Diabetic and Metabolic Emergencies

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Diabetes is a huge problem

Four out of five people with diabetes now live in developing countries

Top 10 countries by prevalence: 2013
Diabetes is a huge and growing problem

- 387 million people have diabetes
- By 2035, this number will rise to 592 million

Treating type 2 diabetes and its complications is costly

Annual costs per patient

- All insured patients: €1,373
- Diabetes, no complications: €1,723 (1.3x increase)
- Diabetes, microvascular complications: €3,355 (2.4x increase)
- Diabetes, macrovascular complications: €3,436 (2.5x increase)
- Diabetes, micro- and macrovascular complications: €5,642 (4.1x increase)

The management of adult diabetes services in the NHS - Public Accounts Committee

......“just 16% of people with diabetes have achieved the recommended levels for blood glucose, blood pressure and cholesterol leaving an unacceptably high proportion of people with diabetes at higher risk of developing related complications”.................
American Diabetes Association/European Association for the Study of Diabetes Position Statement 2015

Healthy eating, weight control, increased physical activity, diabetes education

Initial monotherapy

Not at target HbA1c after ~3 months

Two-drug combinations

Not at target HbA1c after ~3 months

Three-drug combinations

Not at target HbA1c after ~3 months

Combination injectable therapy

Metformin + basal insulin + meal-time insulin or GLP-1 RA

Disease progression

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated haemoglobin; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione

Inzucchi SE et al. Diabetes Care 2015;38:140−149
Mr JW
Presentation

• 66 year old male
• A+E ref: chest pain + vomiting
• HPC:
  – Well previous day
  – Evening: gradual onset, chest pain, nausea.
  – Kept awake at night.
  – No SOB, clamminess.
  – Morning: vomiting: initially clear, then brown
<table>
<thead>
<tr>
<th>Past Medical History</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Type 2 diabetes mellitus</td>
<td>– Sitagliptin 100mg OD</td>
</tr>
<tr>
<td>• Diagnosed 10 yrs ago</td>
<td>– Metformin 3.5g BD</td>
</tr>
<tr>
<td>– Hypertension</td>
<td>– Perindopril 4mg OD</td>
</tr>
<tr>
<td>– Hypercholesterolaemia</td>
<td>– Simvastatin 10mg OD</td>
</tr>
<tr>
<td>– Angiogram 2006 – NAD</td>
<td>– Diclofenac 50mg TDS</td>
</tr>
<tr>
<td>– Ulcerative colitis</td>
<td>– Rabeprazole 20mg OD</td>
</tr>
<tr>
<td></td>
<td>– Tamsulosin 400mcg OD</td>
</tr>
<tr>
<td></td>
<td>– Cetirizine 10mg OD</td>
</tr>
<tr>
<td></td>
<td>– Beclomethazone inhaler BD</td>
</tr>
</tbody>
</table>
Examination

- Looked clapped out
- Retching + vomiting brown fluid
- Persistent pain – despite morphine
- Apyrexial
- BP 142/62, HR 93 regular
- RR 20, O\textsubscript{2} sats 100% on O\textsubscript{2}
- Cardio / resp / abdo unremarkable
- Stool seen in A+E – no blood
Investigations

- ECG – SR, no dynamic changes.
- CXR – NAD
- ABG (air)
  - pH 6.980
  - pCO2 4.85
  - PO2 7.22
  - BE -21.1
  - HCO3 8.1
  - Lactate 14.6
  - Glucose 2.8
Investigations

• Bloods:
  – Na 142, K 6.1,
  – Urea 22.2, Creat 420 (123 prev)
  – C.Ca 2.59, PO4 2.60, Amylase 60
  – Bilirubin 7, ALP 51, ALT 17, Albumin 45
  – Hb 12.5, WCC 21.9, neut 17.6 plt 476
  – INR 1.1
What is the underlying diagnosis?

A. Sepsis
B. Lactic acidosis 2\textsuperscript{nd} metformin
C. Acute renal failure 2\textsuperscript{nd} NSAID / ACEI / dehydration
D. Ischaemic bowel
E. Gastrointestinal bleed
Management Plan

1) Aggressive fluid resuscitation
2) Careful fluid balance
3) IV co-amoxiclav
4) Urine: MC+S + casts
5) Stop metformin
6) ITU + Surgical r/v
Later

- Surgical r/v - ? Ischaemic gut – happy to watch
- ITU – insulin sliding scale, bicarbonate and haemofiltration
- Step down to ward after 4/7
  - Urea 9.6, Creat 254, WCC 9.5.
- Discharged home day 14.
Anion Gap Acidosis

