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@ BACCNUK #BACCNConf2019
• Understand the differences between Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS)

• Explore pathophysiology of DKA and HHS

• Explore the clinical presentation and management of both

• Test your knowledge round
Diabetes mellitus is the term used to denote a complex group of endocrine disorders, which result in a disturbance of normal glucose metabolism.
FACTS AND FIGURES

• About 8.5% of world’s population has diabetes
• There are 3.8 million approx. people with diabetes in the UK, that’s 1:20 people
• Diabetes is the leading cause of blindness in people of working age
• 24,000 people with diabetes die early, 75,000 deaths in total per year.
• www.diabetes.org.uk
HOSPITAL SPECIFIC FACTS

- 1 in 25 inpatients with type 1 diabetes develops DKA during their hospital stay
- In 2010, 14,375 acute hospital admissions with DKA as primary diagnosis
- 1,800 annual admissions to ICU with a diagnosis of DKA
- 169 amputations are carried out each week nationally
- Diabetes accounts for 10% of the NHS budget

Insulin is a polypeptide or protein hormone essential in enabling the uptake of glucose into cells. Insulin homeostasis is essential for the normal metabolism of proteins, carbohydrates & fats.

- Synthesized and stored in beta cells in The Islets of Langerhans.
- In a healthy, normal weight person the average daily secretion of insulin is equivalent to 30-40 units.
- Many synthetic types with varying speed of action and duration.
Insulin deficiency

- Hyperglycemia
  - Osmotic diuresis
    - Dehydration
  - Ketoacid production
    - Acidosis
      - Hyperkalemia
T1DM results from destruction of the beta cells in the Islet of Langerhans in the pancreas, resulting in the more or less absolute deficiency of insulin.

Most cases caused by autoimmune or idiopathic destruction of the Islets.
Caused by impaired insulin secretion and resistance to its action, often secondary to obesity (80% approximately are obese).

May have normal or abnormally high levels of insulin: insulin resistance occurs

The GLUT-4 receptor mechanism on the cell may be the site of impaired insulin transport

Normally develops later in life >40 years
• Genetic defects of beta cell function
• Disease of the exocrine pancreas (pancreatitis/carcinomas)
• Endocrinopathies
• Drug induced
• Infections
• Other genetic syndromes
• Gestational Diabetes
DIABETIC EMERGENCIES

DKA
HHS
Hypos
ICU Nurse!!
• Results from a mismatch between nutrient intake, activity & insulin timing

• Can be mild (<3.9mmol/l), moderate, or severe (<2.2mmol/l)

• Mild hypo – usually adrenergic with symptoms of tremor, palpitation, sweating, hunger

• Severe hypo characterised by rapid deterioration in responsiveness, loss of consciousness & seizures, cardiac arrest. Requires immediate intervention to correct glucose level
NEUROGLYCOPENIA

• A reduction in blood glucose in the brain caused by hypoglycemia

• We know the brain cannot make or store glucose and is dependent on blood supply

• Untreated results in seizures, unconsciousness, irreversible brain damage, death.
Both DKA and HHS result as relative or absolute insulin deficiency, this in turn is associated with hyperglycemia.

T2DM with DKA: syndrome known as ketosis prone diabetes
HHS more common complication of T2DM

HHS has replaced the terms hyperglycemia hyperosmolar nonketotic state (HONK)- this was revised as HHS may consists of variable degrees of clinical ketones

They differ clinically by severity of dehydration, ketosis and metabolic acidosis
EUGLYCEMIC DIABETIC KETOACIDOSIS

Defined as euDKA, DKA without marked hyperglycaemia

Linked to SGLT-2 inhibitors (gliflozins)

Have a tendency to cause DKA in some patients

The biochemical reason for this is unclear, possible linked to noninsulin dependence glucose clearance, hyperglucagonaemia and volume depletion

Delayed recognition and diagnosis is a problem  
TRIAD OF DKA

Hyperglycemia

Other Hyperglycemic States:
- Diabetes Mellitus
- Non-ketotic Hyperosmolar Coma
- Stress Hyperglycemia
- Drug-induced Hyperglycemia

Other Metabolic Acidosis States:
- Normal Anion Gap Hyperchloremic Acidosis
- Diarrhea
- Renal Tubular Acidosis
- Rapid Large Volume Saline Infusion
- High anion gap metabolic acidosis
- Lactic acidosis (L- and D-lactate)
- Salicylate
- Ethylene Glycol, Methanol, Propylene Renal Failure (Uremia)
- Drug-induced Acidosis

