Overview and Comparison of DKA and HHS

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Objectives

- Describe the pathogenesis and epidemiology of DKA and HHS
- Distinguish precipitating factors for DKA and HHS
- Compare and contrast the clinical presentation and diagnostic criteria for DKA and HHS
- Discuss the treatment and management of DKA and HHS
- Evaluate a treatment plan for a patient undergoing hyperglycemic crisis

Introduction

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two of the most serious acute complications of diabetes
- These two metabolic disorders differ in their degree of hyperglycemia and presence or absence of ketoacidosis
- Although both are treated similarly, it is important to detect distinguishing factors so patients are managed correctly
- DKA and HHS are separate entities, however one-third of patients exhibit characteristic of both conditions

Stoner GD. Hyperosmolar Hyperglycemic State. *Am Fam Physician.* 2005 May 1;71(9):1723-1730.

DKA: Diabetic ketoacidosis
HHS: hyperosmolar hyperglycemic state

Epidemiology

- Mortality in HHS is much higher than in DKA
  - HHS mortality is between 5-20%
  - DKA mortality is <1%
- Population affected
  - DKA most commonly occurs in type 1 diabetics
  - HHS occurs exclusively in type 2 diabetics
- Evolution of symptoms
  - DKA usually evolves over 24 hours
  - HHS evolves over days to weeks
- Prognosis of both is poorer in age extremes and with other comorbidities

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

Pathogenesis: DKA

- ↓ insulin concentration in the body
- ↑ Counterregulatory hormone concentrations
  - Catecholamines, cortisol, and glucagon
- Hyperglycemia develops as a result of:
  - Increased gluconeogenesis
  - Accelerated glycogenolysis
  - Impaired glucose utilization
- Magnified by transient insulin resistance (type II)

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Pathogenesis: HHS

- Not as well understood as DKA
- Greater degree of dehydration due to
  - Osmotic diuresis
  - Differences in insulin availability
- Endogenous insulin secretion > than in DKA
- Insulin levels are not enough to facilitate glucose utilization by insulin sensitive tissues
  - Adequate to prevent lipolysis and ketogenesis

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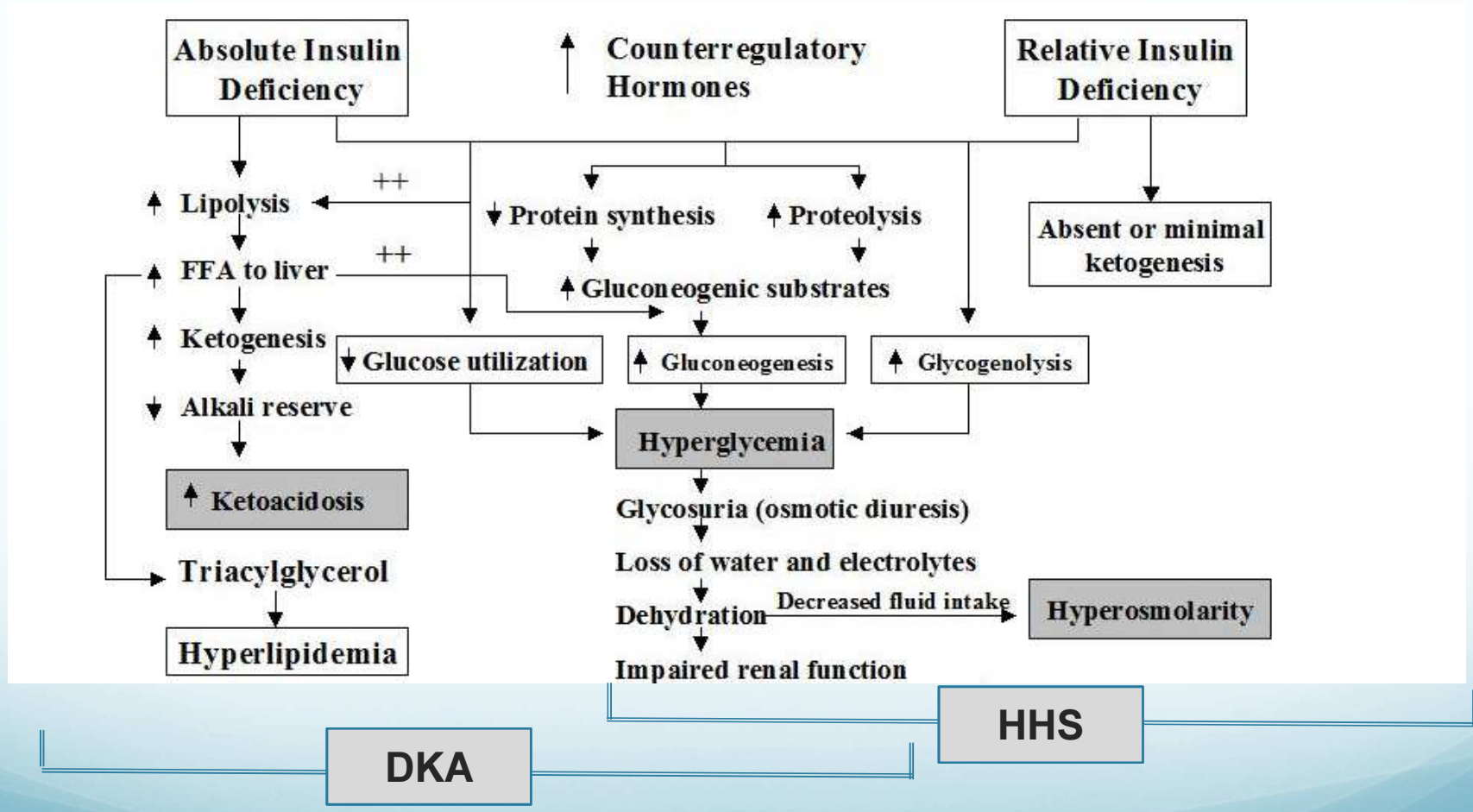
Pathogenesis