Anion gap acidosis

Lactic acidosis

Type A
- Tissue hypoperfusion
- Hypoxemia
- Cardiac arrest

Type B
- Acute thiamine deficiency
- TPN without vitamins
- Inherited mitochondrial disease
  Respiratory chain enzyme deficiency
- Pyruvate carboxylase deficiency
- Short bowel syndrome
  (D-lactic acidosis)
- Hepatic failure
- Toxins
  Biguanides (metformin)
  NRTI therapy

Non-lactic acidosis

Ketoacidosis
- Diabetes
- Ethanol
- Starvation
- Uremia
- Salicylates
- Ethylene glycol
- Methanol
- Paraldehyde
- Isoniazid
Metformin

Chemical Formula: C₄H₁₄N₅
Metformin

• French Lilac plant 1900’s lowered blood sugar but toxic
• Metformin related shorter duration less toxic 1957
• Phenformin & buformin longer acting and more toxic
• Metformin 1970s europe  USA 1995
• Efficacy
  – Lowers A1c by 1.5%
  – UKPDS 36% reduction in mortality
A problem!
• Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate.
• The accumulation of lactic acid may increase under several circumstances.
• The occurrence of metformin induced lactic acidosis is uncommon when the drug is used with caution.
Gerti Cori
Nobel prize 1947
Key points

• Metformin induced Lactic acidosis is rare, but serious, with a mortality up to 50%. It is a type of high anion gap metabolic acidosis.

• Those at Risk:
  – Elderly
  – Frail
  – Other Co morbidities (renal impairment)
Two cases of DKA- eh?
Case 1

• 34 year old male JR
• 24 hour history of abdominal pain & vomiting
• PMHx:
  – Previous alcohol excess;
  – acute pancreatitis
  – type 2 diabetes
  – bronchiectasis
Case 1

• Provisional diagnosis: recurrent pancreatitis
• However ABG showed:
  – pH 6.95  
  – HCO₃ 5.7  
  – Base excess -27.4  
  – Lactate 0.5  
  – Glucose: 10.4
• Urinary ketones: 7.8  
• Amylase 37  
• CT abdomen: atrophic pancreas, no secondary signs of acute pancreatitis
Case 2

- 36 y/o female KH
- PMHx:
  - Polycystic ovarian syndrome
  - Hypertension
  - type 2 diabetes
- October 2014: underwent distal pancreatectomy for 15cm cyst. Shown to be mucinous cystadenoma
Case 2

- Sliding scale stopped 4 days post-op and regular oral diabetic meds restarted
- Within 24hrs:
  - pH 7.34 (7.35 - 7.45)
  - HCO₃ 19.9 (22 - 26mmol/L)
  - Base excess - 4.9 (+/- 2mmol/L)
  - Lactate 0.8 (<1.3)
  - Glucose: 5.9
- Urinary ketones: 15.6 mmol/L
Diabetes classification

Diabetes + acidosis + ketonuria = DKA

- DKA suggests not type 2 diabetes
- Likely pancreatic diabetes (type 3c)
- Major criteria
  1. Pancreatic exocrine dysfunction (insulin & C-peptide)
  2. Abnormal pancreatic imaging
  3. Negative diabetes autoimmune screen
But why was glucose normal?

A. Reduced calorie state
B. Exogenous insulin administration
C. Intercurrent sepsis
D. Unexplained interaction
E. Renal tubular acidosis
Euglycaemic DKA

- Defined as DKA with plasma glucose <11.1mmol/mol
- First described in 1973
- Rare, seen in type 1 diabetes in association with reduced calorie states
The twist in the tale...

JR’s DHx:
• Metformin 1g BD
• Gliclazide 120mg OD
• Levemir 20units ON
• Dapagliflozin 10mg OD

KH’s DHx:
• Metformin 1g BD
• Dapagliflozin 10mg OD
 Majority of glucose is reabsorbed by SGLT2 (90%)

SGLT2, sodium-glucose co-transporter.
SGLT-2 inhibitors

- SGLT-2 responsible for reabsorption of filtered glucose
- SGLT-2 inhibition → insulin-independent lowering of blood glucose
- Main side effect is ↑ genito-urinary tract infections due to glycosuria

And what happened to JR & KH?

