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DIABETES MELLITUS

Acute Metabolic Complications

- Diabetic Ketoacidosis (DKA)
- Hyperglycemic Hyperosmolar State (HHS)
DIABETIC KETOACIDOSIS (DKA)

Definition: A life-threatening state that results from a relative or absolute deficiency of insulin.
DIABETIC KETOACIDOSIS (DKA)

Definition: A life-threatening state that results from a relative or absolute deficiency of insulin.

• Usually occurs in individuals with Type 1 diabetes.

• Insulin levels are very low.

• High levels of “stress hormones”: epinephrine, norepinephrine, growth hormone and cortisol.
DIABETIC KETOACIDOSIS (DKA)

PRECIPITATING FACTORS (VERY IMPORTANT):

- Insufficient or no insulin.
- Physical stress: dehydration, trauma.
- Surgery, infections, heart attacks, etc.
Diabetic Ketoacidosis: Pathophysiology

Liver

Blood Glucose 80-100 mg/dL

Insulin-Stimulated Glucose Transport

Insulin-Mediated Inhibition of Lipolysis

Pancreas

Muscle

Fat

Hepatic Glucose Output

A. Kumagai
Diabetic Ketoacidosis: Pathophysiology

Meanwhile, in the adipocyte...

A. Kumagai
Insulin-regulated carbohydrate metabolism: adipocyte

Insulin inhibits lipolysis by stimulating lipoprotein lipase (LPL) and inhibiting hormone-sensitive lipase (HSL).
Diabetic Ketoacidosis: Pathophysiology

- **Liver**
- **Insulin**
- **Glucagon**
- **Fat**
- **Blood Glucose**
- **Ketones**
- **Muscle**
- **Insulin-Mediated Inhibition of Lipolysis**
- **Epinephrine, Norepinephrine**
- **Free Fatty Acids (FFA)**
- **Free Amino Acids**
- **Epinephrine-Stimulated Myolysis**

**Key Points**
- Insulin mediates inhibition of lipolysis in muscle and fat tissues.
- Glucagon promotes the release of free fatty acids and free amino acids from muscle and fat tissues.
- Ketones are produced in the liver due to the breakdown of fatty acids and are released into the bloodstream.
- Epinephrine and norepinephrine stimulate myolysis in muscle, releasing additional fatty acids into the bloodstream.

A. Kumagai
Diabetic Ketoacidosis: Ketoacids

ACETOACETATE

\[
\begin{align*}
\text{O=}&\text{C} \\
\text{CH}_2\text{COO}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{O=}&\text{C} \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{align*}
\]

Acetone

B-HYDROXYBUTYRATE

\[
\begin{align*}
\text{O=C-}&\text{H} \\
\text{CH}_2\text{COO}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \\
\text{O-C}&\text{H} \\
\text{CH}_2\text{COO}^- \\
\end{align*}
\]

Bicarbonate

NADH + H⁺ → NAD

HCO₃⁻
Diabetic Ketoacidosis: Signs & Symptoms

**HYPERGLYCEMIA**
- Polyuria and polydipsia
- Severe volume depletion
- Electrolyte depletion
- Eventual: renal hypoperfusion, prerenal azotemia, hypotension and shock

**KETONES**
- Acidosis
- Compensatory resp. alkalosis
- Hypotension
- Shock
Diabetic Ketoacidosis:
Clinical Course (Worst Case Scenario)

“Doing Well”

- Precipitating Event
- Polyuria, polydipsia, dehydration
- Anorexia, nausea, vomiting, abd. pain
  - Kussmaul respirations, “Juicy Fruit” Breath
  - Altered consciousness
  - Cardiovascular collapse

Coma & Death
Diabetic Ketoacidosis: Effects on Mental Status

Factors leading to impairment of CNS function:
Diabetic Ketoacidosis: Effects on Mental Status

Factors leading to impairment of CNS function:

HYPEROSMOLALITY

BRAIN
Diabetic Ketoacidosis: Effects on Mental Status

Factors leading to impairment of CNS function:
Diabetic Ketoacidosis: Effects on Mental Status

