IN THE NAME OF GOD

Case Presentation

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Feb 2023

AGENDA

- ✓Patient introduction and therapeutic challenges
- ✓A brief explanation of euglycemic DKA
- ✓The role of SGLT2 inhibitors in the treatment of type 1 diabetes

Patient history

- A 26-Year-old woman
- Born and live in Tehran
- Single
- High school diploma
- Hair stylist
- Occasional smoker but no alcohol user

Chief complaint

- Nausea, vomiting
- Abdominal pain

Present illness

- A 26-year-old woman with diabetes since 8 years ago and Celiac disease since two years ago
- Treated with Lantus and Novorapid up to five months ago
- Five months ago, following a visit to the general practitioner, Novorapid insulin was discontinued and replaced with Metformin and Dapagliflozin.
- During these five months, she has been hospitalized several times and has experienced repeated attacks of hypoglycemia & hyperglycemia.
- Weight loss of about 20 kg in one year

Present illness

- Nausea and vomiting from the previous night
- The pain is in the epigastric region and is not related to eating and is not present in the intervals between admissions.
- No diarrhea, no tenesmus
- Frequent urination every 2 hours with dysuria
- On the day of visit, she was hospitalized with the following tests, and the previous night, the drugs were used according to the routine :

1402-11-14 4PM

Test	Result
WBC	14[10^3/UL]
HGB	14.4[g/dL]
PLT	203[10^3/UL]
Urea	44mg/dL
Cr	0.7mg/dL
AST	14U/L
ALT	19U/L
Alkp	147IU/L
Amylase	63U/L

Test	Result
Lipase	33U/L
Na	141mEq/l
K	4mEq/l
PH	7.37
PCO2	33.7mmHg
HCO3	19mEq/l
BS	85mg/dL
U/A	Ketone neg Leukocyte positive WBC 12-14 Bact few
Beta HCG	<2.4mIU/ml

1402-11-14 8PM

Internal service admission:

- Start ceftriaxone
- Regular protocol
- Ringer lactat 2 lit/24h
- Ondansetron amp QID
- Famotidine amp 40 BD
- Oral medications→hold

