Objectives

- Describe the physiology of normal glucose homeostasis
- Describe the epidemiology of drug-induced dysglycemia
- Illustrate examples of drug-induced dysglycemia employing an interactive case-based approach
- Discuss strategies to prevent and manage drug-induced dysglycemia

Operational Definitions

- **Dysglycemia** – "Abnormal blood glucose levels from any cause that contribute to disease"

http://www.medilexicon.com/medicaldictionary.php?word=dysglycemia

Accessed 9-21-14
Glucose homeostasis: roles of insulin and glucagon. 

Aronoff S L et al. Diabetes Spectr 2004;17:183-190

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Drug Causes of Dysglycemia

Hyperglycemia
- Aycylc Antipsychotics
- Cyclosporine
- Diazoxide
- Glucocorticoids
- Niacin
- Oral Contraceptives

Hypoglycemia
- Beta blockers
- Ethanol
- Insulin
- Pentamidine
- Saliylylates
- Sulfonylurases

Drug-induced Dysglycemia

Hyperglycemia
- Insulin secretion
- Insulin sensitivity
- Pancreatitis
- Hepatic gluconeogenesis
- Weight gain
- Glucose uptake

Hypoglycemia
- Beta blockers
- Ethanol
- Pentamidine
- Sulfonylurases
- Salicylates
- Niacin
- Oral Contraceptives

Differential Diagnosis

Hyperglycemia
- Diabetes mellitus
- Pancreatitis
- Cirrhosis
- TPN
- Cushing Syndrome
- Acromegaly

Hypoglycemia
- Addison's Disease
- CHF
- Alcoholism
- Glycogen Storage Disease
- Factitious hypoglycemia
- Insulinoma
Signs and Symptoms

Hyperglycemia
- The 3 “Ps”
- Weight loss
- Visual changes
- DKA-like
- Lethargy
- Coagulation

Hypoglycemia
- GI distress
- Confusion
- Hypoglycemia
- Hunger
- Seizures
- Coma

Dang DK, Pucino F, Ponte CD, Calis KA. 2010

Risk Factors

Hyperglycemia
- Metabolic syndrome
- Pre-diabetes
- Classic risk factors for T2DM
- Dose (# of drugs)
- Drug-drug Interactions

Hypoglycemia
- History of HypoGly
- Reduced CHO intake
- Altered metabolic clearance
- Diabetes (# of drugs)
- Increased glucose clearance
- Elderly

Dang DK, Pucino F, Ponte CD, Calis KA. 2010

Case Studies

• BG is a 57 yo w who is admitted to MGH for an acute exacerbation of COPD. She is begun on nebulized albuterol/ipratropium, IV methylprednisolone and oral doxycycline in addition to her home medication regimen.

• PMH - significant for chronic bronchitis, HTN, HLD, pre-diabetes and GERD.

• 48 hours into the admission, the floor nurse calls the house officer in a panic. The patient’s finger stick blood glucose is 304 mg/dl.

How do you explain the rather sudden rise in the blood glucose concentration?

• Ht - 5’ 4” Wt - 167 # T - 37.3 C RR - 20
BP - 145/89

• Labs

Electrolytes - WNL (except SrCr - 1.3)
Glucose - 167 (random)
LFTs - WNL
CBC - WNL (except WBC - 11,000)

Case Study

Steroids
Pathogenesis

- Dose-related phenomenon
- Receptor and post-receptor effects
- Gluconeogenesis
- Peripheral utilization of glucose by fat
- Glucose-intolerant person more prone
- Hyperglycemia may abate after drug d/c’d

Case Studies

CP is a 59 yo AA male is brought by his wife to the Family Medicine Center with a 3 day history of increasing somnolence, thirst and frequent urination. She was worried by a recent lack of appetite and difficulty in arousing him.

MH – Schizophrenia, bipolar disorder, pre-diabetes, hypertension, hyperlipidemia and GERD

Meds - Only change in the last 6 months has been the addition of olanzapine 15mg po QD
Others - Valproate, lisinopril, HCTZ, atorvastatin and esomeprazole

Ht - 5’ 10” Wt - 285 # T - 37.6 C RR - 18 BP - 167/94

Labs

Electrolytes - WNL - except Na - 130, K - 3.4, CO2 - 19
BUN/Cr - 25/1.5
Glucose - 853 (random)
Serum osmolality - 307
LFTs - WNL
CBC - WNL (except WBC - 15,000, diff. WNL)
EKG - NSR with occ. PVC’s

Physical Exam findings consistent with moderate dehydration and altered mental status.
Presumptive diagnosis - Hyperosmolar hyperglycemic state (HHS)
How could this happen?
Atypical Antipsychotics and Glucose Intolerance (Diabetes)

- Points to Know
  - Weight gain – children > adults (metformin?)
  - Rapid early weight gain predicts long term weight (obesity)
  - Central appetite stimulation (disinhibition of eating, susceptibility to hunger)
  - APD-induced insulin resistance, impaired insulin secretion and altered glucose homeostasis (in absence of weight gain)
  - Role of neurotransmitter receptors (5-HT₂c, H₁, muscarinic M₃ and dopamine D₂)
  - Clozapine > olanzapine (ziprasidone/ariprazole)

