A complication of diabetes treatment

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Case 1

- 45 year old woman from rural SA

- Presented with a 24 hour history of vomiting, abdominal pain and SOB
- Unwell for the preceding week with reflux, nausea and anorexia
- Depressed and self ceased her insulin for 2 weeks

Background

Diabetes history:

- Type II diabetes mellitus
  - Diagnosed at age 18
  - Proliferative retinopathy – laser
  - Peripheral neuropathy
  - Nephropathy – microalbuminuria

Further history:

- Ischaemic heart disease
  - MI DES to LAD 2014
- Hypertension
- Dyslipidaemia
- Obesity –129kg
- Depression and anxiety
- Graves' disease
- Pyelonephritis 1998
- Recurrent UTIs
- Dysfunctional uterine bleeding

Medications

1. Glargine 70 units morning and 50 units nocte (reduced from 80/60)
2. Exenatide 10mcg BD
3. Dapagliflozin 10mg
4. Metformin XR 1000mg mane
5. Acarbose 100mg BD

- Clopidogrel 75mg
- Aspirin 100mg
- Perindopril 4mg
- Spironolactone 25mg
- Rosuvastatin 20mg
- ISMN 120mg
- Amitriptyline 75mg
- Carbimazole 15mg mane
- Medroxyprogesterone 7.5mg
- Levonorgestrel/ethinyloestradiol 150/30mcg (Levlen ED)
- Pantoprazole 40mg

Examination

- Afebrile
- BP 130/80 mmHg
- HR 120
- RR 30
- SaO2 100% RA

- Abdomen soft, generally tender

Investigations

- Negative septic screen
- Normal lipase
- Normal troponins

- Anti-GAD 3.4 (<10 IU/ml)
- Anti-IA2 4.8 (<10 IU/mL)

SGLT2 inhibitor associated DKA

Glucose (mmol/L)	15
pH	7.08
Bicarbonate (mmol/L)	7.6
Anion gap (mmol/L)	26
Ketones (mmol/L)	6.2
Lactate (mmol/L)	2.84
Potassium (mmol/L)	4.1
Creatinine (umol/L)	70
Hb (g/L)	148
WCC (x 10^9/L)	12.1
CPR (mg/L)	14
HbA1c %	10.2
TSH (mIU/L)	0.79
FT4 (pmol/L)	14
FT3 (pmol/L)	3.7

SGLT2 inhibitor associated DKA

- Precipitated by insulin cessation
- Consider ↓ beta cell reserve
- ? Antibody negative autoimmune diabetes (T1DM/LADA)

- Cardiovascular disease
- Diabetic nephropathy
- Obesity
- Hypertension

- Previous omissions of insulin due to depressed mood
- Recurrent UTIs with previous pyelonephritis

Case 2

- 67 year old woman with T2DM

- Presented with a 2 day history of feeling generally unwell, presyncope, dyspnoea, diaphoretic, nausea and vomiting traveling back from Dubai

Background

- Past medical history:
  - Type II diabetes mellitus
    - HbA1c 8.3%
    - No prior DKA
  - Spinal muscular atrophy
  - HTN
  - Osteoporosis
- Medications:
  - Glargine 8 units mane
  - Novorapid 5 units TDS with meals
  - Metformin 1500 mg
  - Dapagliflozin 10mg
    - 6 months duration
    - Reduction in glargine by 2 units
- Adopted

Investigations

	ED	ICU	ICU 6 hours post Insulin Infusion + 5% Dextrose	ICU 12 hours post Insulin Infusion + 5% Dextrose	ICU 24 hours post Insulin Infusion + 5% Dextrose
pH	7.03	7.02	7.19	7.29	7.41
HCO3-	7	6	11	13	20
K	5.0	4.9	3.4	3.4	3.9
AG	24	23	22	19	18
Lactate	1.3	1.1	1.8	1.6	1.4
BSL	8.6	9.4	11.8	13.6	10.7
Ketones	-	-	-	3.0	0.27
Hb	111				
WCC	11.3				
CRP	3.0				