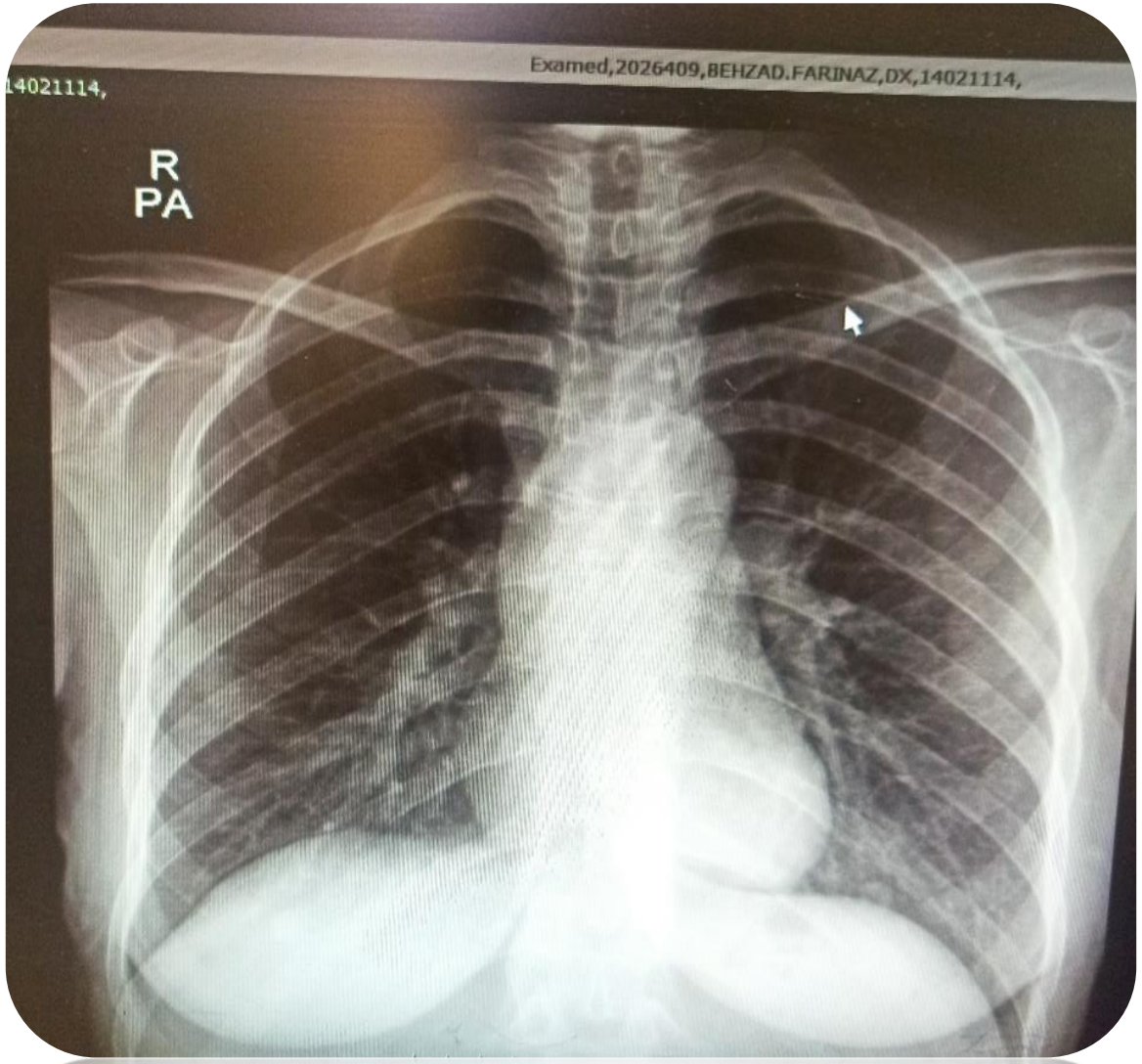
1402-11-15

TIME	BS	PH	PCO2	HCO3	K
6	90	6.9	57	14	4
8	118	7.3	29	16.3	-

Transfer to the endocrinology service:

- B hydroxybutyrate→2.4 mmol/l
- N/S 1lit stat
- D/W 5% 125cc/h
- H/S 125cc/h + 10cc KCL/L
- Regular insulin 1unit/h

1402-11-14



1402-11-15

TIME	BS	PH	PCO2	HCO3	K
17	150	7.39	16.5	9.8	4.7

- D/W 5% 150cc/h + 1 vial D/W 50 %
- H/S 150cc/h + 10cc KCL/L
- Regular insulin 1unit/h

TIME	BS	PH	PCO2	HCO3	K
19	100	7.33	25	14	-

- Regular insulin 1unit/h → hold

1402-11-15

TIME	BS	PH	PCO2	HCO3	K
21	126	-	-	-	-

- D/W 5% 150cc/h + 1 vial D/W 50 %
- H/S 150cc/h + 10cc KCL/L
- Regular insulin 1unit/h was restarted

TIME	BS	PH	PCO2	HCO3	K
2	198	7.4	27.5	17.7	4

- Regular insulin 4unit/h

1402-11-16

TIME	BS	PH	PCO2	HCO3	K
4	330	7.3	27.6	14.7	4

- D/W → D/C
- H/S 250 cc/h
- 10cc KCL/L
- Regular insulin 4 unit/h

1402-11-16

TIME	BS	PH	PCO2	HCO3	K
10	106	7.4	27.5	18	3.7
12	92	7.4	30	18.8	3.6

- 900 cc D/W 5% + 100 cc NACL 5% → 300 cc/h
- 10cc KCL/L
- Regular insulin 0.5 unit/h
- Insulin was continued in the next hours with a dose of 1-2 u/h
- The patient does not tolerate food

1402-11-17

TIME	BS	PH	PCO2	HCO3	K
17	90	-	-	-	-

- Regular insulin → hold
- 1 vial of dextrose 50 was added to the serum

TIME	BS	PH	PCO2	HCO3	K
20	530	7.2	17.3	7.6	-

- N/S 1 lit within 1h
- H/S 150cc/h + 10cc KCL/L
- 900 cc D/W 5% + 100 cc NACL 5% → D/C
- Regular insulin 4unit/h was restarted

1402-11-17

TIME	BS	PH	PCO2	HCO3	K
22	300	7.33	16	8.5	4.9
00	112	7.39	26	13.5	-

- The patient was transferred to ICU

At 12 midnight:

- D/W 5% 900cc + 100cc Nacl 5% → 200cc/h
- 10cc KCL/L
- Regular insulin 1 unit/h
- CV line fix

