SGLT2i and DKA Development: Epidemiology, Pathogenesis, and Prevention

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SGLT2i Associated DKA Hypothesis

Real but rare complication which is preventable with good clinical care.
Disclaimer

I speak, consult, and/or do research for all SGLT2i and Diabetes pharmaceutical companies, so I’m either equally informed or biased depending on your point of view.

*Listen to and question everything we hear and see because were all biased by our experiences.*

My Experience and Background

• Clinical Endocrinologist and Nephrologist (Metabolist) in practice for over 25 years. I’m also involved in clinical research and teaching.

• Interest in SGLT1 since 1988 when working with Ralph DeFronzo, Ele Ferrannini, Luciano Rosseti, and Stefano Del Prato.

• Manage approximately 200 - 300 DKA patients/yr. for the last 28 + years.
Case Study: Hx.

- 50 y/o black lady
- H/o T2D for 2-3 yr. with no h/o DKA.
- Brought in by her family with N/V, polyuria, polydipsia, decreased appetite, and blurred vision for 2d and confusion for < 1d.
- No h/o F/C, CP, abd. Pain, dysuria, cough, diarrhea, URI sx., melena, hematochezia
- The pt. had been switched from sitagliptin to Xigduo XR 10/1000 3d before prior by her family physician due to elevated BS. She was not on other meds.
- FH: Mother, Father, Brother, and Sister have T2D and HTN on ODM. Mother had CRF and died. No h/o DKA.
- SH: Unmarried assistant parole officer with one son. No h/o Etoh, tobacco, or illicit drug use.

Case Study: PE

- VS: T 98.3, P 120, R 24, BP: 158/88, O2 SAT 100%, Ht 5 ft
- General: Kussmaul’s Respirations, mild confusion, lethargy, Obese, and dry mucous membranes.
- Rest of PE was UR
Case Study: Exams

- BS 529, Na 128, K 4.7, Cl 92, TCO2 undetectable, BUN 23, CREA 1.5, AG 34 (without k)
- WBC 26.3, Hgb 16.7, Plat 278k
- U/A: Ketones > 80, glucose > 1k
- ABG: Ph 6.89, pCO2 11, pO2 152, HCO3 2, LA 5.34 (nl up to 2) on RA
- Alb 4, LET nl
- CXR and CT of the head was UR
- EKG Sinus Tach
- A1c 12.9 with MBG 340
- TSH 1.9
- PO4 3.6

Case Study: Initial TX

- NPO
- 2 amps of HCO3
- Aggressive Hydration
- IV Insulin
- BMP q 2 hr
- FSBS q 1 hr
- Protonix
- No Antibiotics
Case Study: Next Day

- Pt was feeling better.
- PO4 0.5, BS 130, BUN 9, CREA 1.1, MG 1.9, Na 138, K 3.7, CL 108, CO2 14, **AG 16**
- WBC 20.7, Hgb 14.4, Plat 192
- The pt was started on SC insulin, 1500 Cal ADA diet, dextrose d/c and IV decreased, and transferred to the floor.

Case Study: D/C

- PO4 2.3, BUN 6, CREA .7, NA 142, K 3.8, CL 108, CO2 24, AG 10
- WBC 5.1, HGB 14.5
- Pt was d/c on Glargine 50 units Bid and Humalog
- GAD65AB < 1
- ISLETCEL Neg
- INSAB 5.4
Case Study: 8 Days Later

- Pt was doing well.
- Glargine decreased to 25 q 12 hr
- Humalog d/c
- **Wt. 184 BMI 35.9**
- Labs: CHOL 208, Trig 74, HDL 48, **LDL 145, Vit D 12, BS 125**, BMP and PO4 UR., ACR < 13
- Restarted **SGLT2i** at initial low dose
- Glargine changed to 45 q am
- Given simvastatin and Vit D supplementation
- Counseled on diet and exercise

