Patient Safety: Medication-Induced Hyperglycemia and Diabetes

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Learning Objectives

- List major causative agents leading to hyperglycemia and diabetes mellitus and their putative mechanisms
- Describe clinical manifestations of medication-induced hyperglycemia
- Identify preventive and management strategies for medication-induced hyperglycemia

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Disclosure Statement

- I have no actual or potential conflict of interest with the content of this presentation.

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AUDIENCE POLL

- 45 yo AA male with schizophrenia, HTN, obesity, asthma, and type 2 diabetes diagnosed 3 years ago.
- He's currently taking clozapine 300 mg/day, fluticasone/salmeterol DPI 500/50 mcg bid, albuterol MDI prn, metformin 1,000 mg bid, sitagliptin 100 mg qday, and atorvastatin 20 mg daily.

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AUDIENCE POLL

- A prescriber asks for your opinion: which medication could have led to the development of this patient's type 2 diabetes?

A. Clozapine
B. Fluticasone
C. Atorvastatin
D. None of the above

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Hyperglycemia
Pathophysiology

- Decreased insulin secretion or destruction of pancreatic beta cells
- Insulin resistance
  - Liver
  - Muscle
  - Adipocytes
- Weight gain

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Mechanisms of Medication-Induced Hyperglycemia and Diabetes

- Alterations of insulin secretion
- Changes in insulin sensitivity
- Changes in gluconeogenesis or glucose metabolism
- Direct cytotoxic effects on pancreatic beta-cells
- Drug-induced pancreatitis
- Direct vs. indirect drug effect
  - Unmasking of hyperglycemia in at risk individuals
- Unknown

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Morbidity and Mortality of Medication-Induced Hyperglycemia and Diabetes

- Hyperglycemic symptoms
- Hyperglycemic emergencies
- Hyperglycemia may resolve upon discontinuation of drug in some patients but may also be permanent in others →
  - Prediabetes
  - Permanent diagnosis of diabetes (some patients may be insulin-dependent)
- Micro- and macrovascular complications of diabetes can occur if the hyperglycemia is persistent

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Differential Diagnoses*

- Cushing's disease or Cushing's syndrome
- Liver cirrhosis
- Metabolic acidosis
- Pancreatitis
- Parenteral nutrition therapy (dextrose administration)
- Renal failure
- Stress hyperglycemia
- Determine by evaluating temporal relationship and possibly through drug withdrawal and rechallenge

*Not an all-inclusive list

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Risk Factors

- Dose
- Use of more than one drug that can induce hyperglycemia
- Drug interactions
  - Pharmacokinetic
  - Pharmacodynamic
- Underlying disease states (e.g. HTN, schizophrenia)

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Risk Factors

- Patients with underlying risk factors for type 2 diabetes mellitus
  - age ≥ 45 years
  - family history (1st degree relative) of diabetes
  - race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
  - overweight or obese: BMI ≥ 25 kg/m^2 (≥ 23 kg/m^2 in Asians)
  - habitual physical inactivity

ADA Standards of Medical Care in Diabetes – 2021.

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Risk Factors

- Patients with underlying risk factors for type 2 diabetes mellitus
  - hypertension (≥ 140/90 mmHg in adults)
  - HDL-C ≤ 35 mg/dl and/or a TG ≥ 250 mg/dl
  - h/o cardiovascular disease
  - history of gestational diabetes mellitus
  - polycystic ovary syndrome
  - previously identified impaired fasting glucose or impaired glucose tolerance
  - HIV

ADA Standards of Medical Care in Diabetes – 2021.

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Major Causative Agents

- Atypical antipsychotics
- Calcineurin inhibitors
- Diazoxide
- Fluoroquinolones – mainly gatifloxacin
- Glucocorticoids
- Mammalian target of rapamycin (mTOR) inhibitors
- Niacin
- Pentamidine
- Protease inhibitors & NRTIs
- Somatostatin analogs
- Tyrosine kinase inhibitors

Not an all-inclusive list

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Commonly Prescribed Causative Agents

- Glucocorticoids
- Atypical antipsychotics
- Protease inhibitors
- HMG CoA reductase inhibitors
- Thiazide diuretics
- Beta blockers
- Combination oral contraceptives, menopause hormone therapy
- Fluoroquinolones – mainly gatifloxacin

Not an all-inclusive list

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Glucocorticoids

- Mechanisms of drug-induced hyperglycemia
  - ↑ gluconeogenesis
  - ↑ insulin resistance
  - ↓ pancreatic insulin secretion
  - ↑ Appetite and weight
- Severity & incidence depend on
  - Dose
  - Route of administration – po & IV > topical & inhaled
  - Duration of use
  - Pre-existing risk factors

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Glucocorticoids

- Typical presentation of ↑ BG
  - Rise in mid-morning BG, continues throughout the day
  - Matches onset of effect of prescribed glucocorticoid
  - Check BG 1-2 hour post-lunch or pre-dinner
  - Elevated BG if higher doses (eg, prednisone ≥ 40 mg/day)
- Other symptoms of supraphysiologic glucocorticoid administration likely present

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Glucocorticoids

- Treatment
  - Close monitoring and escalation of existing DM medication therapy
  - Oral DM medications?
    - Depend on onset of effect
  - Insulin
    - NPH and premixes
    - Long-acting insulin + bolus insulin

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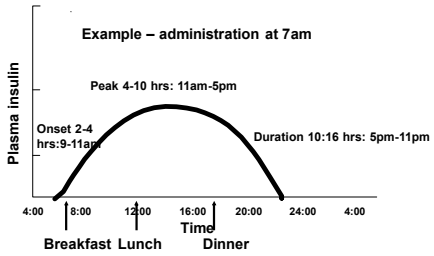
NPH Insulin



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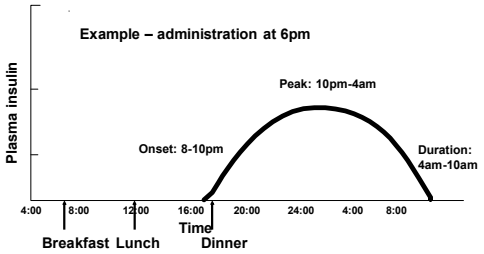
NPH Insulin



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AUDIENCE POLL

- Which of the following clinical manifestation has been reported with olanzapine?