1402-11-18

TIME	BS	PH	PCO2	HCO3	K
8	196	7.35	29.5	15.4	3.8

- 900 cc D/W 5% + 100 cc NACL 5% → 200 cc/h
- 10cc KCL/L
- Regular insulin 4 unit/h

TIME	BS	PH	PCO2	HCO3	K
12	86	7.35	32.8	18.4	-

- 900 cc D/W 5% + 100 cc NACL 5% + 1 vial D/W 50% → 200 cc/h
- 10cc KCL/L
- Regular insulin → hold

1402-11-18

TIME	BS	PH	PCO2	HCO3	K
14	239	7.30	22.4	10.9	-

- H/S 200cc/h
- 10cc KCL/L
- Regular insulin 4 unit/h

TIME	BS	PH	PCO2	HCO3	K
18	148	7.3	26.1	13	-

- 900 cc D/W 5% + 100 cc NACL 5% + 1 vial D/W 50% → 200 cc/h
- 10cc KCL/L
- Regular insulin 2 unit/h

1402-11-19

TIME	BS	PH	PCO2	HCO3	K
2	241	7.3	33.9	20	3.4

- H/S 200cc/h
- 20cc KCL/L
- Regular insulin 4 unit/h

TIME	BS	PH	PCO2	HCO3	K
9	170	7.39	33.6	20.7	3.3

- H/S 500 cc + 10cc KCL whitin 1h
- 900cc D/W 5% + 100cc NACL 5% → 100cc/h
- 20cc KCL/L
- Regular insulin 4 unit/h
- Po If tolerated
- At 13PM Lantus and Novorapid insulin start

1402-11-19

TIME	BS	PH	PCO2	HCO3	K
16	150	7.35	32.9	18.1	4

- H/S 1500cc/24h
- 10cc KCL/L
- insulin drip → hold

TIME	BS	PH	PCO2	HCO3	K
21	405	7.35	23	12.6	3.9

- Urine keton → +
- insulin drip → restart with 4 unit/h
- According to the patient's BS, it was changed at 6 am to 1 unit/h

1402-11-20

TIME	BS	PH	PCO2	HCO3	K
8	120-170	7.4	32	21.4	4.2

- 900cc D/W 5% + 100cc NACL 5% → 200cc/h
- 10cc KCL/L
- insulin drip 1 unit/h
- but she still does not tolerate food

1402-11-21

TIME	BS	PH	PCO2	HCO3	K
8	166	7.4	31.4	20	4.7

- 900cc D/W 5% + 100cc NACL 5% → 150cc/h
- 10cc KCL/L
- insulin drip 0.5-1 unit/h
- The patient was able to tolerate food and finally her nausea and vomiting stopped
- Transfer to the endocrinology department
- Lantus 20 unit every night
- Novorapid 4-4-4

1402-11-22

TIME	BS	PH	PCO2	HCO3	K
8	200	7.4	41.2	25.5	4.4

- Lantus 24 unit every night
- Novorapid 6-6-6
- No nausea, no vomiting, no epigastric pain
- Psychosomatic counseling was requested

1402-11-23

- The patient left the hospital with good general condition without nausea, vomiting or abdominal pain
- Despite the insistence of the psychology service for further counseling and the need for drug treatment, she left the hospital
- She decided to come to the endocrinology clinic next week with SMBG at home.

Past medical history

- In September 1400, due to continuous and severe diarrhea, she was admitted to Al-Ghadir Hospital and underwent endoscopy:

➢ She was diagnosed with **Celiac** disease and since then, following a gluten-free diet, the diarrhea has stopped.

- Last year, after visiting a cardiologist for a checkup, he underwent angiography:

