Diabetic Ketoacidosis

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Objectives

- Describe pathophysiologic process of diabetic ketoacidosis (DKA)
- Identify diagnostic criteria for DKA
- Explain two-bag system of intravenous rehydration
- Discuss complications related to treatment methods of DKA
Type I Diabetes: Insulin-Dependent Diabetes Mellitus (IDDM)

- Severe insulinopenia secondary to β cell injury requiring exogenous insulin to prevent ketosis
- Predominantly occurs during childhood
- Possible genetic predisposition and autoimmune mediated
Diabetes Review:
Type II Diabetes: Non-Insulin-Dependent Diabetes Mellitus (NIDDM)
- Resistant to own insulin secretion secondary to decreased cellular receptor sensitivity
- Rarely develop ketosis
- Predominately occurs after age 40 and in the obese population
- No associated genetic predisposition
What is DKA?

A medical emergency resulting from metabolic decompensation in patients with Insulin Dependent Diabetes Mellitus (IDDM)
Diabetic Ketoacidosis

**D** Diabetic Hyperglycemia
Blood glucose $> 300$mg/dL

**K** Keto Ketonemia
Blood ketones $> 3$ mmol/L
Ketonuria

**A** Acidosis
pH $< 7.3$ or $\text{HCO}_3^- < 15$ meq/dL
Epidemiology

- 12-15 new cases of IDDM per 100,000 children less than age 18 per year
- 1 in 400 children less than age 18 have IDDM
- IDDM is the most common endocrine-metabolic disorder in the pediatric population

Etiology

- Noncompliance
- Acute illness or infection
- Severe stress
Pathophysiology

- DKA triggers
  - Insulin deficiency
  - Excess of glucagon
  - Excess of stress hormones
    - Epinephrine
    - Norepinephrine
    - Cortisol
    - Growth hormones
Insulin

- Stimulates anabolic processes
  - Glucose utilization and storage of the energy as glucose, protein, and fat
- Inhibits catabolic processes
  - Glycogenolysis, gluconeogenesis, proteolysis, lipolysis, ketogenesis
- Insulin deficiency:
  - Decreases glucose utilization by insulin-sensitive tissues
  - Promotes lipolysis in adipose tissue
  - Enhances protein breakdown in muscles
Glucagon

- Increases glycogenolysis
- Increases gluconeogenesis
- Increases ketogenesis
Stress Hormones

- **Epinephrine and Norepinephrine**
  - Activates glycogenolysis, glyconeogenesis, and lipolysis
  - Inhibits insulin release by pancreas

- **Cortisol**
  - Stimulates gluconeogenesis
  - Decreases glucose utilization by muscle
  - Leads to increased serum glucose concentration

- **Growth Hormone**
  - Increases lipolysis
  - Impairs insulin’s action on muscle
Ketogenesis

- Insufficient insulin available to facilitate movement of glucose into cells for use in cellular metabolism
- Lipids become primary energy source as they break down into free fatty acids and acetoacetic acid
- Free fatty acids generate the ketone bodies: $\beta$-hydroxybutyric acid, acetoacetic acid, and acetone
Metabolic acidosis

- Develops from metabolism of fats and accumulation of their by-products including ketones
Insulin Deficiency

Cortisol

↓ Glucose utilization

Hyperglycemia

Glucagon, Cortisol, Catecholamines

↑ Protein breakdown

Gluconeogenesis

↑ Amino Acids

Lipolysis

↑ Free Fatty Acids

Fatty acid oxidation

Ketone formation

Ketoacidosis

↑ Serum Lipids

↑ Triglycerides & VLDL

Serum Lipids

Fatty acid oxidation

Ketone formation

Ketoacidosis

↑ Triglycerides & VLDL

Coma

Dehydration & Hypovolemia

Loss of H₂O, Na⁺, K⁺, PO₄⁻

Glycosuria/ Osmotic diuresis

↓ Glucose utilization

Hyperglycemia

Circulatory collapse/ Shock

Death
Diagnosis

- Diabetic Ketoacidosis
  - Hyperglycemia
  - Ketonemia
  - Acidosis
  - Glucosuria
  - Ketonuria
Differential Diagnosis

- Adrenocortical dysfunction
- High-dose steroids
- Pheochromocytoma
- Pancreatitis
- Cystic fibrosis
- Exogenous catecholamines
Differential Diagnosis

- Stress response
- Diabetes Insipidus
- Alcoholic ketoacidosis
- Starvation
- Inborn errors of metabolism

Clinical Manifestations

- History:
  - IDDM
  - Precipitating factors
    - Acute illness or infection
    - Stress
    - Trauma
    - Noncompliance
  - Excessive thirst, drinking, and urination
  - Weight loss
Clinical Manifestations

