Case study

Topic- Euglycemic Diabetic Ketoacidosis in a patient of Type 2 DM on Alternative Medicine precipitated by dengue infection.

ABSTRACT

AIM

Diabetic ketoacidosis (DKA) is a serious acute complication of diabetes mellitus (DM) that can become life threatening. DKA is recognized by hyperglycemia ,metabolic acidosis and presence of serum and/or urine ketones. DKA can occur with only a moderate increase in blood glucose (BG) levels or, in rare instances, in the setting of normal glucose concentrations. This latter, uncommon form of DKA, known as euglycemic or normoglycemic DKA .The aim of this case report is to alert the physician about the possibility of euglycemic DKA in a patient presenting with dengue fever with past history of diabetes on alternative medicine therapy presenting with metabolic ketoacidosis .

PRESENTATION OF CASE

A 70 year old female presented to us with high grade (102 deg F) , intermittent type fever since 3 days. She also reported nausea , vomiting and bilateral knee joint pain. She reported to have diabetes since last 10 years for treatment of which she was on alternative therapy medication. Laboratory work-up showed dengue fever , severe metabolic acidosis and 3+ ketonuria . RBS was 186 mg/dl . She was treated with IV fluids for hydration, paracetamol (antipyretics) ,regular insulin and dextrose drip. Her health improved with the above mentioned treatment.

DISCUSSION

Euglycemic or Normoglycemic DKA, was originally defined as DKA with a BG level of <300 mg/dL, but it is now recognized as that in the presence of a BG concentration of <200 mg/d . DKA can go undiagnosed if the patient has blood sugar levels of <200 mg/dl at the time of intial presentation . Moreover DKA occurs rarely in a patient presenting with dengue fever.

CONCLUSION:

Euglycemic DKA occurs in a small subset of patients with DKA and can go undiagnosed at initial presentation. It is thought to be due to starvation and food restriction and inhibition of gluconeogenesis seen mainly in patients with previous history of diabetes and insulin

deficiency. It may also be seen in patients with diabetes (on alternative therapy medications) presenting with dengue fever.

Keywords- Diabetic Ketoacidosis , Euglycemic, Dengue,Alternative Medicine

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious acute complication of diabetes mellitus that can become life threatening. DKA is recognized by hypergylcemia ,metabolic acidosis and presence of serum and/or urine ketones. It is induced as a result of a profound deficiency of insulin action in the body, often developing in individuals with poorly controlled type 1 diabetes or in those with type 2 diabetes who are subject to external stress such as infection, injury, or surgery. Although DKA is typically associated with marked hyperglycemia and resultant dehydration, it can occur with only a moderate increase in blood glucose (BG) levels or, in rare instances, in the setting of normal glucose concentrations. This latter, uncommon form of DKA, known as euglycemic or normoglycemic DKA, was originally defined as DKA with a BG level of <300 mg/dL, but it is now recognized as that in the presence of a BG concentration of <200 mg/d (1).We report here a case of euglycemic DKA in a patient who is a known diabetic and presented with dengue fever . The patient was on alternative medicine for treatment of diabetes.This case report highlights the fact that euglycemic DKA should be considered in the differential diagnosis of an ill patient with diabetes presenting with metabolic acidosis and absence of hyperglycemia.

PRESENTATION OF CASE

A 70 year old female presented to us with Fever since 3 days. Fever was of high grade (102 deg F) and intermittent type. She also reported nausea , vomiting and bilateral knee joint pain. There was no history of chest pain or abdominal pain or headache. She denied history of loss of consciousness or change in bowel or bladder habits. She reported to have diabetes since last 10 years for treatment of which she was on alternative therapy medication .The composition of the alternative medicine is not known as she took it from an unregistered AYUSH practitioner (AYUSH doctor is a registered medical practitioner of alternative medicine in India) . There was no history suggestive of hypertension or bronchial asthma or tuberculosis.

On examination she was oriented to time ,place and person but was in a confused state . Her BP was 130/84 mm hg ,PR-115/min, Temperature -102 deg F ,Respiratory Rate -18/min and Oxygen saturation was 97 percent on room air. Pallor,Icterus,Clubbing,Cyanosis,Edema and Lymphadenopathy were absent.

On systemic examination , normal heart sounds were heard .There were no murmurs. Bilateral vesicular breath sounds of equal intensity were heard .There were no added sounds. Abdomen was

soft and non tender. No organomegaly was present. Pupils were bilaterally normal in size and eaually reactive to light . Superficial and Deep reflexes were normal bilaterally.