- Shocked requiring inotropes
- Septic screen negative
- Bedside echocardiogram excluded cardiogenic shock
- CT chest/abdo/pelvis and CTPA was normal
- Consideration for exploratory laparotomy

- Anti-IA2 5.8
- Anti-GAD >2000

SGLT2 inhibitor associated euglycaemic DKA in T1DM

SGLT2 inhibitor associated DKA

- Missed diagnosis of type I diabetes mellitus
- Missed diagnosis of DKA by treating doctors
- Precipitated by missed insulin due to time zone changes with international flying

SGLT2 Inhibitor–Associated Euglycemic Diabetic Ketoacidosis: A South Australian Clinical Case Series and Australian Spontaneous Adverse Event Notifications

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Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age and Sex	67 F	67 F	38 F	82 M	55 F	53 M	64 F	70 M	52 M	45 F	59 F	75 F	67 F
T1D/T2D	T1D*	T2D	T1D*	T2D	T1D	T2D	T1D	T2D	T1D	T2D	T2D	T2D	T2D
T1 AB titres (<10.0 IU/mL)	Anti-GAD >2000, Anti-IA2 5.8	Anti-GAD 3.8 Anti-IA2 5.2	Anti-GAD 3.5, Anti-IA2 36.4	UNK	Anti-GAD 78.2, Anti-IA2 8.4	Anti-GAD 3.4 Anti-IA2 4.9	UNK	Anti-GAD 3.1, Anti-IA2 4.6	Anti-GAD 33.4, Anti-IA2 4.9	Anti-GAD 3.4, Anti-IA2 4.8	Anti-GAD 3.4 Anti-IA2 5.0	Anti-GAD 1.8 Anti-IA2 0.5	Anti-GAD 1.5 Anti-IA2 0.0
Duration of diabetes	> 20 years	11 years	6 months	14 years	12 years	UNK	35 years	10 years	15 years	27 years	47 years	UNK	UNK
Insulin	Glargine 8, Novorapid 3 TDS	Humalog mix25: 45/12	None	None	Novomix 30/12	None	Glargine 14/5 Novorapid 1-5 TDS	Glargine 56	Glargine 20	Glargine 70/50	None	UNK	Glargine 14u, Novorapid 3u TDS
SGLT2 inhibitor	Dapagliflozin 10mg	Dapagliflozin 10mg	Dapagliflozin 10mg	Dapagliflozin 10mg	Empagliflozin UNK	Dapagliflozin 10mg	Dapagliflozin 10mg	Dapagliflozin 10mg	Empagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin UNK	Dapagliflozin 10mg	Empagliflozin 25mg
Duration of SGLT2 inhibitor	6 months	6 months	5 months	3 months	1 month	2 weeks	2 weeks	2 months	6 months	6 months	UNK	UNK	3 weeks
OAH	Metformin	Metformin	Metformin Linagliptin	Gliclazide MR Metformin	Metformin	Metformin XR Sitagliptin	Metformin	Metformin	Metformin	Metformin, Acarbose	Metformin Sitagliptin	Metformin	Metformin Gliclazide
HbA1c % (mmol/mol)	8.3 (67)	6.5 (48)	10.1 (87)	9.3 (78)	10.9 (96)	9.6 (81)	9.7 (83)	13.4 (123)	9.8 (84)	10.2 (88)	7.6 (60) (anaemic)	UNK	6.8 (51)
Potential contributors	Reduced oral intake, missed insulin, missed T1DM	Diarrhoea, AKI, UTI	Missed T1DM	CABG	Gastroenteritis, missed insulin	No precipitant	Missed insulin	Influenza A, Staphlococcal pneumonia and bacteraemia	Necrotising fasciitis	Ceased insulin 2 weeks prior	Chemotherapy for breast cancer, blood dyscrasia, candiduria	Takotsubo cardiomyopathy LV thrombus Cardiogenic shock Cardiopulmonary arrest	Missed insulin 3 days Acute cholecystitis
Insulin reduction	Yes Glargine by 2u	Insulin ceased 6 weeks prior	UNK	UNK	Yes	UNK	Yes Glargine by 4u	No	No	Ceased insulin	UNK	UNK	Missed insulin
BSL (3.2-5.5 mmol/L)	8.6	9.7	13	6.8	20	13.8	11	29	UNK	15	34.6	29.7	18.7
pH (7.38-7.45)	7.0	NA	NA	7.3	NA	7.3	7.1	7.2	UNK	7.1	6.9	6.9	UNK
Ketones (Beta OH Butrate <0.30 mmol/L)	3.0 (12 hours)	7	13	7	3.5 (24 hours)	5.8	6.0	6	UNK	6.2	5.2	7	UNK
Bicarbonate (22-32mmol/L)	6	13.8	2	14	4	14	5	11	5	7.7	3	7	6
Anion gap (7-17mmol/L)	24	24	32	26	41	32	32	34	38	26	48	42	40
Admission date	Dec 2015	Dec 2015	Jan 2016	Jun 2016	Jun 2016	July 2016	Aug 2016	Sep 2016	Sep 2016	Oct 2016	Oct 2016	Mar 2017	Mar 2017
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Insulin infusion duration	48 hours	UNK	48 hours	24 hours	24 hours	48 hours	48 hours	24 hours	48 hours	48 hours	UNK	UNK	UNK
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Deceased	Recovered