- Physical Examination:
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Kussmaul respiration
  - Mental status changes/ Weakness
  - Dehydration
Clinical Manifestations

- Physical Examination:
  - Nausea/ Vomiting
  - Acute abdominal pain
  - Cardiac arrhythmia
  - Tachycardia
  - Hypotension/ Hypovolemia
  - Poor perfusion, shock
Clinical Manifestations

- Laboratory/Test results:
  - Hyperglycemia: serum glucose > 300 mg/dL
  - Serum pH < 7.3
  - Serum bicarbonate < 15 mmol/L
  - Hyperosmolality > 300 mOsm/kg
    - Serum Osm = 2Na + BUN + Glucose
      - 2.8 + 18
  - Electrolyte imbalances: Sodium/Potassium
    - Levels vary from high to low
Sodium & Potassium

- **Sodium:**
  - Falsely high serum Na due to hemoconcentration
  - Total body Na depletion 2° to osmotic diuresis
  - Correction: serum sodium add 1.6 mEq/L per each 100 mg/dL serum glucose over 100 mg/dL

- **Potassium:**
  - Estimated total K deficit at 5 mmol/kg
  - May be falsely normal in presence of acidosis
    - Potassium moves from intracellular to extracellular space
Clinical Manifestations

- Laboratory/Test results:
  - Glucosuria
  - Ketonuria
  - Elevated Glycosylated hemoglobin (Hgb A₁c) (indicates poor glucose control over past 2-3 months)
  - Elevated white blood cell count with shift to left
  - CT scan may be diagnostic of cerebral edema
Lab studies for new onset DKA

- Insulin level
  - Must be drawn prior to first insulin dose!!
- HgA1C
- TPO antibody
- Antithyroglobulin antibody
- Total T₄
- Total T₃
- TSH

- Antibodies:
  - ICA 512
  - Anti GAD-65
  - Insulin
  - Endomysial (tissue transglutaminase)
  - Adrenal
- BMP, Ca, Mg, PO₄
- VBG
Treatment

Goals:

- Correction of metabolic imbalances
  - Hyperglycemia
  - Ketonemia
  - Acidosis
- Treatment of underlying/precipitating factors
- Prevention and early identification of precipitating factors
- Prevention of recurrence
Correction of metabolic imbalances

- Estimate degree of dehydration
  - Initially at least 10% dehydrated
  - 10 cc/kg bolus NSS, then reassess blood pressure
    - Additional 10cc/kg bolus’ until blood pressure stabilizes

- Replace estimated deficit plus ongoing losses over 36-48 hours
  - First ½ of replacement over initial 18 hours
  - consider replacing excessive urine output (> total input)

- Dextrose-stick for serum glucose level q 1h
- Serum electrolytes q 2h initially
Treatment: IV fluids

- IV rehydration
  - Replenishes intravascular volume
  - Decreases serum concentrations of counterregulatory hormones
  - Improves insulin sensitivity of the tissues
Treatment: IV fluids

Guidelines:

- Serum glucose levels should drop by 50-150 mg/dL/hr
- When serum glucose levels = 250mg/dL: add 5% dextrose to IV fluids
- When serum glucose levels = 150 mg/dl: add 10% dextrose to IV fluids

Treatment: Two Bag System

The two bag system

- Bag #1: 0.9 % NaCl + 20 mEq KCL + 20mEq KPO$_4$/liter
- Bag #2: 10% Dextrose + 0.9% NaCl + 20mEq KCl + 20mEq KPO$_4$/liter
  - Do not add phosphorous if serum calcium < 7.5 as phosphorous often decreases calcium levels.
- Connect both bags together to run into the same IV line
- Titrate rates of each bag to desired dextrose concentration

Two Bag System

Treatment: Two Bag System

Benefits:

- More precise control of total fluid, electrolyte, and dextrose
- Tailor the IV fluids to meet the patient’s individual needs
- Decreased time to institute ordered changes in fluid therapy from >30 minutes to <10 minutes
Treatment: Two Bag System

Benefits:

- Safer infusions
  - Less IV fluid bag changes and less chances for errors than the traditional single bag system

- Cost-effective
  - Two bag system costs $500 less per DKA admission than one bag system
  - Estimated savings of about $75,000 per year
Treatment: Insulin

- Insulin infusion
  - Crucial in restoring acid-base balance and eliminating ketoacidosis
  - Standard rate .05-0.1U/kg/hr
  - Rate of insulin remains constant while dextrose concentration titrated to achieve desired serum glucose levels
  - Ideal glucose levels 200-300 mg/dL until NaHCO₃ > 15 meq/L
Treatment: Insulin