Ketosis

Other Ketotic States:
- Starvation Ketosis
- Alcoholic Ketosis

Metabolic Acidosis

DKA
PRECIPITATING CAUSES

Infection
Missed doses of insulin / poor adherence to treatment
New diagnosis of diabetes mellitus
Alcohol or drugs
Pancreatitis
Cardiovascular disease / Stroke
Diarrhoea and vomiting
Psychological illness relating to eating disorders
Severe physiological stress
Pregnancy
Drugs that affect carbohydrate metabolism
# THE 5 I’S

<table>
<thead>
<tr>
<th><strong>Infection</strong></th>
<th>Urinary, respiratory, skin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infarction</strong></td>
<td>Myocardial infarction, stroke, bowel, bone, skin</td>
</tr>
<tr>
<td><strong>Infant on board</strong></td>
<td>Pregnancy</td>
</tr>
<tr>
<td><strong>Indiscretion with diet</strong></td>
<td>Non-compliance with diabetic diet (e.g., sugar, carbohydrates or alcohol)</td>
</tr>
<tr>
<td><strong>Insulin lack</strong></td>
<td>Pump failure, skipping insulin doses</td>
</tr>
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CLINICAL PRESENTATION

DKA
History (rapid onset)
Hyperventilation ‘Kussmaul’ breathing
Polyuria
Polydipsia
Weight loss
Nausea and vomiting
Confusion, altered consciousness, coma
Dehydration
Lethargic
Ketonic breath
Abdominal pain

HHS
History (gradual onset)
More common in the elderly
Polyuria
Dehydration
Confusion, agitation, drowsy
Focal neurological deficit, seizures, obtunded and coma
## Table 1—Diagnostic criteria for DKA and HHS

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/l)</td>
<td>15–18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Urine ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Small</td>
</tr>
<tr>
<td>Serum ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Small</td>
</tr>
<tr>
<td>Effective serum osmolality (mOsm/kg)†</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Anion gap‡</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>Variable</td>
</tr>
<tr>
<td>Alteration in sensoria or mental obtundation</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>
ICU ADMISSION CRITERIA

Capillary ketones over 6 mmol/L
Bicarbonate level below 5 mmol/L
Venous/arterial pH below 7.1
Hypokalaemia on admission (under 3.5 mmol/L)
Glasgow coma score less than 12 or abnormal AVPU scale
Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
Systolic blood pressure (BP) below 90 mm Hg
Pulse over 100 or below 60 bpm
Anion gap above 16.2
GOAL OF CLINICAL MANAGEMENT

DKA: treat the underlying cause
Fluid Resuscitate
Suppression of ketogenesis
Reduction of blood glucose
Correction of electrolyte disturbance

HSS: treat the underlying cause
Normalise the osmolality
Replace fluid and electrolyte losses
Normalise blood glucose
TREATMENT LETS DISCUSS YOUR PRACTICE AREAS
The Management of Diabetic Ketoacidosis in Adults

For young people under the age of 18 years use British Society of Paediatric Endocrinology and Diabetes (BSPED) guidelines: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf

BOX 1: Immediate management: time 0 to 60 minutes

(T>0 at time intravenous fluids are commenced)

If intravenous access cannot be obtained request critical care support immediately

**Action 1:** Commence 0.9% sodium chloride solution (use large bore cannula via infusion pump

See Box 2 for rate of fluid replacement

**Action 2:** Commence a fast rate intravenous insulin infusion (IVI) (determined based on repleting of weight 50 units human soluble insulin (Actrapid® or Humulin® P to achieve an initial goal of 0.1 U/kg/hour for patients with 0.9% sodium chloride solution. If patient normally takes long acting insulin (NPH, Lente®) continue at usual dose and time.

**Action 3:** Assess patient

• Respiratory rate, temperature, blood pressure, pulse, oxygen saturation

• Full clinical examination

**Action 4:** Further investigations

• Capillary and laboratory glucose

• Venous BG

**Action 5:** Establish monitoring regime

• Hourly capillary blood glucose

• Hourly capillary ketone measurement if available

• Venous bicarbonate and potassium at 60 minutes, 2 hours and 2 hours thereafter

• 4 hours plasma electrolytes

• Continuous pulse oximetry if required

**Action 6:** Consider and precipitating causes and treat appropriately

**HbA1c level 2 facility and/or insertion of central line may be required in following circumstances (request urgent senior review)

• Young people aged 18-25 years

• Elderly

• Pregnancy

• Heart or kidney failure

• Other serious co-morbidities

• Severe dehydration

• Blood ketones above 6 mmol/L

• Venous bicarbonate below 5 mmol/L

**BOX 2: Initial fluid replacement

Restoration of circulating volume is priority

**Syntetic BP (SBP) below 90mmHg

• Give 500mls of 0.9% sodium chloride solution over 15-30 minutes. If SBP remains below 90mmHg, repeat whilst requesting senior input. Most patients require between 500 to 1000mls given rapidly.