Available at: http://diabetesmanager.pbworks.com/f/pathogenesis%20of%20dka.jpg. Accessed October 27, 2014.

Precipitating Factors: DKA & HHS

- Illness
  - Infection
  - Pancreatitis, myocardial infarction or stroke
- Dehydration (HHS)
- Inadequate or discontinuation of insulin therapy
- New onset or unrecognized diabetes
- Drug-induced hyperglycemia

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Precipitating Factors: Illness

- Infections are the most common cause
  - Pneumonia, sepsis, UTI
- Acute illnesses
  - Myocardial infarction, stroke, pancreatitis
- Increases release of counterregulatory hormones
  - Cortisol
  - Catecholamines
  - Glucagon

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

Precipitating Factors: Dehydration

- Release of counterregulatory hormones
  - Compromises access to water
  - May result in severe dehydration
- Restricted water intake may also be due to
  - Patient being bedridden
  - Altered response to thirst by elderly
  - Altered mental status and not responding to signs of hyperglycemia

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

Precipitating Factors: Insulin

- May result from inadequate insulin therapy
- Psychological problems
  - Eating disorders
- Younger patient's may discontinue due to:
  - Fear of weight gain
  - Fear of hypoglycemia
  - Forgetting to take insulin
  - Embarrassed by stigma
  - Medication cost

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Precipitating Factors: Diabetes

- New onset diabetes is a very common cause
- DKA is often the presenting “symptom” of diabetes
- Patients new to diabetes cannot recognize hyperglycemic symptoms
- Some common symptoms include:
  - Polyuria, polydipsia, polyphagia and weight loss
- Elderly patients with new-onset type II diabetes are at high risk for HHS

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Precipitating Factors: Drugs

- Drugs that affect carbohydrate metabolism include:
  - Corticosteroids
  - Thiazides
  - Sympathomimetic agents
    - Norepinephrine, albuterol, etc.
  - Typical and atypical antipsychotics
- May induce peripheral insulin resistance by:
  - Antagonizing receptors on pancreatic ß-cells
  - Inhibiting α2-adrenergic receptors

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Clinical Presentation

	DKA	HHS
Hyperglycemia symptoms	+	+
Abdominal symptoms (pain, nausea/vomiting)	+ (>50%)	< Common
Dehydration	+	+
Fruity breath (from ketones)	+	
Kussmaul breathing	+	
Weakness	+	+
Neurological deficits	+	+ (>Coma)

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Diagnostic Criteria

	DKA	HHS
Plasma glucose	> 250 mg/dL	> 600mg/dL
Ketonuria/ketonemia	Present	Small amount or absent
Arterial pH	< 7.3	≥ 7.3
Serum bicarb	≤ 18meq/L	>18
Anion gap	Elevated (>10)	Variable
Serum osmolarity	Variable	>320 mOsm/kg

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Other Lab Abnormalities

- Leukocytosis
  - Cell counts in the 10,000-15,000 mm^3 range
  - Attributed to stress
- Hyponatremia
  - Osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia
  - Correction: Add 1.6 mg/dl to the measured Na^+ for each 100 mg/dl of glucose above 100 mg/dl
- Hyperkalemia
  - Extracellular shift of potassium caused by insulin deficiency and acidemia

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Treatment

- Goals of treatment include:
  - Correction of dehydration
  - Correction of hyperglycemia
  - Correction of electrolyte imbalances
  - Identification of comorbid conditions
- Before initiating treatment certain information must be obtained:
  - Thorough medical history
  - Baseline labs

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Treatment Steps

1. Hydrate with isotonic saline
   - Used to expand extracelluar volume and stabilize cardiovascular status
   - Increases insulin responsiveness by lowering osmolality, reducing vasoconstriction and stress hormone levels
2. Correct potassium deficit
   - Administration of insulin will decrease K+ levels
   - Choice of fluid replacement may be influenced by K+ levels
3. Begin IV insulin infusion
4. Replace bicarbonate in certain cases (DKA only)

Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract. 2011;94(3):340-51.