- Guidelines for switching to subcutaneous injections of insulin:
  - Serum glucose levels $\leq 300$mg/dL
  - Resolved acidosis $\text{HCO}_3^- > 16-18$
  - Stable cardiopulmonary status
  - Tolerating solid PO intake
  - Recommendations: .5 U/kg SQ of which 1/3 Humalog and 2/3 intermediate acting (Lente or NPH)
    - Give first dose prior to a meal
  - Give Humalog insulin SC and immediately discontinue infusion.
Treatment: Bicarbonate

- Controversial treatment for acidosis
- No evidence that bicarbonate facilitates metabolic recovery
- Detrimental effects:
  - Paradoxical CNS acidosis
  - Worsening hypokalemia
  - Prolongation of intracellular acidosis secondary to increased CO₂ production
- Not recommended for use in treating pediatric DKA
Bicarbonate

- Glaser et al. NEJM 2001
  - Evaluated associations between cerebral edema and demographic factors, therapeutic interventions, and changes in biochemical values during treatment
  - Of the therapeutic variables, only treatment with bicarbonate was associated with cerebral edema $P=0.008$
Treatment

- Treatment of underlying/precipitating factors
  - Address issues related to precipitating disease process such as gastroenteritis or pancreatitis
  - Address issues related to stressors in child’s life that may have precipitated DKA event
Treatment

- Prevention and early identification of precipitating factors
  - Changes in mental status should improve, if decompensation in neurologic status, suspect cerebral edema
    - Neurological checks q 1 hour
  - Respiratory status should improve with resolution of Kussmaul breathing, monitor patient for respiratory failure
    - Have intubation equipment and medications in room
Treatment

- Prevention of recurrence
  - Once DKA crisis resolved, counsel child and family on prevention strategies
  - Inform families and child of acute and chronic complications associated with DKA
  - Give families information on support groups and resources for children with diabetes
    - Involve all necessary services including endocrinology, child life, and social work
Complications

- Acute
  - Hypoglycemia
  - Persistent acidosis
  - Lactic acidosis
  - Hypokalemia
  - Cerebral edema
  - Fluid overload and CHF
  - Aspiration secondary to decreased LOC
Complications

- Chronic
  - Poor growth
  - Insulin resistance
  - Hypertrophy and lipoatrophy of injection sites
  - Limited joint mobility
  - Vaginitis and candidiasis
Long Term Complications

- Complications associated with poorly controlled diabetes:
  - Macrovascular/ Microvascular disease
    - Retinopathy
    - Nephropathy
    - Neuropathy
Cerebral Edema: Etiology

- Unknown
- Possibly multifactoral
  - Rapid correction of hyperglycemia or acidosis
  - Rapid decrease in serum sodium level
  - Overly aggressive fluid management
  - Administration of bicarbonate
  - Elevated endogenous vasopressin levels
Time between initiation of therapy and neurologic deterioration in children with DKA and cerebral edema. Note majority of neurological changes occurred between 3 and 6 hours. This time period is typically when severe acidosis is partially corrected, blood glucose level is falling, adequate circulation is restored, and the patient appears to be recovering well.

Cerebral Edema: Signs/Symptoms

- Decrease in GCS
- Decrease sensations
- Sudden/severe headache
- Incontinence
- Vomiting
- Combativeness
- Disorientation
- Agitation
- Ophthalmoplegia

- Pupillary changes
- Papilledema
- Posturing; seizures
- Change in vital signs
  - Hypothermia
  - Hypotension
  - Hypertension
  - Tachycardia
  - Bradycardia
  - Gasping respirations
  - Apnea
  - Arrhythmia
Changes in intercaudate diameter of the lateral ventricles. First CT done as soon as possible after glucose level < 250 mg/dL. Second CT done after resolution of DKA episode just prior to discharge. All initial scans showed narrowing of lateral ventricles.

Changes in diameter of the third ventricle. First CT done as soon as possible after glucose level < 250 mg/dL. Second CT done after resolution of DKA episode just prior to discharge. All initial scans showed narrowing of third ventricle.

Cerebral Edema: Diagnostic Studies/Treatment

- Mannitol: 1g/kg over 15 minutes
  - Repeat as needed
- CT Scan
- ICP monitor
- Intubation
- Hyperventilation
Websites

- American Diabetes Association
  - http://www.diabetes.org

- Juvenile Diabetes Research Foundation International
  - http://www.jdfcure.org/

- National Institute of Diabetes & Digestive & Kidney Diseases
  - http://www.niddk.nih.gov/

- International Diabetes Federation
  - http://www.idf.org

- Children with Diabetes
  - http://www.childrenwithdiabetes.com