Factors leading to impairment of CNS function:

- Hyperosmolality
- Hypotension
- Acidosis

A. Kumagai
Diabetic Ketoacidosis: Diagnosis

The Diagnostic Triad of DKA:

- Blood Glucose
- Serum Ketones
- "Gap" Metabolic Acidosis
Diabetic Ketoacidosis: Diagnosis

The “Anion Gap” represents the presence of unmeasured anions.

\[
\text{Anion Gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)
\]

(Normal = 12)

Organic acids, such as acetoacetate and β-hydroxybutyrate, decrease the HCO_3^- (which is a biologic buffer) and aren’t measured in the gap. Therefore, the gap increases.
Diagnosis of Diabetic Ketoacidosis

Signs and symptoms of DKA may be accompanied by those of the underlying precipitating disorder; HOWEVER,

DKA *per se* DOES NOT CAUSE FEVER.

Therefore, if a fever is present, assume there is an infection until proven otherwise!!
Diabetic Ketoacidosis: Treatment

1. Intravenous insulin.

2. IV Fluids: Initially rapid because of severe volume depletion - loss of 7-10 L of total body water.


4. Carbohydrate replacement (5-10% dextrose) once serum glucose is below 250 mg/dL

5. Administration of bicarbonate for acidosis is NOT recommended.

6. Diagnose and treat PRECIPITATING EVENT!
Treatment of Diabetic Ketoacidosis: Don’t Let an Elevated K⁺ Fool You!

Bottom Line: “As soon as you see pee, give K⁺!

During acidosis, H⁺ shifts into cells to be buffered by intracellular buffers. K⁺ shifts out of cells in exchange. Consequently, serum K⁺ is usually elevated DESPITE total body K⁺ depletion.

Treatment with insulin causes K⁺ to shift back into cells, and serum K⁺ may drop like a rock during therapy.
Acetone is produced during the normal regeneration of bicarbonate and is detected by most serum ketone assays. Therefore, the serum ketones normally increase during recovery from DKA.
Treatment of Diabetic Ketoacidosis:
Finally,

Diagnose and treat the underlying precipitating event!
DIABETES MELLITUS

Acute Metabolic Complications

Diabetic Ketoacidosis (DKA)

Hyperglycemic Hyperosmolar State (HHS)
Hyperglycemic Hyperosmolar State

- Life-threatening metabolic disorder of extreme hyperglycemia without ketosis.
- Typically seen in elderly with type 2 diabetes, some 30% of whom are previously not diagnosed with diabetes.
- Common precipitating events: myocardial infarction, stroke, sepsis.
- Potentially deadly: mortality may exceed 40%.
Hyperglycemic Hyperosmolar State
Pathogenesis

Relative Insulin Deficiency → HYPERGLYCEMIA → THE VICIOUS CYCLE OF HHS → POLYURIA → VOLUME DEPLETION → HEMO-CONCENTRATION → Relative Insulin Deficiency
Hyperglycemic Hyperosmolar State

Clinical Aspects

Increasing volume depletion and hemocoagulation may result in:

- Hyperviscosity and increased risk of thrombosis
- Disturbed mentation and obtundation
- Neurologic signs
  - Focal signs, e.g., sensory or motor deficits or focal seizures
  - Motor abnormalities, e.g., flaccidity, depressed reflexes, tremor or fasciculations.

Ultimately, without treatment, coma and death
Hyperglycemic Hyperosmolar State
Treatment

Similar to the treatment of DKA:

- Volume correction with normal saline.
- Replacement of electrolytes.
- IV insulin.
- Diagnosis and treatment of underlying cause.
Diabetes Mellitus

Chronic Complications
Diabetes Mellitus: Chronic Complications

Microvascular Complications
- RETINA
- KIDNEYS
- NERVES

Macrovascular Complications
- HEART, BRAIN & LARGE VESSELS
Diabetes: Chronic Complications

Microvascular Complications

- Diabetic Retinopathy
- Diabetic Nephropathy
- Diabetic Neuropathy
Diabetic Retinopathy