Treatment: Hydration

1. Initiate NS IV 1L/hr (15-20ml/kg/hr) x 1 hour
2. Assess hemodynamics, hydration and electrolytes

- If hemodynamically unstable:
  - Continue NS at 1L/hr and **ADD** vasopressors
- If hypovolemic shock:
  - Continue NS at 1L/hr
- If dehydration with low Na^+ or normal-high Na^+:
  - NS at 250-500ml/hr (low Na^+)
  - ½ NS at 250-500ml/hr (normal-high Na^+)

NS: Normal Saline

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Treatment: Hydration

3. Change fluid to D5½NS and reduce rate by half
   - Once plasma glucose reaches:
     - 200mg/dL (DKA)
     - 300mg/dL (HHS)
   - Dextrose is added to fluids because insulin cannot be stopped until there is complete resolution of symptoms
   - Fluid deficit is usually corrected within 24 hours

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Treatment: Potassium

- Patients often present with hyperkalemia even though total body stores of K^+ are low
- K^+ at presentation can be low, high, or normal
- Once glucose and acidemia correct, **K^+ will drop**
- Maintenance goal for plasma K^+ is 4 – 5 mEq/L
- K^+ should be monitored carefully during therapy
  - EKG is also recommended for low or high levels of K^+
- Before replacing K^+ adequate renal function should be established

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Treatment: Potassium

- Normokalemia: replacement should be given with the start of insulin therapy
  - Add 20-30 meq K^+/L to IV fluids to keep K^+ (4-5meq/L)
- Hypokalemia: replacement should be started **immediately,** before beginning insulin therapy
  - Add 40 meq K^+/L/hour (may be added to fluid bolus)
  - K^+ should be monitored hourly until normal level achieved
- Hyperkalemia: replacement should be initiated when K^+ falls to normal
  - Replacement given as potassium chloride
  - Continue throughout insulin drip

Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract. 2011;94(3):340-51.

Treatment: Insulin

- Mainstay of treatment of hyperglycemic crisis
  - May use any route of administration
  - IV commonly used because it works rapidly
- Give regular insulin via IV route as infusion
  - Started after initial fluid bolus is complete
  - Typically 100units/100mL concentration
  - Short half-life and easy titration
  - Requires placement in the ICU
    - **Hourly glucose checks**
  - Hold until $K^+ \geq 3.3$meq/L

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

Treatment: Insulin

- Recommended insulin dose based on ADA guidelines
  - 0.1 units/kg IV bolus, then 0.1units/kg/hour infusion
  - 0.14 units/kg/hour (using actual body weight)
    - Equivalent to 10 units/hour in a 70 kg patient
- Based on a recent randomized prospective trial, bolus is not necessary if higher maintenance dose is used
- In absence of bolus, <0.1units/kg/hour resulted in an insulin concentration too low to suppress hepatic ketone body production

Kitabchi AE, et al. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care 2008;31.

Treatment: Insulin

- BG should be decreased at a rate of 50–75 mg/dL/hr
- If BG has not decreased by ≥ 10% in 1st hour, double insulin dose
- ↓ insulin infusion rate to 0.02-0.05 units/kg/ when BG:
  - ≤ 200 mg/dl (DKA)
  - ≤ 300 mg/dl in (HHS)
  - May also add dextrose to IV fluids
- Continue insulin until event resolves
  - Anion gap closes and acidosis resolves (DKA)
  - Mental status resolves (HHS)

BG: Blood glucose

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

Treatment: Insulin

- Transition to subcutaneous insulin
  - Event has resolved
  - Able to tolerate oral intake
- Overlap first subcutaneous insulin injection with insulin infusion to give sufficient time for absorption
  - Insulin-naïve: 0.5 – 0.8 unit/kg/day (Basal/Bolus)
  - Non-naïve: resume prior regimen

Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract. 2011;94(3):340-51.

Treatment: Bicarbonate

- Bicarbonate replacement therapy is controversial
- Not indicated in HHS, only for DKA
- Only if severely acidotic (pH <6.9):
  - Add 100mEq of $NaHCO_3$ in 400mL sterile water with 20mEq of KCl
  - If the K^+ is <5.3 mEq/L should administer over 2 hours
- pH and bicarbonate should be monitored every 2 hours
- Bicarbonate replacement may slow the rate of recovery of the ketosis

Kitabchi AE, et al. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment. UpToDate. 2014. Accessed November 3, 2014.