➢ Medical follow up

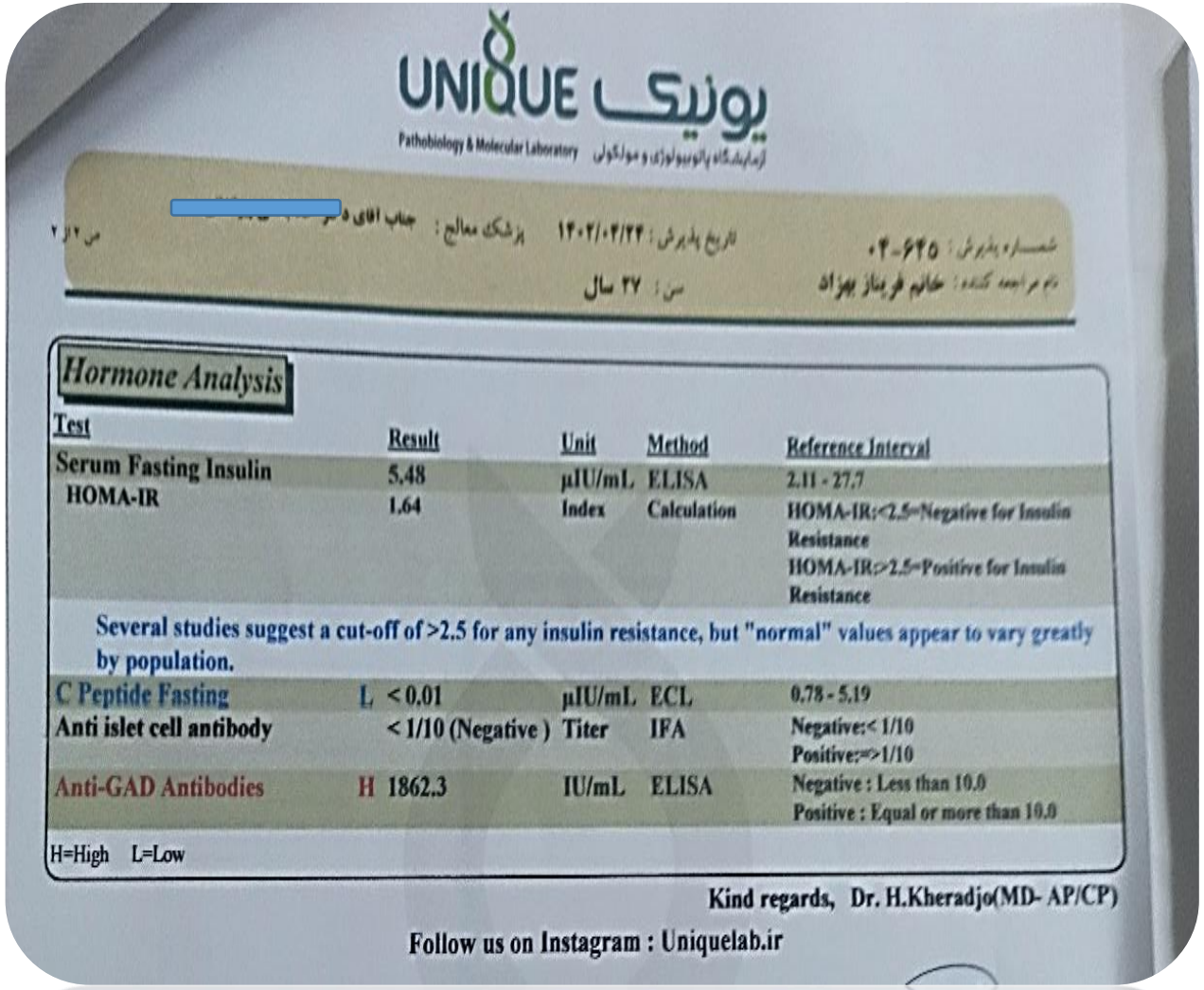
Past medical history

- From June 1402 to September 1402, every month due to nausea, vomiting and epigastric pain, uncontrolled DM, she was admitted to the endocrinology service and underwent two rounds of endoscopy, as described below:

- Mild chronic gastritis
- Mild villous atrophy
- Crypt hyperplasia
- Interaepithelial lymphocytosis (30-100)

Past medical history

In Shahrivar 1402, following a visit to the general physician, after conducting the following tests, **Novorapid was stopped and Dapagliflozin & Metformin was started.**



UNIQUE يونیک

Pathobiology & Molecular Laboratory

[redacted] جناب آقای دکتر ... پزشک معالج : تاریخ پذیرش : ۱۴۰۲/۰۴/۲۴ شماره پذیرش : ۰۴-۶۴۵