- Both treated with insulin sliding scale and fluids as per DKA protocol
- Started on s/c insulin regimen
- Full recovery and discharge from hospital
SGLT-2 inhibition and euglycaemic DKA

SGLT inhibition and euglycaemic diabetic ketoacidosis

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are now widely used as an adjunctive treatment in managing type 2 diabetes.1 Due to their ovarian syndrome, then underwent a distal pancreatectomy for a mucinous cystadenoma. In intensive care after surgery, insulin sliding scale was stopped and dapagliflozin therapy was reintroduced. Within 24 h, she developed a metabolic acidosis, with pH 7.34, bicarbonate 19.9 mmol/L, base excess −4.9 mmol/L. lactate risk of progression to life-threatening metabolic derangement. Accurate diagnosis of diabetes type is essential in cases where SGLT inhibition is being considered, to enable informed risk assessment and avoid inappropriate patient exposure to these drugs. Increased monitoring for ketones will be essential if SGLT2

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Hine et al. Lancet May 27 2015
FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

[ 05-15-2015 ]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking
Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes

**Primary outcome**

HR: 0.86 (95% CI: 0.74; 0.99)
p = 0.04 for superiority

**Death from cardiovascular causes**

HR: 0.62 (95% CI: 0.49; 0.77)
p < 0.001

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Key points

• Suspect DKA in *any* patient with diabetes presenting with abdominal pain and vomiting
• Diagnosing correct mechanism for diabetes is important in guiding management
• Caution with SGLT-2 inhibitors; use carefully in patients at risk of insulin deficiency
• SGLT2 will be increasingly used in diabetes
Sir Edward Sharpey-Shafer

1895: Suggested that the islets of Langerhans may function as a gland that regulates blood Sugar... “insuline”
(3) The substance (insuline) produced by the pancreas islets may be a chalonic autocoid which tends to inhibit the formation of glucose from glycogen, and incidentally to promote the storage of glycogen, so that in its absence the glycogen which is present in the liver is rapidly converted into glucose.
Primary Effects of Insulin On Blood Glucose

Decrease hepatic Glucose production

Liver

Pancreas

Increase peripheral Glucose uptake

Muscle
In normal physiological conditions, what is the major action of insulin?

A. Suppressing hepatic glucose output (LIVER)
B. Pushing glucose into tissues (PERIPHERY)
\[ Ra \downarrow \]
(liver)

\[ Ra \downarrow Rd \uparrow \]
(muscle)
How Do We Find Out?

A Pilot ‘Dynamic Tracer Study’ in Mrs H - a newly diagnosed IDDM
Insulin Distribution In Normal Physiology

Peripheral tissues

Adipose

Muscle

Systemic circulation

Food

Pancreas

Insulin

Portal circulation

Glucose
Insulin Distribution In Diabetes With Exogenous Administration

Peripheral tissues

Adipose

Muscle

Liver

Food

Pancreas

Glucose
Molecular modifications of insulin

Residues preserved in naturally occurring insulins

Residues critical for receptor binding

Insulin degludec: structure

*Des*(B30) *Lys*B29(β-Glu Nε-hexadecandioyl) human insulin

**desB30 Insulin**

Human insulin with one amino-acid removed and a C-16 fatty diacid side chain attached via a spacer

**Hexadecandioyl**

C-16 fatty diacid side chain

Insulin degludec multi-hexamers

Main picture shows elongated IDeg structures in absence of phenol; inset (white box) shows absence of elongated IDeg structures in presence of phenol.

Kurtzhals P. EASD 2011; 092-P #1049 (MoP + NN1250-1993)
Degludec pharmacokinetic profile: single dose and steady state

People with type 1 diabetes (n=12)
0.4 U/kg once daily for 6 days

Measurement of blood ketones

RSCH ADULT DIABETIC KETOACIDOSIS
Management Guideline and Prescription Chart

Date........................................... Ward...........................................
Consultant.........................................................
Patient weight (kg)...............................................
Time of diagnosis ..................................................

For people with type 1 diabetes. Full details can be found in the red book.

Confirm diagnosis of DKA – all of the following present:
• Significant ketonuria (>2+) or blood ketone >3mmol/L
• Blood glucose >11mmol/L or known diabetes mellitus
• Bicarbonate <15mmol/L or venous pH <7.3

IMMEDIATE ACTION
• Rapid ABC with measurement of RR, temp, pulse, BP, EWS, GCS, and pulse oximetry
• Capillary blood glucose check and blood ketones
• Obtain urgent IV access and commence IV fluids (Box A action 2) if there is a problem request critical care support
• Stat dose of 10 units rapid acting S/C insulin
• Venous sample for – U&Es, FBC, Glucose, bicarbonate and pH measured via venous blood gas

The presence of one or more of the following may indicate severe DKA – obtain immediate senior review and consider admission to HDU/ITU:
• Blood ketones above 6mmol/L
• Venous bicarbonate level below 5mmol/L
• Venous or arterial pH below 7.1
• Hypokalaemia on admission (below 3.5mmol/L)
• Anion gap above 16 (Na⁺ – K⁺) – (Cl⁻ + HCO₃⁻)
• GCS less than 12
• Oxygen saturations below 92% (assuming baseline respiratory function) May indicate lung adult respiratory distress syndrome, ARDS or severe cardiac failure.
• Systolic BP below 90mmHg
• Pulse over 100 or below 60 bpm