• Consider inotropic (Thriftcardiac) support

• Give 0.9% sodium chloride over next 60 minutes. Addition of potassium likely to be required in second litre of fluid

**Syntetic BP on admission 90mmHg and over

• Give 1000mls of 0.9% sodium chloride over next 60 minutes

**Potassium replacement (mmol/L)

• Potassium replacement mmmol/L of infusion solution

• 5.5 40mmHg

• 3.5 40mmHg

• 3.5 40mmHg

• Senior review – additional potassium required

**BOX 3: 60 minutes to 6 hours

**Aims of treatment

• Rate of fall of ketones of at least 0.5 mmol/L or bicarbonate rate of 3 mmol/L and blood glucose fall at 3 mmol/L

• Maintain serum potassium in normal range

• Avoid hypoglycaemia

**Action 1:** Re-assess patient, monitor vital signs

• Hourly blood glucose (fast blood glucose if no meter available)

• Hourly blood ketones if meter available

• Venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hours thereafter

• If potassium is outside normal range, re-assess potassium replacement and check hourly. If abnormal after further hour seek immediate senior medical advice

**Action 2:** Continuous fluid replacement via infusion pump as follows:

• 0.9% sodium chloride, with potassium chloride over next 2 hours

• 0.9% sodium chloride, with potassium chloride over next 2 hours

• 0.9% sodium chloride, with potassium chloride over next 4 hours

• Add 10% glucose 12.5mEq/L of blood glucose fall below 14 mmol/L

• More continuous fluid replacement in young people aged 18-25 years, elderly, pregnant, heart or renal failure. (Consider HbA1c and/or central line)

**Action 3:** Assess response to treatment

• Blood glucose falling by at least 0.5 mmol/L over 2 hours

• Venous bicarbonate not rising by at least 3 mmol/L

• Venous pH over 7.3 and venous bicarbonate over 18 mmol/L

• Resolution is defined as ketones <0.3 mmol/L, venous pH>7.3

• If not resolved review fluid Box 4 Action 1 and insulin infusion Box 3 Action 3

**If DKA resolved go to Box 6

**BOX 4: 6 to 12 hours

**Aims of treatment

• Continue fluid replacement

• AVOID hypoglycaemia

• Assess for complications of treatment e.g. fluid overload, cerebral oedema

• Treat precipitating factors as necessary

**Action 1:** Re-assess patient, monitor vital signs

• If patient not improving by criteria in Box 3, seek senior advice

• Continue fluid replacement via infusion pump at reduced rate

• 0.9% sodium chloride 1L with potassium chloride over 6 hours

• Add 10% glucose 12.5mEq/L of blood glucose fall below 14 mmol/L

Reassess cardiovascular status at 12 hours further fluid may be required

Check for fluid overload

**Action 2:** Review biochemical and metabolic parameters

• At 6 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose

• Resolution is defined as ketones <0.3 mmol/L, venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage)

• Urine referral has been made to diabetes team

If DKA not resolved review insulin infusion (see BOX 3 Action 3)

If DKA resolved go to BOX 6

**BOX 5: 12 to 24 HOURS

**Expectation:** By 24 hours the ketonemia and acidosis should have resolved. Request senior review if not improving

**Aim:**

• Ensure that clinical and biochemical parameters are continuing to improve or are normal

• Continue insulin replacement if not eating and drinking

• Ketone and patient is not eating and drinking move to a variable restricted diet as appropriate

• Re-assess for complications of treatment e.g. fluid overload, cerebral oedema

• Continue to treat precipitating factors

• Transfer to subcutaneous insulin if patient is eating and drinking normally

**Action 1:** Re-assess patient, monitor vital signs

**Action 2:** Review biochemical and metabolic parameters

• For all patients, check venous pH, bicarbonate, potassium, capillary ketones and glucose

• Resolution is defined as ketones <0.3 mmol/L, venous pH>7.3

• If not resolved review fluid Box 4 Action 1 and insulin infusion Box 3 Action 3

**If DKA resolved go to Box 6

**BOX 6: Resolution of DKA

**Expectation:** Patient is eating and amounting and can receive normal insulin

If DKA not resolved identify and treat the reasons for failure to respond. This situation is unusual and requires senior and specialist input.