Retinal Fundus Photographs

- Retinal capillaries
- Macula
- Optic nerve

NORMAL RETINA

Source: Undetermined
Diabetic Retinopathy

Retinal Fundus Photographs

- Retinal capillaries
- Macula
- Optic nerve
- Macular edema
- Exudates

Disease Progression

NORMAL RETINA

NON-PROLIFERATIVE OR “BACKGROUND” RETINOPATHY

Source Undetermined (Both Images)
Diabetic Retinopathy

Retinal Fundus Photographs

Normal Retina

Non-proliferative or “Background” Retinopathy

Proliferative Retinopathy

Source Undetermined (All Images)
Diabetic Retinopathy

Later stages of retinopathy involve death of endothelial cells and capillary “drop out,” progressive ischemia and proliferative neovascular changes.

Exudates
- leakage of plasma proteins into neuroretina.

Microaneurysms

EM Photograph of Plastic Cast of Retinal Capillaries from Diabetic Retina

Source Undetermined
Diabetic Retinopathy

Remember:

Diabetic retinopathy is the leading cause of new adult blindness in the United States.
Diabetic glomerulosclerosis is characterized by basement membrane thickening and mesangial cell proliferation.

Diabetic nephropathy may be diagnosed in its earliest—and potentially, reversible—stages by detection of extremely small amounts of albumin in the urine, so-called “microalbuminuria.”
Diabetic Nephropathy

Remember:

Diabetic nephropathy is the leading cause of renal failure requiring dialysis in the United States.
Symmetrical neuropathy is the most common:

- Primarily involving the distal extremities with “stocking-glove” distribution.
- Sensory: decreased vibration, temperature, proprioception.
- Initially may present with painful paresthesias: “burning” or “pins-and-needles” sensation. Eventually leads to complete loss of sensation.
- Predisposed to skin breakdown, ulcer formation and unrecognized trauma.
DIABETIC NEUROPATHY:
Peripheral Sensory Neuropathy

Of bottlecaps and bathtubs ...
DIABETIC NEUROPATHY: Autonomic Neuropathy

- Gastroparesis
- Constipation or Diarrhea

- Chronic edema
- Postural hypotension

- Cardiac arrhythmias
- Sudden Death

- ERECTILE DYSFUNCTION
- Urinary retention

Abnormal sweating and increased callus formation
Diabetic Neuropathy

Remember:

Diabetes is the leading cause of non-traumatic lower extremity amputations in the United States.
DIABETIC COMPLICATIONS

MACROVASCULAR COMPLICATIONS

Gangrene is 14 times more common in people with diabetes than those without.

Coronary Heart Disease:
- Twice as common in people with diabetes.
- Occurs at an earlier age and places women on equal risk with men.
- For MI’s: individuals with diabetes have a higher mortality rate and lower 5-year survival rate.
- MI’s often occur WITHOUT CHEST PAIN.

Risk of death from stroke is approximately 3 times greater for people with diabetes than for those without.
DIABETIC COMPLICATIONS: Diabetes and Pregnancy

1. Problems for the Mother:
   - Insulin Requirements increase and metabolic control often worsens during pregnancy.
   - Diabetic retinopathy and possibly nephropathy may worsen.

2. Problems for the Baby:
   - Infant mortality is higher in babies from diabetic mothers.
   - Congenital malformations are more frequent.
   - Respiratory distress syndrome (RDS) is more common.
DIABETIC COMPLICATIONS:
Diabetes and Pregnancy

High blood sugars in pregnancy can lead to...

BIG BABIES
Hyperglycemia lowers resistance to infection and interferes with wound healing.

At BGs of >250 mg/dL, WBC motility and opsinization of bacteria are significantly impaired.
DIABETIC COMPLICATIONS

• Complications from influenza are more common in individuals with diabetes.
• Infections with tuberculosis and pneumococcal pneumonia are common.
• Yeast infections are common among diabetes women.
• Wound healing is delayed in poorly controlled diabetes.
"Diabetes is a dreadful affliction, the melting down of flesh and limbs into urine...Life is short, unpleasant and painful...

-- Areteus of Capadocia, 2nd C. A.D.