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The article of this issue is:

ACUTE METABOLIC COMPLICATIONS OF DIABETES MELLITUS

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Diabetes-related emergencies are:

1- Ketoacidosis
2- Hyperosmolar non-ketotic state.
3- Lactic acidosis
4- Hypoglycemia

DIABETIC KETOACIDOSIS

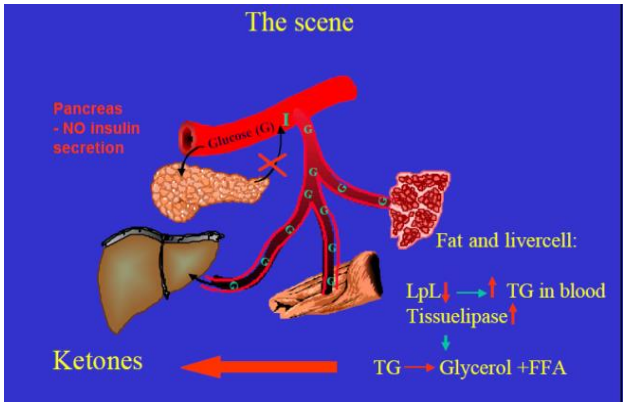
Diabetic ketoacidosis is a medical emergency characterized by the triad of hyperglycemia, ketosis and acidosis.

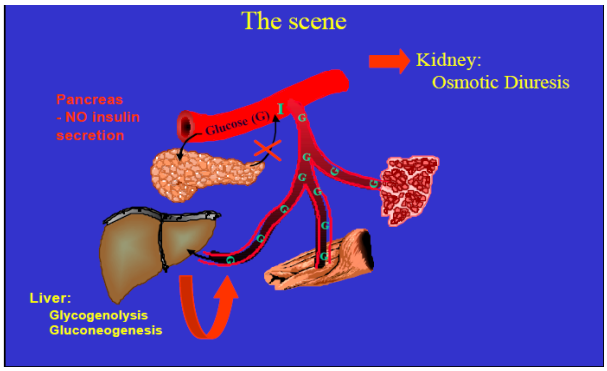
Essential Laboratory Criteria

- Blood glucose >250 mg/dL
- PH <7.30
- Serum bicarbonate <18 mmol/L
- Anion gap >15
- Ketonemia and ketonuria

Pathogenesis

Diabetes is a state of starvation despite the abundance of glucose. This state of starvation is caused by absolute or relative insulin deficiency. Hyperglycemia causes osmotic diuresis leading to dehydration and loss of sodium and potassium (Figures 1, 2). Potassium losses are also aggravated by secondary hyperaldosteronism. Insulin deficiency, elevated glucagon and adrenalin result in unrestrained lipolysis and increased supply of FFA's for hepatic ketogenesis. In the presence of even little amounts of insulin, formation of ketoacids in the liver is inhibited (figure 3). Insulin stimulates the enzyme co-carboxylase and increases malonyl Co A formation from acetyl CoA, the exact opposite effect of glucagon. Malonyl CoA inhibits carnitine palmitoyl transferase, the key enzyme that carries fatty acids into mitochondria for ß- oxidation.





Figures 1 & 2: The metabolic complications resulting from insulin deficiency and the resulting fasting state.

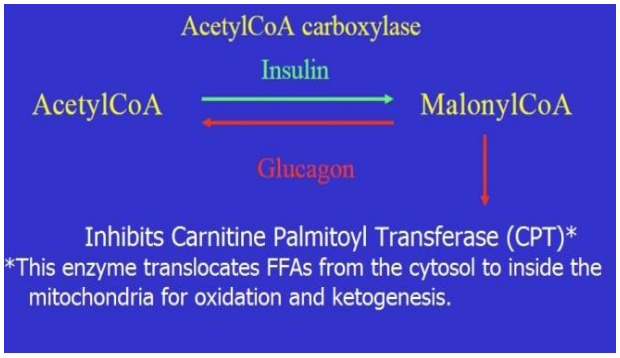
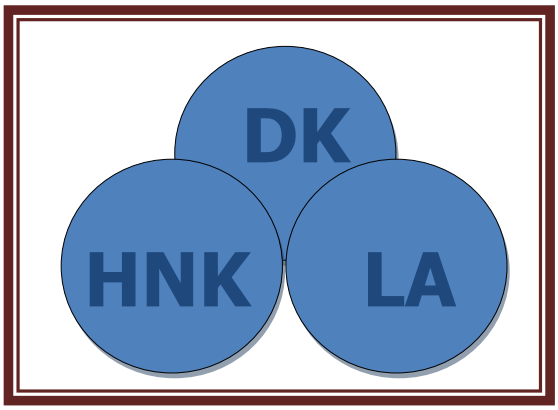