Case Study: Now at 3 Months

- Doing well. She wants to get off insulin and says metformin caused diarrhea.
- On Glargine 25 units q am and SGLT2i and metformin
- **Wt. 174, 10 pound wt. loss**, BMI 34
- **A1c 6.8** with MBG 148
- Vit D 34, FBS 90, BUN 11, CREA .7, Na 142, K 3.9, CL 106, CO2 22, eGFR 107, LDL 85, Trig 77, HDL 60.
- SGLT2i dose increased
- Continue titrating Glargine
- Started Long acting GLP-1
Case Study: Key Points

1) Pt. developed DKA shortly after initiation of SGLT2i without contributing factors.
2) A1c was 12.9.
3) Blood Sugars were greater than 250.
4) SGLT2i restarted with insulin without the development of DKA, but with improvement of A1c, while decreasing insulin, and losing Weight.
5) Only case out of a large denominator in my experience, so rare.

Epidemiology (General)

- **General lack of information** (Cases reported, but no information given or inadequate information).
- **Information is available:**

1) Pt. was not in DKA
2) Pt. had Type 1 DM or LADA
3) Pt. had contributing factors that are well recognized to cause DKA, even in Type 2 DM
4) **Type 2 DM with no known contributing factors.**
Epidemiology (General)

- **Type 2 DM**
  - No Contributing Factors
  - *Contributing Factors (release of stress hormones)*
    - Sepsis
    - MI
    - CVA
    - Surgery
    - Pancreatitis
    - Starvation
    - Etc..

- **Type 1 DM**

Epidemiology (Timeline)

- **Pharmaceutical Industry Experience**
  - Approved for Treatment of Type 2 DM

- **Real World Experience (Case Reports)**
  - Updated Drug Safety Communication on December 4, 2015 with a prescribing information change. Now 73 cases at least 16 cases in Type 1 DM/LADA.
  - EMA reported on May 19, 2015 147 cases.
Pharmaceutical Industry Experience: Approved Drugs (Type 2)

- **Janssen** (Canagliflozin)
  - 10 treated/10,687 vs. 2 placebo/6,904 pt., 6 treated had T1.
  - All treated had BS > 300 at presentation.
  - All pts. had contributing factors.

- **AstraZeneca** (Dapagliflozin)
  - 1 case/5936 pt. in Phase IIb/III studies.
  - DECLARE <0.1% out of 17,150 blinded pt.
  - FDA has reported 21 cases.
  - EMA has reported 46 cases, 12 in T1, only 16 hospitalized.

- **Boehringer Ingelheim/Lilly** (Empagliflozin)
  - 7 cases on empa (3 not felt due to empa) and 6 on placebo.

Pharmaceutical Industry Experience: Investigational (Type 1)

- **Janssen** (Canagliflozin)
  - 17 treated and 0 placebo/351 pt.
  - All cases had contributing factors, but the same contributing factors were present in the placebo group without DKA.

- **Boehringer Ingelheim/Lilly** (Empagliflozin)
  - 2 cases/117 patients, both with significant insulin reduction.

- **Lexicon** (Sotagliflozin)
  - 2 pt. both on insulin pumps
Summary of Pharmaceutical Industry Experience In Type 2

**Rare** cases with a frequency <0.1% in patients studied usually with an **A1c of 7 – 10.5**, usually with contributing factors, with one study up to an A1c of 12.

Real World Experience Case Studies

- **No Contributing Factors**
  - My Case: **A1c > 12.5**
  - Dr. Foiqa Chaudhry, Poster at 2015 AACE National Meeting, DIABETIC KETOACIDOSIS FOLLOWING SGLT2 INHIBITOR THERAPY IN DM2.
    - Both patients had **A1c > 12.5** without other contributing causes.
    - Another poster at AACE with similar patients with **A1c > 12.5**

- **Contributing Factors**
  - A1c > 7
Pt Profile for SGLT2i Associated DKA

• A1c > 12.5 **without** other contributing risk factors
  • All pharmaceutical studies have excluded this group.

• A1c generally > 7 **with** contributing risk factors.

Other Contributing Factors

That Can Lower The A1c Threshold

• Intercurrent illnesses
  • Infection, MI, surgery, pancreatitis, etc...

• Reduced fluid intake

• EtOH

• Very low carb / high fat diet (Ketogenic Diet)
Explanation for Causality and Prevention of DKA in Patients on SGLT2i

• **Third Level of Evidence:**

Hypothesis based on known physiologic and pathologic mechanisms and observations/experience.