Investigations-

At time of presentation -Hb-13.2 gm/dl , TLC-2600/mm3 ,RBC-4.5 lakhs/mm3 ,Platelets Count-30,000 , RBS-186 mg/dl ,HbA1C- 10

ABG- pH- 7.20 pO2- 88 mm hg , pCO2- 25 mm hg ,Bicarbonate- 10 meq/l

USG whole abdomen was normal

Urine Ketone Level - 3+ ketonuria was present

NS1 Ag was positive for Dengue Fever

Dengue infection with Euglycemic Diabetic Ketoacidosis was suspected . For dengue fever she was administered IV Fluids to maintain hydration and was given anti pyretic (Paracetamol) for fever. As per the common consensus , DKA was treated with Regular Insulin and Dextrose drip. Her health improved with above mentioned treatment . At the time of discharge her vitals were stable,ABG report was normal and RBS was 110 mg/dl. Urine ketones were absent. TLC and Platelet count were normal.

DISCUSSION

The diagnostic criteria of DKA, established by the American Diabetic Association, consists of a plasma glucose of >250 mg/dL, positive urinary or serum ketones, arterial pH of <7.3, serum bicarbonate <18 mEq/L, and a high anion gap (2,3) .In 1973, Munro et al. reported 37(17.5%) euglycemic DKA cases out of 211 DKA episodes (4) and in 1993 Jenkins et al reported 23 (3%) euglycemic DKA cases out of 722 DKA episodes (5). They defined euglycemia as glucose level ≤300 mg/dL and acidosis as a bicarbonate level ≤10 mEq/L (4). Currently it is advocated that a glucose level ≤200 mg/dL (11.1 mmol/L) should be used to define true euglycemic DKA (6,7) . Based on this, only 16 of the 37 episodes in the study by Munro et al (4) and 6 of the 23 episodes in the study by Jenkins et al (5) would be considered as euglycemic DKA, representing 7.6% and 0.8% of DKA patients, respectively.

Euglycemic DKA is thought to be facilitated by factors such as partial treatment of DKA, food restriction, alcohol intake, and inhibition of gluconeogenesis. Studies have shown euDKA to be also a side effect of use of SGLT2 inhibitors . In Japan, there are six SGLT2 inhibitors (ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin) on the market. The postmarketing reports of adverse events of the drugs displayed on the websites by the manufacturers showed a total of 28 cases of DKA or ketoacidosis.(1) The blood glucose levels at the onset of these events were <200 mg/dL in seven cases (including that described by Hayami *et al*)(8), 200–299 mg/dL in two cases, >300 mg/dL in five cases, and not determined in 14 cases (1). As per U.S. Food and Drug Administration communication ,20 cases of euDKA associated with SGLT2 inhibitors had been reported from March 2013 (date of approval of the first drug in this class) through 6 June 2014 (10)

There are multiple proposed theories exploring the link between SGLT2 inhibitors and euDKA. One possible mechanism describes that there is a decreased secretion of insulin from pancreatic cells in

response to the lowered blood glucose levels via urinary excretion. This results in a decrease of circulating insulin and its antilipolytic activity which leads to increased free fatty acid production (1,11) SGLT2 inhibitors also stimulate the secretion of the counterregulatory hormone glucagon, which in turn contributes to the overproduction of ketone bodies (1,8,12)

Euglycemic DKA may also be seen in patients on alternative therapy for treatment of diabetes. The exact mechanism for this is difficult to explain due to paucity of data available . It may be possible that mechanisms similar to that explained above for SGLT2 inhibitor may lead to development of euDKA. We suspect that our patient with diabetes on alternative therapy medication for treatment developed euDKA that was precipitated by dengue fever.

Some of the alternative medicine options for treating diabetes include -

a) Yoga - Helps in decreasing insulin resistance and improve insulin sensitivity (13)

b) Massage - Provides relaxation to body ,thus decreasing stress hormones and increading effective utilisation of insulin (14)

c) Acupuncture - It can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in lowering of blood sugar (15)

d)Aromatherapy- Helps in decreasing the stress of coping with chronic condition such as diabetes (16)

e) Medicinal Herbs -Some herbs have found to have hypoglycaemic action and some help in regeneration of Beta cells in pancreas .eg)Momordica charantia,Gymnema sylvestre (17,18,19)

f) L-Carnitine -Improves insulin sensitivity in insulin resistant diabetic patients (20)

g) Vitamin E - Has Antioxidant activity . It increases insulin sensitivity and secretion (21,22)

Thus patients with type 1 or type 2 diabetes (on alternate medicine therapy) who experience nausea, vomiting, malaise or develop a metabolic acidosis should be promptly evaluated for the presence of urine and serum ketones to rule out euDKA.