South Australia case series from December 2015 to March 2017.

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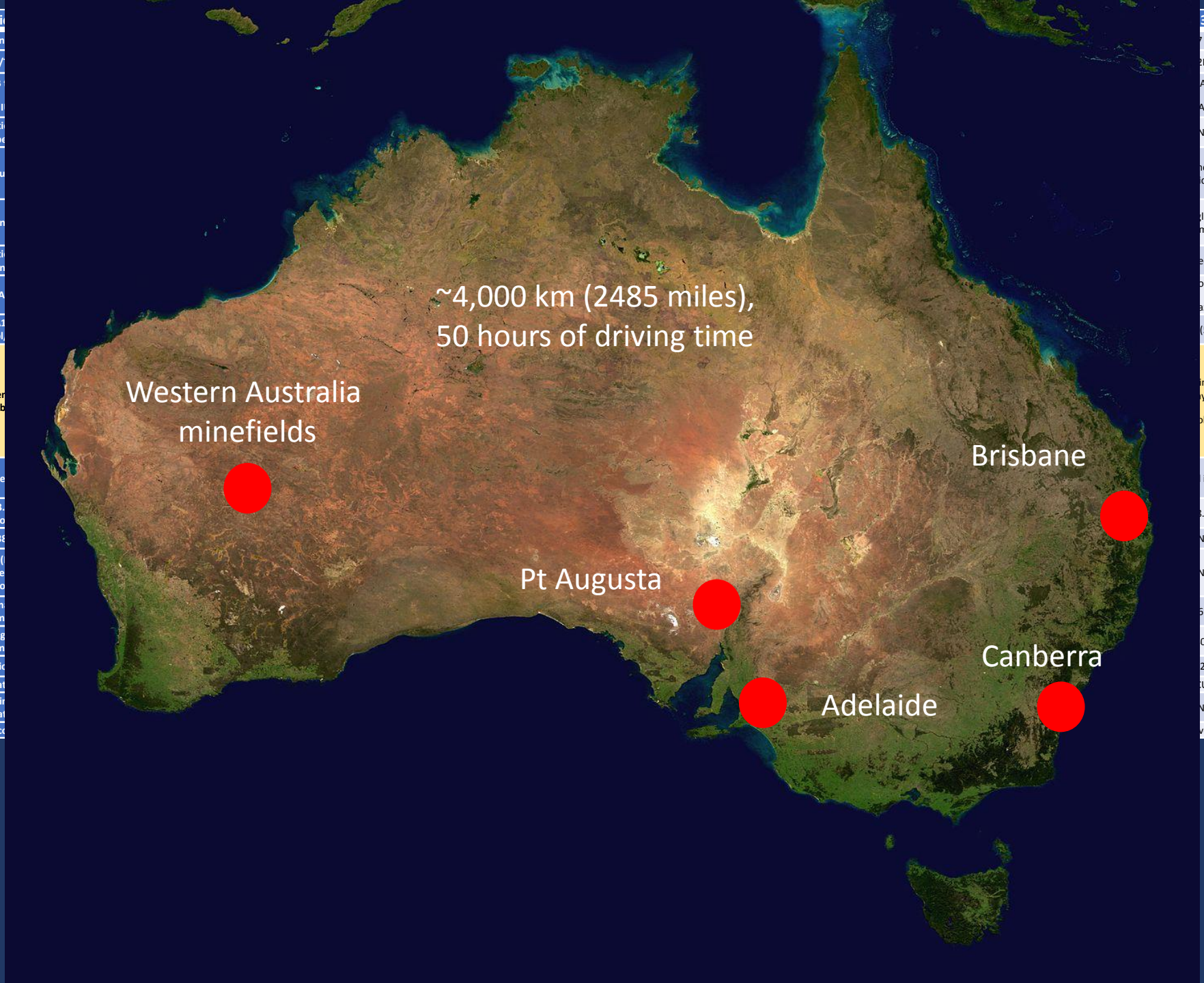
~4,000 km (2485 miles),
50 hours of driving time
Western Australia
minefields
Brisbane
Pt Augusta
Canberra
Adelaide