Important causes of DKA
• Insulin deficiency
  o Insulin reduced or not increased during intercurrent illness
  o Insulin stopped deliberately
  o Untreated newly diagnosed patient
• Infection
  o Chest / urinary tract / skin
• Myocardial infarction
  o May be painless in older diabetic patients
• Trauma, surgery, burns

Ketone strips are expensive and should be used appropriately. 6 ketone strips are provided in the emergency purple pack. Further ketone strips can then be obtained on a patient named basis via EAU. Please ask EAU Sister in charge.

RSCH ADULT DIABETIC KETOACIDOSIS PRESCRIPTION CHART

ACIDOSIS PRESCRIPTION CHART (FIRST 24 HOURS)
Tip does not require duplication on Trust drug chart

UIDS should be commenced via a large IV cannula (green or grey). If problems should be requested immediately.

<table>
<thead>
<tr>
<th>Time/hour</th>
<th>Rate ml/hour (circle as appropriate)</th>
<th>Potassium (circle as appropriate) in Sodium chloride 0.9%</th>
<th>Prescriber</th>
<th>Administered by</th>
<th>2 nurse check</th>
<th>Batch number</th>
<th>Date / Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>/other * ...........</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional volume of infusion should be considered in patients <25 or over 70 years of age, pregnant, patients with failure. If systolic BP<90mmHg give 500ml over 15 minutes.
RSCH DKA data (03/14 – 08/15)

- 45 episodes with DKA.
  - 29 under the age of 70 years.
  - 4 people readmitted > 2 times within the same year.
  - People with repeated admissions with DKA were converted to insulin degludec.
  - This has been 100% successful at preventing readmission.
Key points

- DKA practice is changing
- Not just young people
- Availability of capillary ketone measurement allows more aggressive approach
- Fixed insulin infusion rate rather than sliding scale in first 24 hours
- Very long acting insulin analogues may be helpful for recurrent attenders
Diabetes in the Emergency Department

• 2 sites
  – Royal Surrey County Hospital
  – Frimley Park Hospital

• Data on all emergency attendances coded as ‘diabetes and endocrinology’ over a year

• Diabetes team not involved or aware of many emergency episodes

Results

• 251 patients coded as Diab/Endo
• Records traced for 221 patients
• Hypoglycaemia most common reason for attendance
  • 94/221 (37%)
• Hyperglycaemia
  • 33/221 (15%)

Treatment of hypoglycaemia
Key points

• Hypoglycaemia was the commonest reason for attendance
• 12 different treatment methods used
• Most patients were discharged
• 50% had no follow-up
• No advice given about driving
  – 1 patient was involved in road traffic accident
  – 3 patients were found collapsed in their car
Number of BG <1.5 associated Patient (Counted Once per 24hrs)
Events over Time by A1-A3/Path
Management of Raised Glucose (MoRG)

Management of raised glucose, a clinical decision tool to reduce length of stay of patients with hyperglycaemia


Centre for Endocrinology, Diabetes and Research, Royal Surrey County Hospital, Guildford, UK

What would you do?

35 year presents with primary hyperglycaemia (BM18)

A. Discharge with GP review the next day
B. Admit for diabetes review
C. Start oral glucose lowering medication
D. Request plasma glucose, ketones and renal function to aid decision
E. Discharge with DSN review the next day
Management of Raised Glucose

Please fill in these results and circle your patients outcome on the flow chart

Lab glucose

Capillary ketones

U&E Creatinine

Calc plasma Osmo = 2(Na+K) +urea+glucose
<table>
<thead>
<tr>
<th>Did the pathway make a difference??</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong> PRE MoRG</td>
<td><strong>Phase 2</strong> with MoRG</td>
</tr>
<tr>
<td>Patients admitted</td>
<td>72</td>
</tr>
<tr>
<td>Hyperglycaemia primary admitting diagnosis</td>
<td>32</td>
</tr>
<tr>
<td>Suitable for discharged</td>
<td>13</td>
</tr>
<tr>
<td>Actually discharged</td>
<td>0</td>
</tr>
</tbody>
</table>
Key points

Clinical decision tool can be used for all patients with a raised blood glucose:

- Safe early discharge/Admission avoidance
- Improved patient care (whether admitted or not)
- Improved patient satisfaction
- COST SAVING
Mr BT

- 54 year old man
- Stroke call
- Right arm numbness

BUT:
- Stroke SpR noted patient had 6/7 “shivers & sweats”

- Pyrexial in ambulance
- Bloods:
  - WCC 21 (neuts 17), CRP 227
  - Na 126, K 5.2,
  - Ur 12.7, Creat 82
  - Glu 18.8mmol
- CT head – No evidence acute ischaemic event
Imaging
What would you do next?