CONCLUSION

Although euglycemic DKA is a rare entity, it must be correctly diagnosed to tailor an appropriate therapy. It should be considered in the differential diagnosis of ketoacidosis in a patient with dengue fever since correction of fluid and IV insulin infusion and dextrose drip, correction of fluid/electrolyte abnormalities, and restoration of carbohydrate metabolism (1,2,3,13) are the mainstays of therapy for euglycemic DKA. The present case is additional evidence that DKA can occur in the setting of normal glucose concentration in a patient with dengue fever on alternative medicine for treatment of diabetes.

CONSENT

Written Informed consent was obtained from the patient for this case report

REFERENCES

1) Ogawa W, Sakaguci K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Invest. 2016;7(2):135–8

2)Janna Prater and Joumana T. Chaiban (*2015*) Euglycemic Diabetic Ketoacidosis with Acute Pancreatitis in a Patient Not Known to Have Diabetes. AACE Clinical Case Reports: Spring 2015, Vol. 1, No. 2, pp. e88-e91.

3) Thawabi M, Studyvin S. Euglycemic diabetic ketoacidosis, a misleading presentation of diabetic ketoacidosis. N Am J Med Sci. 2015;7(6):291–4

4) **Munro JF, Campbell IW, McCuish AC, Duncan LJ.**Euglycaemic diabetic ketoacidosis. *Br Med J.* 1973;2:578-580

5) Jenkins D, Close CF, Krentz AJ, Nattrass M, WrightAD. Euglycaemic diabetic ketoacidosis: does it exist? *Acta Diabetol.* 1993;30:251-253.

6) Joseph F, Anderson L, Goenka N, Vora J. Starvation-induced true diabetic euglycemic ketoacidosis in severe depression. *J Gen Intern Med*. 2009;24:129–131. [Crossref] [Google Scholar]

7) Davies RG, De P, Child DF, Gemmell L, Rincon C. Euglycaemic diabetic ketoacidosis. *Hosp Med*. 2003;64:557–558. [Crossref] [Google Scholar]

8) Hayami T, Kato Y, Kamiya H, *et al* Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Investig 2015; 6: 587–590.

9) Pandey A, Tripathi P, Pandey R, Srivatava R, Goswami S. Alternative therapies useful in the management of diabetes: A systematic review. J Pharm Bioallied Sci. 2011;3:504–12. [PMC free article] [PubMed]

10)Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors Julio Rosenstock, Ele Ferrannini
Diabetes Care Sep 2015, 38 (9) 1638-1642; DOI: 10.2337/dc15-1380

11. Simeon IT, Blau JE, Kristina IR. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab. 2015;100(8):2849–52. Epub 2015 Jun 18. [PMC free article] [PubMed]

12. Kibbey RG. SGLT-2 inhibition and glucagon: cause for alarm? Trends Endocrinol Metab. 2015;26(7):337–8. Epub 2015 Jun 6. [PMC free article] [PubMed]

13) Sahay BK. Role of yoga in diabetes. J Assoc Physicians India. 2007;55:121–6. [PubMed]

14) Ezzo J, Donner T, Cox M. Is massage useful in the management of diabetes? A systematic review. Diabetes Spectr. 2001;14:223.

15) Hu H. A review of treatment of diabetes by acupuncture during the past forty years. J Tradit Chin Med. 1995;15:145–54. [PubMed]

16) Grey M. Coping and Diabetes. Diabetes Spectrum. 2000;13:167–169.

17) Akhtar MS, Athar MA, Yaqub M. Effect of Momordica charantia on blood glucose level of normal and alloxan diabetic rabbits. Planta Med. 1981;42:205–12. [PubMed]

18) Puri D, Prabhu KM, Murthy PS. Mechanism of action of a hypoglycemic principle isolated from fenugreek seeds. Indian J Physiol Pharmacol. 2002;46:457–62. [PubMed]

19) Kanetkar P, Singhal R, Kamat M. Gymnema sylvestre: A Memoir. J Clin Biochem Nutr. 2007;41:77–81. [PMC free article] [PubMed]

20) Giancaterini A, De Gaetano A, Mingrone G, Gniuli D, Liverani E, Capristo E, et al. Acetyl-L- Carnitine infusion increases glucose disposal in type-2 diabetes patients. Metabolism. 2000;49:7047. [PubMed]

21) Select Vitamins and Minerals in the Management of Diabetes.

Belinda S. O'Connell

Diabetes Spectrum Aug 2001, 14 (3) 133-148; DOI: 10.2337/diaspect.14.3.133

22) Mooradian AD, Failla M, Hoogwerf B, Marynuik M, Wylie-Rosett J. Selected vitamins and minerals in diabetes. Diabetes Care. 1994;17:464–79. [PubMed]