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OAH	Metformin	Metformin	Metformin Linagliptin	Gliclazide MR Metformin	Metformin	Metformin XR Sitagliptin	Metformin	Metformin	Metformin	Metformin, Acarbose	Metformin Sitagliptin	Metformin	Metformin Gliclazide
HbA1c % (mmol/mol)	8.3 (67)	6.5 (48)	10.1 (87)	9.3 (78)	10.9 (96)	9.6 (81)	9.7 (83)	13.4 (123)	9.8 (84)	10.2 (88)	7.6 (60) (anaemic)	UNK	6.8 (51)
Potential contributors	Reduced oral intake, missed insulin, missed T1DM	Diarrhoea, AKI, UTI	Missed T1DM	CABG	Gastroenteritis, missed insulin	No precipitant	Missed insulin	Influenza A, Staphlococcal pneumonia and bacteraemia	Necrotising fasciitis	Ceased insulin 2 weeks prior	Chemotherapy for breast cancer, blood dyscrasia, candiduria	Takotsubo cardiomyopathy LV thrombus Cardiogenic shock Cardiopulmonary arrest	Missed insulin 3 days Acute cholecystitis
Insulin reduction	Yes Glargine by 2u	Insulin ceased 6 weeks prior	UNK	UNK	Yes	UNK	Yes Glargine by 4u	No	No	Ceased insulin	UNK	UNK	Missed insulin
BSL (3.2-5.5 mmol/L)	8.6	9.7	13	6.8	20	13.8	11	29	UNK	15	34.6	29.7	18.7
pH (7.38-7.45)	7.0	NA	NA	7.3	NA	7.3	7.1	7.2	UNK	7.1	6.9	6.9	UNK
Ketones (Beta OH Butrate <0.30 mmol/L)	3.0 (12 hours)	7	13	7	3.5 (24 hours)	5.8	6.0	6	UNK	6.2	5.2	7	UNK
Bicarbonate (22-32mmol/L)	6	13.8	2	14	4	14	5	11	5	7.7	3	7	6
Anion gap (7-17mmol/L)	24	24	32	26	41	32	32	34	38	26	48	42	40
Admission date	Dec 2015	Dec 2015	Jan 2016	Jun 2016	Jun 2016	July 2016	Aug 2016	Sep 2016	Sep 2016	Oct 2016	Oct 2016	Mar 2017	Mar 2017
Location	ICU	UNK	UNK	ICU	ICU	HDU	ICU	ICU	ICU	Ward	ICU	ICU	ICU
Insulin infusion duration	48 hours	UNK	48 hours	24 hours	24 hours	48 hours	48 hours	24 hours	48 hours	48 hours	UNK	UNK	UNK
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Deceased	Recovered