Figure 3: Malonyl CoA formed from Acetyl CoA in the presence of insulin inhibits the enzyme carnitine palmitoyl transferase (CPT). In the absence of insulin, glucagon increases acetyl CoA formation at the expense of malonyl CoA. CPT becomes free to translocate fatty acids into mitochondria for oxidation.

It must be remembered that the 3 acute metabolic complications of diabetes i.e. diabetic ketoacidosis, hyperosmolar nonketotic state and lactic acidosis are not mutually exclusive. In diabetic ketoacidosis, some increase in serum osmolartiy and/or lactic acid may be present, but the predominant biochemical change is excess accumulation of ketoacids (Figure 4).

SUSCEPTIBILITY

In type 1 diabetes; DKA is the initial presentation in up to 25% of children and adolescents. Inter-current infection, stress caused by trauma or surgery, and/or missed insulin



doses can precipitate ketoacidosis in the remaining 75%. In type 2 diabetes; severe stress or infection is required to cause ketoacidosis e.g. MI, surgery or sepsis.

Figure 4: Biochemical features of diabetic ketoacidosis (DK), hyperosmolar nonketotic state (HNK) and lactic acidosis (LA) can be present in the same patient.

CLINICAL MANIFESTATIONS

Symptoms

- Polyuria , thirst and polydipsia.
- Abdominal pain may be severe and unnecessary laparotomy performed.
- Weight loss and marked weakness.
- Blurred vision, nausea, vomiting and leg cramps are recognized symptoms.

Physical Signs

- Dehydration, hypotension and tachycardia (caused by contraction of intra- and extra-cellular fluid volumes).
- Air-hunger and acetone smell (ketones).
- Hypothermia, confusion or coma occurs in less than10% of cases.

LABORATORY FINDINGS

In DKA, common **laboratory** test results are:

- Glucose ≥ 250 mg/do.
- Sodium: normal or reduced.
- Potassium: serum K normal, reduced or elevated, but total body potassium is always reduced.
- Bicarbonate: reduced to less than 18 mmol / L.
- Ketones: ++ (in serum and urine).
- Lactate (in blood): N or slightly increased.
- Osmolarity: N or +
- PH: reduced to less than 7.3.
- Anion gap which is the difference between the sum of measured cations (sodium + potassium) and the sum of anions (chloride + bicarbonate). Normally the difference is < 12. In DKA the AG is >15. AG = [Na + K - (Cl + HCO3)]

CLINICAL ASSESSMENT

In ketoacidosis of moderate severity the average amount of fluid and electrolyte losses in an adult patient are usually as shown below:

1. Water 6 L (3L extracellular: replace with saline and 3L intracellular: replace with dextrose 5%).
2. Sodium 500 m.mol.
3. Chloride 400 m.mol.
4. Potassium 350 m.mol.

INVESTIGATIONS

Important but should not delay fluid replacement and insulin treatment.

1. Venous blood: urea & electrolytes, glucose, bicarbonate.
2. ABG's: are performed in severe acidosis (plasma bicarb. < 12 mmol / L).
3. Urine for ketones by test strip.
4. ECG.
5. Infection screen: CBC, urine and blood culture, C-reactive protein and CXR.

N.B. The presence of leucocytosis is common in ketoacidosis and does not necessarily indicate bacterial infection; it is part of the stress response.

DIFFERENTIAL DIAGNOSIS

The diagnosis of DKA is usually straightforward in patients with known diabetes.DKA must be differentiated from acidosis and coma due to other causes:

- Hypoglycemia
- Uremia
- Gastroenteritis with metabolic acidosis
- Lactic acidosis
- Salicylate intoxication
- Encephalitis.

LABORATORY MONITORING

Regular monitoring is crucial in management of patients with ketoacidosis.