من ۲ از ۲ سن : ۳۷ سال نام مراجعه کننده : خانم فریناز بهزاد

Hormone Analysis

Test		Result	Unit	Method	Reference Interval
Serum Fasting Insulin		5.48	µIU/mL	ELISA	2.11 - 27.7
HOMA-IR		1.64	Index	Calculation	HOMA-IR:<2.5=Negative for Insulin Resistance HOMA-IR:>2.5=Positive for Insulin Resistance
Several studies suggest a cut-off of >2.5 for any insulin resistance, but "normal" values appear to vary greatly by population.					
C Peptide Fasting	L	< 0.01	µIU/mL	ECL	0.78 - 5.19
Anti islet cell antibody		< 1/10 (Negative)	Titer	IFA	Negative:< 1/10 Positive:=>1/10
Anti-GAD Antibodies	H	1862.3	IU/mL	ELISA	Negative : Less than 10.0 Positive : Equal or more than 10.0

H=High L=Low

Kind regards, Dr. H.Kheradjo(MD- AP/CP)

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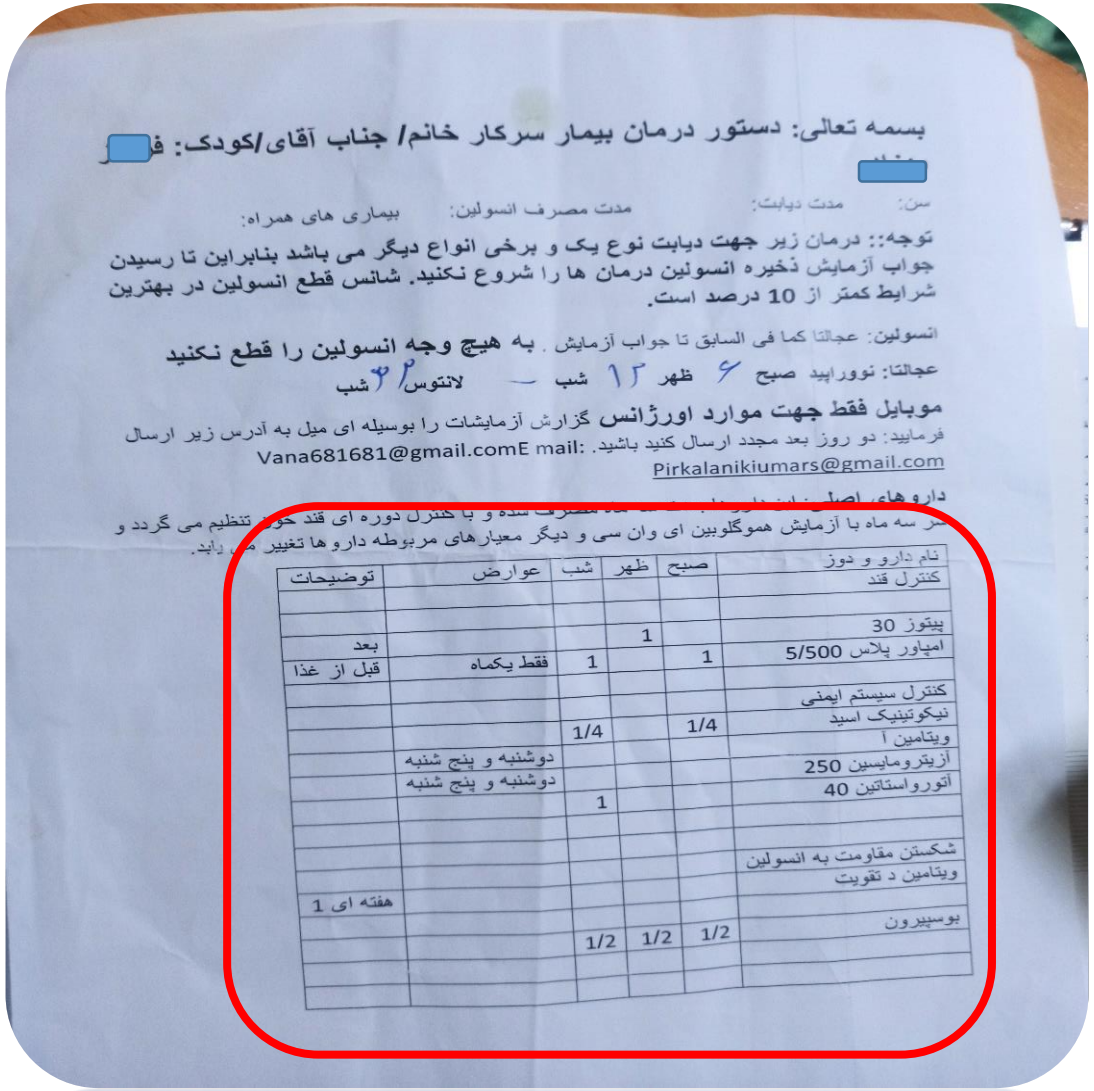
Past medical history