Adverse events rate

- 85,851 SGLT2 inhibitor prescriptions in SA were filled over the period of the case series (December 2015 -March 2017)
- Estimate an adverse event rate of **1.8 cases of SGLT2 inhibitor associated DKA per 1000 patient years**

Summary of notifications of adverse events

Total number of unique case reports	**82**
Male:Female	50:28 (Sex unreported in 4)
Age (years)	60 (Range: 25-88)
Type of diabetes (n)	Type 2 diabetic: 24 Type 1 diabetic: 9 **Non diabetic: 2** Unreported: 47
SGLT2 inhibitor (n)	Dapagliflozin: 56 Empagliflozin: 23 Canagliflozin: 3
Duration of SGLT2 inhibitor use prior to DKA presentation (n=28)	Average: 11.6 weeks Range: 1 day-76 weeks
Number prescribed insulin prior to DKA (n)	12

Biochemical parameters

pH (n=13)	7.06 (Range: 6.69-7.30)
Glucose (mmol/L) (n=22)	14.4 (Range: 4.8-35)
Ketones (mmol/L) (n=11)	6.2 (Range: 4.1-11)
Anion gap (mmol/L) (n=7)	23.7 (Range: 20-27)
Bicarbonate (mmol/L) (n=10)	7.35 (Range: 2.8-17)
HbA1c% (n=4)	8.25 (Range: 7.7-9)

Precipitating factors (n = 22)

Intercurrent illness	• Acute coronary artery event • ST segment elevation myocardial infarction • Cardiopulmonary arrest and permanent pacemaker insertion • Oesophageal rupture • Urosepsis • Influenza • Cellulitis • Acute on chronic renal failure and liver enzyme derangement • Gastric disorder (unspecified)
Surgery (15%)	• Coronary artery bypass graft • Cardio-thoracic surgery • Orthopaedic surgery • Knee replacement surgery • Knee surgery • Hysterectomy and oophorectomy • Surgery (unspecified)

Reduced oral intake	• Low carbohydrate diet • Fasting preoperatively • Fasting preoperatively
Medication changes	• Increase empagliflozin from 10 to 25mg oral daily • Insulin reduction post sleeve gastrectomy • Ceased Actrapid insulin
Health system factors	• Missed diagnosis of Type 1 DM • Co-prescription of dapagliflozin and canagliflozin in 1 case

Key Issues

1. Most patients did not recognize DKA
2. Treating physicians often did not initially recognize DKA due to relative euglycaemia → delayed treatment
3. Most cases were severe, one associated death
4. Identifiable precipitants were often present → potential for risk mitigation
5. 2 cases with off label use
6. Retrospective diagnosis of type I diabetes mellitus

Recommendations

- Illness prodrome similar to DKA in T1D, however often occur in the absence of marked hyperglycaemia
- Thus early detection of the ketotic state while symptomatic in the context of precipitants → temporary cessation of SGLT2 inhibitor, hydration, carbohydrate consumption and administration of full dose insulin
- Temporary cessation of these drugs during acute illness and surgery
  - 30% pf surgery performed at our hospital is in patients with diabetes
- Consider excluding a diagnosis of T1D before prescribing and re-evaluating diabetes diagnosis upon DKA presentation
- In T1DM use with caution (off label)
- Awareness of colleagues and patient education

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