- Glucose , urea & electrolytes and HCO3 are measured at : **baseline , 1hr , 2hr , 3hr , 6hr , 12hr 24hr**
- Creatinine is measured at **baseline, 6 , 12 and 24hr**
- Arterial blood gases at baseline are not necessary if venous plasma bicarbonate is > 15 m.mol/L .With severe acidosis (serum HCO3 is < 12 m.mol/L) measure at baseline, 2 and 6 hrs.

CLINICAL MONITORING

- Close monitoring and recording of vital signs (HR, BP and RR) is important.
- Consciousness level monitoring: important to diagnose hypoglycemia and brain edema during treatment, if deterioration in consciousness occurs.
- Fluid balance chart with accurate recording.
- CVP line insertion: especially if cardiovascular and/or renal compromise is present.

MANAGEMENT: Diabetic ketoacidosis is a medical emergency that should be treated in a hospital ICU.

However, mild cases can be treated in the ward.Principal components of treatment are:
1. Fluid repletion.
2. Soluble (short acting) insulin.
3. Potassium replacement.
4.Antibiotics if infection is present or suspected

Fluid Replacement: is started with 0.9% N saline I.V. as follows:
- 1L over 30 minutes.
- 1L over 1 hr**.**
- 1L over 2 hrs.
- 1L over next 2 to 4 hrs.
- This replenishes most of the extracellular fluid compartment (6L in first 24 hrs). Additional fluid replacement should be based on clinical response and urine output.
- When blood glucose is < 15 mmol/L (270mg/dL), start 5% dextrose 1L / 8 hourly I.V
- If still dehydrated continue 0.9% saline.

N.B. 5% dextrose infusions are needed to correct intracellular dehydration (average 3 L).

Insulin treatment
- 50u soluble insulin in 50mL 0.9% saline I.V. by an infusion pump:
  - 6u /hr initially.
  - 3u /hr when blood glucose is 15 mmol/L (270 mg/dL).
  - 2u /hr if blood glucose is < 10 mmol/L (180 mg/dL).
- Check blood glucose hourly initially; if no reduction in the first hour, increase the insulin rate.
- Aim for fall in blood glucose is 3 to 6 mmol /L (55 to 110 mg/dL) per hour.
- Soluble insulin can be given I.M. (loading 20 to 30 unit followed by 5u hourly.
- A fast acting insulin analogue can be given by S.C. injection (0.3u/kg then 0.1u/kg, hourly).
- No place for long acting or premixed insulin in the treatment of ketoacidosis.

N.B. Insulin is used to treat both ***ketoacidosis and hyperglycemia and*** insulin should ***never*** be stopped because of adequate blood glucose levels, if ongoing acidosis persists.
- When the acidosis is corrected, the continuous insulin infusion may be discontinued and subcutaneous insulin initiated.
- With this regimen, DKA is usually fully corrected in 36 to 48 hours.

Potassium replacement:
The baseline serum potassium determines when and how much K + to give:
- None in first L of i.v. saline unless plasma potassium is < 3.0 m.mol/L, if so give K Cl 40 m.mol/L. When < 3.5 m.mol/L, give 20 m.mol/hr.
- When plasma k is 3.5 to 5.0 m.mol/L , give 10 m.mol/hr. Remember total body potassium deficit usually ranges from 300 to 350 m.mol

Phosphate replacement
Usually phosphate deficiency is mild and does not require replacement in the average case of DKA of few days duration. If plasma phosphate level is <1mmol/L, give K PO4 instead of K Cl. Check serum calcium level frequently during phosphate replacement.

Additional procedures
- Catheterization if no urine is passed for3 hrs. After admission.
- Nasogastric tube to keep the stomach empty, if patient is unconscious or repeatedly vomiting.
- CVP line if cardiovascular compromise is present to guide fluid replacement.
- Plasma expander if systolic BP is < 90 mm Hg and/or doesn't rise with i.v. saline infusions.
- Antibiotics are given if infection is evident or suspected.
- ECG monitoring for rhythm changes caused by hyper- or hypo – kalemia (in severe cases).

COMPLICATIONS
- **Cerebral edema** Is common in young children and causes unexplained loss of consciousness and high mortality**.**
  - May be caused by rapid lowering of blood glucose or Use of hypotonic fluids and/or bicarbonate.
  -Treatment: mannitol i.v. and oxygen.
- **Other complications** include: Hypo-glycemia, ARDS, thrombo-embolism ,DIC, acute circulatory failure and sudden death from hypo- or hyper-kalemia.