بسمه تعالی: دستور درمان بیمار سرکار خانم/ جناب آقای/کودک: ف[redacted]

سن: مدت دیابت: مدت مصرف انسولین: بیماری های همراه:

توجه:: درمان زیر جهت دیابت نوع یک و برخی انواع دیگر می باشد بنابراین تا رسیدن جواب آزمایش ذخیره انسولین درمان ها را شروع نکنید. شانس قطع انسولین در بهترین شرایط کمتر از 10 درصد است.

انسولین: عجالتا کما فی السابق تا جواب آزمایش . **به هیچ وجه انسولین را قطع نکنید**

عجالتا: نوواپید صبح ۶ ظهر ۱۲ شب — لانتوس ۲۲ شب

موبایل فقط جهت موارد اورژانس گزارش آزمایشات را بوسیله ای میل به آدرس زیر ارسال فرمایید: دو روز بعد مجدد ارسال کنید باشید. E mail: Vana681681@gmail.com

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داروهای اصلی [redacted] هر سه ماه با آزمایش هموگلوبین ای وان سی و دیگر معیارهای مربوطه دارو ها تغییر می یابد.

نام دارو و دوز	صبح	ظهر	شب	عوارض	توضیحات
کنترل قند					
پیتوز 30		1			بعد
امپاور پلاس 5/500	1		1	فقط یکماه	قبل از غذا
کنترل سیستم ایمنی					
نیکوتینیک اسید	1/4		1/4		
ویتامین آ				دوشنبه و پنج شنبه	
آزیترومایسین 250				دوشنبه و پنج شنبه	
آتورواستاتین 40			1		
شکستن مقاومت به انسولین					
ویتامین د تقویت					هفته ای 1
بوسپیرون	1/2	1/2	1/2		

Past medical history

Hospitalized with a similar complaint a month ago (In the internal service) :

- PH: 7.36/HCO3: 20.4/PCO2: 37.4/BS: 89
- Insulin dose adjustment
- Oral medications **were not discontinued**

Familial history

- The patient's mother has a history of recently diagnosed hypertension and cardiac disease.
- The patient's father has a recently diagnosed cardiac disease.
- She does not mention a history of diabetes and Celiac disease in the family.

Drug history

- Lantus insulin 20-30 unit / every night
- Tab atorvastatin 40 mg / daily
- Tab Metformin 500 mg / bd
- Tab Dapagliflozin 10 mg / daily

Review of system & physical exam

- Nausea with non-bloody vomiting
- The mucous membranes were not dry and dehydrated
- Epigastric pain but no guarding, no tenderness
- Normal heart & lung auscultation
- No abdominal & hypogasteric tenderness
- No costovertebral tenderness
- Normal sensory and neurological examination of limbs
- Other examinations were normal

Physical exam

- Bp: 115/75 mmHg
- PR: 95
- T: 37^{o}C
- RR: 12
- BMI: 21.4 kg/m^{2}

Problem list

- A 26-year-old woman with diabetes type 1 since 8 years ago (on oral treatment with dapagliflozin from september and lantus)
- Celiac disease since two years ago
- Nausea, vomiting (Food intolerance)
- Epigasteric pain
- Euglycemic DKA
- UTI

Euglycemic DKA

Introduction

- Euglycemic diabetic ketoacidosis (EDKA) is a clinical syndrome occurring both in type1 and type 2 diabetes mellitus characterized by euglycemia (blood glucose less than 250 mg/dL) in the presence of severe metabolic acidosis (arterial pH less than 7.3, serum bicarbonate less than 18 mEq/L) and ketonemia.

The American Journal of Emergency Medicine

Euglycemic Diabetic Ketoacidosis, *Last Update: January 29, 2023*

Etiology

- anorexia, gastroparesis, fasting, use of a ketogenic diet, and alcohol use disorder can lead to states of carbohydrate starvation and subsequent ketosis.

- Additional triggers for EDKA include pregnancy, pancreatitis, glycogen storage disorders, surgery, infection, cocaine toxicity, cirrhosis, and insulin pump use.

- T1DM who underwent bariatric surgery patients experience DKA in over 20% of postoperative cases and may be especially prone to EDKA.