Patient Case

- RW is 55 year old female who presented to the hospital with hypercapnic respiratory failure, progressive weakness and altered mental status
  - Ht: 61 inches, Wt: 46.3kg
  - PMhx: hyperlipidemia, hypertension, diabetes, chronic pancreatitis, and tobacco dependency
  - U/A: (+) for protein, (-) for ketones
- TL is a 23 year old female who presented to the hospital with nausea, vomiting, dizziness, tachycardia
  - Ht: 62 inches, Wt: 64kg
  - PMhx: diabetes, HTN, eczema, and GERD
  - U/A: (+) for protein and ketones

Patient Case

Labs (RW)	Values
Na	137
K	4.6
Cl	96
CO_2	36
Scr	1.7
Glucose	1283
pH	7.17
HCO_3	37.2
WBC	17.0
Anion gap	3.8
Osmolality	354

Labs (TL)	Values
Na	129
K	3.5
Cl	98
CO_2	8
Scr	0.32
Glucose	555
pH	
HCO_3	
WBC	7.3
Anion gap	23
Osmolarity	294

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Osmolarity	**294**

Patient Case

- Identify the metabolic disorder
- RW presented with…
  - HHS
- TL presented with…
  - DKA

Patient Case: DKA

- In the ED, DKA was given:
  - 1 liter NS bolus
- 1 hour later…
  - Continued NS @ 150ml/hr
  - Started on insulin drip @ 5units/hour (0.08units/kg/hour)
- 5 hours later…
  - Changed IVF to D5 ½ NS @125ml/hr
- 9 hours later…
  - Changed IVF to D5 ½ NS with 20meq KCl @150ml/hr

Patient Case: DKA

Labs	10/19 @2258	10/20 @0600	10/20 @0952	10/20 @1327
Na	129	141	138	140
K	3.5	2.7	4.7	4.1
Cl	98	115	115	115
CO_2	8	13	16	19
Scr	0.32	0.38	1.44	0.42
Glucose	555	180	232	188
Anion gap	23	13	7	6
Osmolarity	294	295	292	294

Patient Case: DKA

- What was done correctly?
  - Initial fluid bolus
  - Keeping NS since sodium was low
  - Starting insulin drip
- What changes would you have made?
  - Given higher dose of insulin infusion or insulin bolus
  - Started potassium in the fluids from the beginning
  - Drawn labs every 2 hours after admission

Patient Case: DKA

- 20 hours later…
  - Insulin drip was discontinued
    - Overlapped with insulin pump
- DKA was transferred to the floor for monitoring 1 more day and was discharged home the next day
- All symptoms of DKA were resolved upon discharge

Patient Case: HHS

- In the ED, HHS was given:
  - 8 units IV regular insulin (0.18units/kg/hour)
- 1 hour later…
  - Started NS @ 150ml/hr
  - Started on insulin drip @ 2units/hour (0.04units/kg/hour)
- 3 hours later…
  - Increased NS to 300ml/hr for 2L then ½ NS @250ml/hr
  - Increased insulin drip to 4 units/hour (0.09units/kg/hour)
- 6 hours later…
  - Bolused K^+ 40meq x1

Patient Case: HHS

Labs	10/8 @0318	10/8 @0823	10/8 @1319	10/8 @1601	10/8 @1924
Na	137	153	155	153	150
K	4.6	3.0	3.7	3.7	4.9
Cl	96	114	120	118	119
CO_2	36	33	31	31	26
Scr	1.7	1.47	1.18	1.35	1.21
Glucose	1283	539	151	60	108
pH	7.17	7.27	7.49	7.32	
HCO_3	37.2	30.5	29.4	30.2	
Anion gap	3.8	8.5	5.6	4.8	5.0
Osmolality	354	344	326	317	313

Patient Case

- What was done correctly?
  - Keeping NS since sodium was low
  - Starting insulin drip
- What changes would you have made?
  - Given initial fluid bolus in ED
  - Given higher dose of insulin infusion
  - Added potassium to fluids instead of giving bolus
  - Drawn labs every 2 hours after admission
  - Insulin was doubled without reason

Patient Case: HHS

- 12 hours later…
  - NS bolus 500ml x 1
- 16 hours later…
  - Changed IVF to D5 ½ NS @150ml/hr
- 3 days later…
  - Decreased IV insulin infusion sliding scale level 1
- 4 days later…
  - Transition patient to subcutaneous sliding scale insulin
- HHS had a complicated admission and was discharged 12 days later

Take Home Points

- DKA and HHS are dangerous metabolic disorders that warrant immediate medical attention
- It is essential to monitor patients and their lab values every 2 hours to ensure patient safety
- Following guidelines when managing these patients is important and can reduce complications
- Pharmacists can play a large role in the management of these patients

References

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Questions