A. Urgent incision and drainage
B. Urgent orthopaedic review
C. Urgent vascular review
D. Referral to MDFT (happens weekly)
E. 48 hours IV antibiotics and review response
Admitted to Stroke unit

X-ray: Gas in tissues

Treatment timeline

Day 1
- Admitted to Stroke unit

Day 2
- X-ray: Gas in tissues
- Ortho opinion: Request MRI
- Refer to MDFT (next one 10/7)

Day 3
- I&D
- Cardiac arrest in theatre

Day 4
- ORTHO opinion: expeditate transfer to vascular centre
- Transferred to Vascular centre at 12:45pm

Day 5
- Worsening sepsis & AKI

Day 6
- Trauma meeting outcome 0800hrs
- MRI (“if allowed with cardiac stents”)
- Referral to diabetic foot team
- Referral to MDFT

Day 7
- Below knee amputation

Day 8
- Cardiac arrest in theatre

Day 21
- Subsequent transfer to renal unit for dialysis

Day 49
- Multiple CVAs

Day 77
- Back to vascular centre for palliative care

Died
THE GUILDFORD FOOTPATH - Immediate care of patients with acute DIABETES FOOT problems

- Patients with diabetes must have both feet examined by a doctor on admission even if there are no symptoms (neuropathy)
- You must take down any dressings
- Subsequent daily inspection by nurses is mandatory
- The minimum assessment (RIGHT) is needed to use this pathway

ON CALL T&O
Do any of the following apply:
- Wet gangrene
- White cold pulseless foot
- Critically ischaemic limb

ON CALL T&O
Are any of the following present:
- Hot red swollen foot
- Boggy tissue when pressed
- Collection of pus on exam
- Crepitus or gas in the tissues on a plain XR

ON CALL MEDICINE
- Spreading cellulitis
- Ulcer infected

ON CALL MEDICINE
Dry gangrene of toe (toes)

ON CALL MEDICINE
Non-infected foot ulcer in patient admitted with another diagnosis

ON CALL T&O
Warm, slightly swollen, non infected foot

CIRCLE OUTCOME and FILE IN NOTES

ON CALL T&O
TRANSFER NOW to regional vascular hub
Contact on call vascular consultant via switch

This is a FOOT ATTACK!
This patient may lose a limb or die if you do not act

ORTHO REVIEW AT TRAUMA MEETING
- ? Osteomyelitis
- Is urgent vascular opinion needed?

ON CALL T&O
URGENT (within 6hrs) incision and drainage
On call T&O to undertake

F&A ORTHO
CARE OF ALL PATIENTS WITH DIABETES FOOT PROBLEMS
- Pressure mattress
- Minimal weight bearing
- No anti-embolism stockings if neuropathy or impaired pulses
- Inform diabetes registrar when patient admitted

WHO LOOKS AFTER THE PATIENT?
- ON CALL T&O = admitting ortho surgeon until T&O meeting next working day
- F&A ORTHO = foot and ankle ortho . Weekday rota
- ON CALL MEDICINE = admitting physician
- DIABETES = Diabetes ward

Minimum assessment:
- Foot pulses R L
- Sensation R L
- FBC Hb WCC
- CRP
- Creatinine
- Plain x ray of foot

ORTHOCARE OF ALL PATIENTS WITH DIABETES FOOT PROBLEMS
- Manage conservatively
- Refer inpatient podiatry
- Diabetes consultant IP review
- F&A Ortho review
- Prevention see purple box adjacent

F&A ORTHO
Possible Charcot
Strict non weight bearing

ON CALL MEDICINE
- Non-urgent (<3 days) inpatient vascular review
- DSN review if needed
Key point

• Diabetes foot complications are an increasing problem that everyone will be exposed to.
• It is a battle ground between specialities
• A clear pathway is essential for good management
Definition Of Success:
The Circle of Life

At age 4….success is….not peeing in your pants.

At age 12….success is….having friends.

At age 16….success is….having a drivers license

At age 20….success is….having sex.

At age 35….success is….having money.

At age 80….success is….not peeing in your pants.

At age 75….success is….having friends.

At age 70….success is….having a drivers license.

At age 60….success is….having sex.

At age 50….success is….having money.
Thank you