Etiology

- The newer oral antidiabetic medication category of **SGLT2 inhibitors**, including canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin, can also directly result in EDKA.

➢ EDKA may be more common in patients with diabetes on SGLT2 inhibitors with lower body mass index and decreased glycogen stores.

➢ Episodes can be triggered by surgery, infection, trauma, a major illness, reduced food intake, persistent vomiting, gastroparesis, dehydration, and reduced insulin dosages.

Epidemiology

- **2.6% to 3.2%** of DKA admissions are euglycemic.
- DKA-associated with the use of SGLT2 inhibitors has rates ranging from 0.16 to 0.76 events per 1000 patient-years in patients with type 2 diabetes.
- The SGLT2 inhibitors increase the risk of DKA in T2D patients by 7-fold.
- Incidence of DKA from SGLT2 inhibitor use of approximately **0.1%.**
- Data on patients with type 1 diabetes who presented with DKA associated with SGLT2 inhibitors showed rates varying from **5 to 12%**; however, euglycemia was not present in all cases.
- SGLT2 inhibitors are not approved for use in patients with type 1 diabetes.

Pathophysiology

- The underlying mechanism of EDKA is secondary to a carbohydrate deficit resulting in generalized decreased serum insulin and excess counter-regulatory hormones like glucagon, epinephrine, and cortisol.
- The increased glucagon/insulin ratio leads to increased lipolysis, increased free fatty acids, and ketoacidosis.
- Volume depletion resulting from decreased oral intake, vomiting, and osmotic diuresis from glucosuria further exacerbates elevations in glucagon, cortisol, and epinephrine, worsening lipolysis and ketogenesis.
- Additionally, decreased gluconeogenesis by the liver occurs in fasting where hepatic glycogen is already depleted, or increased glucosuria by the kidneys contributes to EDKA.

Pathophysiology

- SGLT2 inhibitors are a newer class of antidiabetic drugs that increase the risk of EDKA **unrelated to the duration** of exposure.
- The use of SGLT2 inhibitors in T1DM is not recommended by the U.S. Food and Drug Administration and is discouraged because the risk of ketone-associated effects can be as high as **9%**.
- The mechanism of action of SGLT2 inhibitors is to enhance excretion and block reabsorption of filtered glucose from the proximal convoluted tubule.
- The loss of urinary glucose again creates a state of carbohydrate starvation and volume depletion, increasing the glucagon/insulin ratio and resulting in a state of severe dehydration and ketosis.

Pathophysiology

- Additionally, SGLT2 inhibitors have been found to directly stimulate the release of glucagon from the pancreas, further worsening the glucagon/insulin imbalance, as well as suppressing the removal of beta-hydroxybutyrate and acetoacetate by the kidneys.
- Euglycemia is maintained due to the loss of urinary glucose and SGLT2 inhibitor-triggered hypoinsulinemia.
- SGLT2 inhibitors also increase ketone reabsorption, such that ketosis is common in patients taking SGLT2 inhibitors after a trigger such as pregnancy, alcohol, surgery, infection, or starvation.

Key points in treatment

- Successful diagnosis is dependent on early screening with serum or urine ketones, even when serum glucose is normal, whenever EDKA is suspected.
- After volume expansion with crystalloid, the foundation of therapy is a combination of dextrose (5 to 10%) and insulin (0.05 to 0.1 u/kg/hr) infusion until acidosis resolves.
- Insulin infusion should not be avoided due to normal glucose levels but instead is essential to successful treatment.
- Ketosis does not resolve with intravenous crystalloid hydration alone.
- SGLT2 inhibitor treatment should be discontinued as soon as EDKA is diagnosed.
- Sodium bicarbonate infusion is not indicated.

Use of Adjunctive Drugs in T1DM

- The in Tandem1 trial (n= 793) was a 1-year study of the dual SGLT1/SGLT2 inhibitor sotagliflozin, 200 or 400 mg once daily before breakfast **combined with optimized insulin therapy.**
- The DEPICT-2 trial (n= 813) was a 24-week study of the SGLT2 inhibitor dapagliflozin, 5 or 10 mg once daily.

➢ Both studies showed that, compared with placebo, adjunctive use of an SGLT inhibitor was associated with modest but durable dose-dependent improvements in HbA1c, reductions in insulin dose, and weight loss.

SGLT inhibitors are yet **not FDA approved** for use in T1DM.

