hr on day two, and 999 units/hr on day three. The patient's blood glucoses remained 350-400 mg/dL with persistent DKA. Insulin was concentrated to 4 units/mL on day four and peaked at a rate of 600 units/hr (equivalent to 2400 units/hr at the standard 1 unit/mL concentration) before blood glucoses trended down and DKA resolved. Arsenic treatment was given for ten days and dexamethasone was tapered over a total of seven days. The insulin infusion was discontinued after ten days and the patient was transitioned to subcutaneous insulin and discharged on 15 units of basal insulin daily with 3 units of rapid acting insulin with meals.

The patient followed up with oncology and family medicine after discharge. He stopped using insulin since he reported blood glucoses consistently less than 100 mg/dL at home. However, his glycemic control has worsened with blood glucoses mostly in the 175-275 mg/dL range since restarting cycles of arsenic trioxide as consolidation chemotherapy for APML. He has not received glucocorticoids since discharge. His HgA1c is being rechecked and his physicians will likely need to restart insulin or at least add oral antidiabetic medications.

DISCUSSION

Glucocorticoids cause hyperglycemia and insulin resistance by complex mechanisms involving genomic and non-genomic pathways in beta-cells, hepatocytes, adipocytes, and skeletal muscle.[1-3] More specifically, glucocorticoids reduce the uptake and oxidation of glucose and may reduce insulin secretion by decreasing the efficacy of calcium on the secretory process.[2] The patient was susceptible to significant hyperglycemia and insulin resistance with glucocorticoid exposure, as his HgA1c was 12.1% when he was diagnosed with diabetes two years earlier while periodically taking steroids for migraines and back pain. While glucocorticoids are a common and well known cause of hyperglycemia in the hospital setting, the degree of insulin resistance was extreme, with requirements of insulin per hour that have rarely been reported.

Arsenic treatment may also have been a major contributor to the severe insulin resistance. Arsenic has been shown to cause beta-cell dysfunction and insulin resistance in mice.[4,5] The mechanism likely involves interference with transcription factors involved in insulin-related gene expression and production of reactive oxygen species.[4,5] In addition, several studies have shown an association between arsenic and diabetes in areas with relatively high levels in the drinking water.[6-9] While chronic exposure to relatively low levels of arsenic has been associated with higher rates of diabetes, acute insulin resistance and rates of diabetes after short-duration and high-dose exposure to arsenic has not been comprehensively studied.

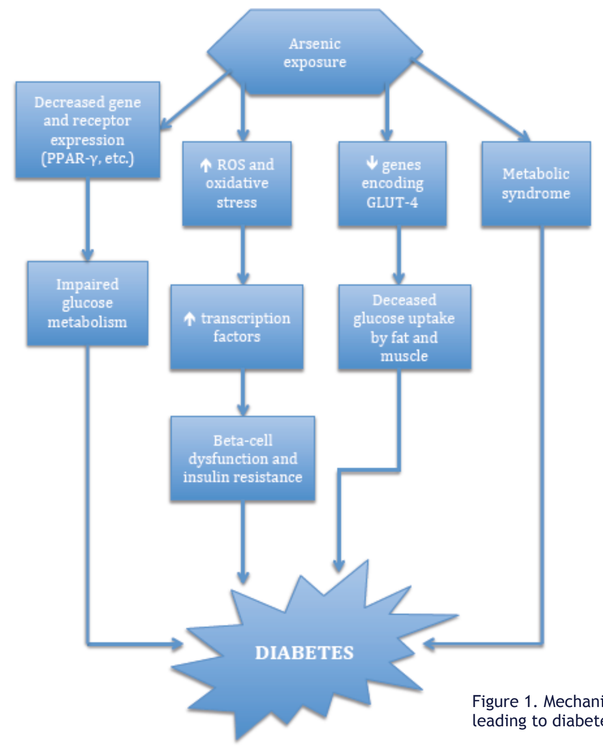

Figure 1. Mechanisms of arsenic leading to diabetes

CONCLUSION

The combination of high-dose glucocorticoids and arsenic induced a state of severe insulin resistance in this patient with a new diagnosis of APML. Once glucocorticoids were tapered and arsenic treatment was completed, the patient transitioned from a high dose insulin infusion to relatively low dose subcutaneous insulin. More research is needed on the effects of chronic and acute arsenic exposure with regard to its impact on insulin resistance and the development of diabetes.

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