• Since there are known RCT or observational studies, particularly in individuals with A1c > 12.5. The registration trials for canagliflozin, dapagliflozin, and empagliflozin generally excluded anyone with an A1c > 10 to 10.5.

Hypothesis for DKA by SGLT2i in Type 2 Unstable Patient

1. **High risk patient** for DKA with SGLT2i have A1c ≥ 12.5. (Which were excluded from the registration pharmaceutical trials.)

2. Patients with A1c ≥ 12.5 have very low β-cell function and resultant insulin secretion.

\[ \text{Insulin Deficient} \]
\[ \text{Insulin Resistance} \]
\[ \text{β-cell Function} \]

**Glucose Toxicity**

\[ (+) \text{ feed back loop} \]
3. **Adding an SGLT2i**, to an individual with very little endogenous insulin production, potentially further decreases insulin production acutely, by lowering glucose in a renal non-insulin dependent mechanism that decreases the stimulation for insulin secretion. This alone may result in inadequate insulin levels to prevent ketosis.

4. In addition, patients with extremely high A1c (≥ 12.5) are functionally dehydrated and adding an SGLT2i will cause a diuresis with further intravascular volume contraction leading to a rise in stress hormones (catecholamines, cortisol, GH, glucagon) to maintain pressure status. This can accelerate the ketogenic process leading to DKA.
Hypothesis for DKA by SGLT2i in Type 2 Amplification

5. The rise in stress hormones will increase blood glucose further exacerbating fluid loss and loss of negative feed back control.

6. This results in the need for increased insulin production to prevent ketosis that the β-cell is incapable of responding to, resulting in DKA.

Prevention of SGLT2i Associated DKA in Type 2 DM

• Consistent with good clinical medicine and the guidelines (AACE, TDC, and ADA), strongly consider starting basal insulin therapy in all DM patients with A1c ≥ 9 to 10, and always in pt. with A1c > 12.5, as well as following the SGLT2i’s package inserts, and starting patients on SGLT2i with normal intravascular volume (BUN/CREA of ≤ 15/1) should prevent DKA in patients with Type 2 DM initiated or on SGLT2i’s.

• Initiate long acting insulin at .5 units/kg or greater

• Consider educating patients if they have N/V/abd. pain to stop their SGLT2i and seek medical attention.
Prevention of SGLT2i Associated DKA in Patients with Contributing Factors

Consistent with good clinical Practice, patients with Diabetes (1&2) who are critically ill, including post surgical, should be treated with IV insulin.

SGLT2i: Associated DKA in Type 1 DM

Two types of Type 1 DM:

• Classic Type 1 DM in lean individuals

• Non classic Type 1 DM with VIRAS/obesity

VIRAS: Visceral Insulin Resistant Adiposity Syndrome
Insulin Requirements

• Classic Type 1 DM (approx. 1/3):
  • Usually require approximately .5 units/kg/day of insulin

• Non Classic Type 1 DM with VIRAS (approx. 2/3):
  • Generally requires ≥ 1 unit/kg/day of insulin

Strategies to Prevent SGLT2i Associated DKA in Type 1 DM

1. Do to the low insulin requirements in Classic Type 1 DM SGLT2i use may need to be avoided, because using an SGLT2i in them, may require reducing the insulin dosage below the ketogenic threshold to prevent unacceptable hypoglycemia.

2. SGLT2i use may be considered in Non Classic Type 1 DM as long as insulin dosages do not drop below .5 units/kg/day.

3. Educate patients if they have N/V/abd. pain to stop their SGLT2i and seek medical attention.

4. If pt has an episode of DKA on SGLT2i, think hard about restarting the SGLT2i, because the pt maybe better off not being on one.
Summary of SGLT2i associated DKA

• Generally rare in T1 and T2 DM
• Key factor is insulin deficiency from whatever cause.
• Preventable with appropriate insulin therapy.
• A need to teach physicians that the diagnosis of DKA does not depend on how high the BS is, but more the S/S with the detection of ketones and AG acidosis in a diabetic individual.