WILLIAMS TEXTBOOK OF ENDOCRINOLOGY, FOURTEENTH EDITION

American Diabetes Association. Diabetes Care

Diabetes Care. 2018 Sep; 41(9): 1970–1980. PMCID: PMC6105319
Published online 2018 Jun 24. doi: 10.2337/dc18-0343 PMID: 29937430

Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study

John B. Buse,[1] Satish K. Garg,[2] Julio Rosenstock,[3] Timothy S. Bailey,[4] Phillip Banks,[5] Bruce W. Bode,[6] Thomas Danne,[7] Jake A. Kushner,[8] Wendy S. Lane,[9] Pablo Lapuerta,[5] Darren K. McGuire,[10] Anne L. Peters,[11] John Reed,[12] Sangeeta Sawhney,[5] and Paul Strumph[5]

Table 1

Summary of adverse events and events of special interest, overall treatment period (baseline to 52 weeks)

	Placebo (*n* = 268)	Sotagliflozin 200 mg (*n* = 263)	Sotagliflozin 400 mg (*n* = 262)
Any adverse event	216 (80.6)	215 (81.7)	209 (79.8)
Serious adverse event	20 (7.5)	27 (10.3)	29 (11.1)
Severe adverse event	7 (2.6)	12 (4.6)	12 (4.6)
Death	1 (0.4)*	0	0
Positively adjudicated adverse events			
≥1 severe hypoglycemia event†	26 (9.7)	17 (6.5)	17 (6.5)
≥1 severe nocturnal hypoglycemia event†,**	10 (3.7)	10 (3.8)	2 (0.8)
≥1 DKA event	1 (0.4)	9 (3.4)	11 (4.2)
≥1 DKA event among CSII users	1/160 (0.6)	8/156 (5.1)	7/157 (4.5)
≥1 DKA event among MDI users	0/108	1/107 (0.9)	4/105 (3.8)
Major adverse cardiovascular events			
Myocardial infarction or hospitalization for unstable angina	3 (1.1)	4 (1.5)	0
Stroke	1 (0.4)	0	1 (0.4)
Heart failure hospitalization	0	0	0
Coronary revascularization	2 (0.7)	2 (0.8)	0
Drug-induced liver injury	0	0	2 (0.8)
Events of special interest			
Any	266 (99.3)	260 (98.9)	259 (98.9)
Genital mycotic infection	9 (3.4)	24 (9.1)	34 (13.0)
Diarrhea†	18 (6.7)	22 (8.4)	27 (10.3)

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Diabetes Obes Metab. 2020 Sep; 22(9): 1516–1526.
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PMCID: PMC7496089
PMID: 32311204

Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 52-week results from a randomized controlled trial

Chantal Mathieu, MD,[✉1] Gottfried Rudofsky, MD,[2] Moshe Phillip, MD,[3] Eiichi Araki, MD,[4] Marcus Lind, PhD,[5,6] Niki Arya, MSc,[7] Fredrik Thorén, MD,[8] Markus F. Scheerer, PhD,[9] Nayyar Iqbal, MD,[7] and Paresh Dandona, MD[10]

TABLE 3

Summary of events adjudicated as diabetic ketoacidosis (DKA)

	Dapagliflozin 5 mg + insulin (N = 271)	Dapagliflozin 10 mg + insulin (N = 270)	Placebo + insulin (N = 272)
Participants with events sent for adjudication, n (%)	27 (10.0)	23 (8.5)	11 (4.0)
Participants with definite DKA, n (%)	11 (4.1)	10 (3.7)	1 (0.4)
Number of events of definite DKA, n	11	10	1
Incidence rate, per 100 patient-years	4.47	4.06	0.42
Severity of event as adjudicated, n (%)[a]			
Mild	4 (36.4)	4 (40.0)	0
Moderate	5 (45.5)	4 (40.0)	1 (100.0)
Severe	2 (18.2)	2 (20.0)	0
Number of events of euglycaemic DKA, n[b]	3	2	0
Primary cause of definite DKA events, n (%)[a]			
Insulin pump failure	1 (9.1)	3 (30.0)	0
Missed insulin dose	4 (36.4)	1 (10.0)	0
Severe illness	1 (9.1)	1 (10.0)	0
Not identified	4 (36.4)	1 (10.0)	1 (100.0)
Other	1 (9.1)	4 (40.0)	0

Thank you for your attention