Transfer to subcutaneous Insulin

Convert to subcutaneous regimen when biochemically stable (capillary ketones <0.5 mmol/L, pH over 7.3) and the patient is ready and able to eat. Do not discontinue Intravenous Insulin infusion until 30 minutes after subcutaneous short acting insulin has been given

Conversion to subcutaneous insulin should be managed by the Specialist Diabetes Team. If the team is not available use local guidelines. If the patient is newly diagnosed it is essential they are seen by a member of the specialist team prior to discharge.

Arrange follow up with specialist team

Groups represented: Association of British Clinical Diabetologists; British Society for Endocrinology and Diabetes and Association of Children’s Diabetes Clinicians; Diabetes Inpatient Specialist Nurse (DINSN) Group; Diabetes UK; NHS Diabetes (England); Northern Ireland Diabetologists; Society of Acute Medicine; Welsh Endocrine and Diabetes Society; Scottish Diabetes Group.
HHS MANAGEMENT

• Goals-
• Fluid resuscitate, replace 50% of fluid losses in first 12 hours
• Replace electrolytes-risks with K+ pending on renal function
• Vigorous fluid resuscitation should clear hyperglycaemia
• If ketones present commence FRII insulin 0.05units/kg/hr
• VTE prophylaxis
• Foot protection / pressure area care
Patients not on insulin at presentation have a worse outcome compared to those with prior insulin therapy. Venkatesh et al (2015)

Elevated plasma urea concentration is associated with increased mortality >25mmols/L. Venkatesh et al (2015)

Gald et al (2019) recent retrospective study had 5 deaths in a cohort of 84 patients. 3 of these deaths related to DKA directly. The link to these deaths is unclear, however the study did identify that almost half of the patients had hypokalaemia in the first 24 hours.
1. What class of drugs have been linked to euglycemic diabetes? Can you give an example?

   - Glifozins, dapaglifozin, canaglifozin, canaglifozin/metformin

2. How do steroids cause T2DM?

   - Steroids can cause the liver to become resistant to insulin, it carries on releasing glucose

3. What counter regulatory hormones are released during DKA?

   - Glucagon, growth hormone, cortisol and catecholamines-resulting in high BM secondary to accelerated gluconeogenesis.

4. What are the three components that result in DKA?

   - Hyperglycemia, acidemia, ketonemia

5. How does HHS differ from DKA clinically?

   - Severity of dehydration, ketosis and metabolic acidosis
1. List 4 common clinical presentation features of DKA and HHS
   - Abdo pain, nausea and vomiting, confusion and dehydration

2. List 3 clinical presentation features that may differ from DKA in HHS
   - History, gradual onset, high osmolality, focal neurological deficit
   - Stop ketogenesis, reverse acidosis, normalise BM, fluid resuscitate

3. What is the goal of treatment in DKA?
   - Insulin can push K+ from the extracellular to intracellular space

4. How does insulin cause hypokalemia?
   - Heart failure, cerebral oedema

5. What are the risk of rapid fluid resuscitation in the elderly?
CASE STUDY, HARVEY

PMH: Unwell 3 months ago with influenza, last 36 hours polyuria, nausea, vomiting and increased thirst.
Fit and well, third year student. No known drug / ETOH intake.
Weight 90 kg approx.
On arrival to ICU:
Vital signs: RR 35 labored, SpO2 90% NRB, HR 125 reg, BP 90/50mmhg, Temp 37.5. GCS 13/15. Confused and agitated.
Last venous gas pH 7.1, Bicarbonate 10, K+ 3.0mmols Na+ 135mmols/L K+ 6.0mmols/L
BM –Hi
Capillary ketones 6 mmols/L
Treatment to date: 1 L Normal Saline, 2nd liter running over 1 hour, antiemetic, Actrapid Insulin Infusion fixed rate 6 units/hour.
Cardiac arrest call to ward: found to be unresponsive? Cause CT head pending, managed with PR lorazepam and loading does phenytoin. Vitals on arrival to ICU: RR 10, Spo2 96% NRB, HR 90 reg, BP 88/44mmhg. Postictal GCS 11/15. Guidel airway insitui. Incontinent of urine.


BM 35mmols/L, blood ketones 2 mmols/L, pH 7.35, serum osmolality 376 mosmol/ kg K+ 3.8mmols/L Na 153mmols/L.
The patient experience
Prevention and education
Insulin regimes and continuing long acting insulin
Point of care testing, the patient
Best clinical area to monitor and care for patients
Standardised protocols
Euglycemic DKA, pharmacokinetics and pharmacodynamics of SGLT-2 inhibitors
Prediction of mortality
SUPPORT

www.diabetes.org.uk
helpline@diabetes.org.uk
Diabetes UK 0345-123-2399
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