Hasnain M et al. CNS Drugs 2010 24(3):193-206
Deng C. Endocrinology and Metabolism Clinics (September 2013)

Case Studies

- Ilufta Cooke – 55 yo woman – comes to the Family Medicine clinic for a new intake HM exam. New to the area. Will start work soon as an executive chef. Not been to a physician in 5 years (“no time, always busy”). Loves to “taste” her cooking.
- NKDA
- Meds – MVI, calcium supplement
- SM – divorced, two children (A&W), 1-2 glasses of wine per day quit cigarettes 3 years ago (40 pack yrs), no regular exercise routine (occasional walks)

Case Studies

- FH - father died (59 yo) - AMI
  - brother - CHD, HTN, gout
  - mother - type 2 DM, HTN, CHF, colon CA
  - adopted sister - A&W
  - Physical Exam - pleasant “jovial” obese woman in NAD, appears stated age
  - Ht. - 5’5" Wt. - 92 kg (BMI - 33.8 kg/m²)
  - BP - 138/88 (Pulse 90)
  - RR - 16
  - PE - Unremarkable

- Labs
  - Electrolytes - WNL (except SrCr - 1.3)
  - Glucose - 200 (fasting)
  - Lipid Panel - TC-190, TG - 300, HDL - 35, LDL - 167, Non-HDL - 155
  - AST/ALT/TBili/ALKP - WNL
  - A1C - 6.6

Case Studies

- Follow-up Visit (3 month)
  - The patient reports being frustrated with lifestyle modifications. This summer she began writing a cook book and her walking has suffered. She feels like a “fat slug” and she’s more thirsty lately.
  - Ht. - 5’5" Wt. - 100 kg (BMI - 36.6 kg/m²)
  - BP - 145/90 (Pulse 72)
  - PE - Unremarkable
Case Studies

- Labs
  - Electrolytes: WNL (except SrCr = 1.3)
  - Glucose: 173 (fasting)
  - Lipid Panel: TC = 210, TG = 286, HDL = 35, LDL = 165, Non-HDL = 175
  - AST/ALT/TBili/ALKP: WNL
  - A1C: 7.3

The medical resident seeing IC would like to initiate a “statin” as part of the overall treatment plan due her presumptive diagnosis of T2DM and her other co-morbid conditions. However, the preceptor (attending physician) expresses some concern about the recent association between statins and diabetes. What say yee?

The Rest of the Story

3 meta-analyses & observational trial
Bottom Line – 12% chance of developing DM
Dose relationship?
Higher risk earlier in treatment
MOA? (impaired insulin secretion vs insulin resistance)
Increase in A1C (0.3%)

• Monitor high risk individuals (elderly, women and Asians) and adjust drug regimen(s) accordingly

The Evidence

The JUPITER Trial
- DB Placebo-controlled RCT
- 17,802 healthy adults
- LDL < 130mg/dl, CRP >2 mg/L
- Rosuvastatin 20mg po daily

Primary outcomes - myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or CV death

Adverse events – (Median-follow-up 1.9 yrs.)
- Physician-reported diabetes (270 vs 216, p=0.01), A1C (0.9 vs 5.8%, p=0.001)
- NNH 167

Good News!

Danish Retrospective Study (Patient Registry)
- Statin users (15,679) vs non-statin users (47,037)
- Primary outcome – diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, or gangrene of the foot
- Median follow-up – 2.7 yrs
- Outcomes (statin vs non-statin users):
  - Diabetic retinopathy (HR 0.60, 95% CI 0.54-0.66, p<0.0001)
  - Diabetic neuropathy (HR 0.64, 95% CI 0.54-0.75, p<0.0001)
  - Gangrene of the foot (HR 0.88, 980-9.97, p<0.010)
Consequences of Drug-Induced Dysglycemia

• May be no different than morbidity (mortality) caused by hyperglycemia and hypoglycemia from any cause

Prevention Strategies

Use the appropriate tools to assist you in evaluating drug-drug interaction potential:

- Compendia (DI Facts, Micromedex)
- On-line references [drugs.com, interactions checker]
- Smart Phone/PDA apps (Epocrates, Lexi-Comp)
- Colleagues (MD/DO, PharmD/RPh, RN)
- Drug and Health Information Centers

Prevention Strategies

• Review current Rx and nonprescription drug regimens (Head to Toe or Review of Systems (ROS) Approach)
• Evaluate concomitant medication/co morbid conditions that may interfere with the P' Kinetics/P' Dynamics of drug in question
• Evaluate co morbid condition(s) that may be affected by the drug choice

Prevention Strategies

• Obtain baseline data when initiating drugs with known effects on glucose regulation
  - Weight
  - FS BG
• Limit patient exposure to drugs with effects on glucose regulation (dose, duration)
• Continue prospective monitoring of high risk patients

DI Assessment Tools

- Remember
- Concordance may vary among compendia
- Always search 2 or more data bases for information

The Unthinkable

• What if?
1. Interacting drugs can’t be avoided
   - Monitor, monitor, monitor!
2. Interaction results in a morbid event
   - Reduce dose/discontinue offending drug(s)
   - Supportive care if necessary (manage hyper-hypoglycemia)

Learn from the incident – Don’t do that again!