A. Type 2 diabetes

B. DKA

C. Weight gain

D. All of the above

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Atypical Antipsychotics

- Mechanisms of drug-induced hyperglycemia (proposed)
  - ↓ peripheral insulin sensitivity
  - ↓ insulin secretion
  - promote weight gain
- Olanzapine & clozapine > risperidone, paliperidone, & quetiapine > ziprasidone, aripiprazole, iloperidone, lurasidone, & asenapine

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	Risk of weight gain	Risk of diabetes*	D_2 dopamine	$5HT_{2c}$ serotonin	$5HT_{1a}$ serotonin	M_3 muscarinic	α_2 adrenergic	H_1 histamine
Role in weight regulation			✓	✓				✓
Role in insulin secretion			✓		✓	✓	✓	
First-generation antipsychotic								
Chlorpromazine	+++	+++	++++	++++	+	++++	+	++++
Perphenazine	+	+	++++	++++	+	+	+	+++
Haloperidol	++	+	++++	++	–	+	+	+/–
Second-generation antipsychotic								
Clozapine	+++	+++	+++	+++	++	+++	++	+++
Olanzapine	+++	+++	+	+++	+	+++	+	+++
Quetiapine	++	++	+	+	+	+	+++	++
Risperidone	++	++	+++	++++	++	–	++++	++
Ziprasidone	+	+	+++	++++	++++	–	++	+
Aripiprazole	+	+	++++	+++	++++	–	++	+
Paliperidone	++	+	+++	++++	+	–	+++	++
Lurasidone	+	+	++++	++	++++	–	N/A	–

↑higher risk of diabetes and weight gain is associated with high M_3 Muscarinic and H_1 Histamine receptor affinity

*Relative to other antipsychotics. Not all the risk of diabetes or weight gain is related to the antipsychotic

Holt RIG. *Curr Diab Rep*. 2019;19:9.

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Antipsychotics – Monitoring Recs from ADA/AACE/APA/NAASO (2004)

	Base-line	4 wks	8 wks	12 wks	q3mo	qYear	q5yrs
Personal/family hx	X					X	
Wt (BMI)	X	X	X	X	X		
WC	X					X	
bp	X			X		X	
FPG	X			X		X	
Fasting lipids	X			X			X

Diabetes Care 2004; 27:596-601.

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Protease Inhibitors

- Mechanisms of drug-induced hyperglycemia
  - ↑ insulin resistance directly or indirectly
  - promote lipodystrophy
  - ↓ insulin secretion
- Example protease inhibitors
  - Ritonavir, atazanavir, indinavir, amprenavir, tipranavir, etc.
- Protease inhibitors differ in degree of drug-induced hyperglycemia
  - Appears to be lowest with atazanavir

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Nucleoside reverse transcriptase inhibitors (NRTIs)

- Mechanisms of drug-induced hyperglycemia
  - ↑ insulin resistance
  - promote lipodystrophy
  - pancreatitis
    - more common with didanosine and stavudine
  - inhibit insulin release secondary to hypokalemia – didanosine

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HMG-CoA Reductase Inhibitors

- Mechanisms of drug-induced hyperglycemia
  - ↓ peripheral insulin sensitivity
  - ↓ insulin secretion

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HMG-CoA Reductase Inhibitors

- Increased incidence of DM seen with
  - Atorvastatin – worse glycemic control with atorvastatin 80 mg/d compared to pravastatin 40 mg/d in the Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) substudy
  - Rosuvastatin – 28% increase in DM compared to placebo in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study
  - Women's Health Initiative (WHI) – 48% increased risk for DM in postmenopausal women taking statins (appears to be class effect unrelated to potency or individual statin)
  - Meta-analyses also show small increase in risk of DM

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HMG-CoA Reductase Inhibitors

- However….the West of Scotland Coronary Prevention Study (WOSCOPS) reported a 30% decrease in the incidence of diabetes patients (men 45-64 yo) treated with pravastatin 40 mg/d
- 2/28/2012 FDA change in labeling to include warning that "increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors" *for all statins except pravastatin*

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2013 Apr 15;111(8):1123-30

HMG-CoA Reductase Inhibitors

- 2010 meta-analysis of 13 statin RCT with 91,140 patients
  - NNH 255 over 4 years (OR 1.09)
  - However, 5.4 MACE (CHD death, non-fatal MI) prevented
- 2013 meta-analysis of statin RCTs with 113,394 patients
  - Lowest risk with pravastatin
  - Intermediate risk with atorvastatin
  - Highest risk with rosuvastatin (25% ↑ risk)

Sattar N et al. *Lancet* 2010;375:735-42.

Pio Navarese et al. *Am J Cardiol* 2013; 111:1123-30.

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HMG-CoA Reductase Inhibitors
Evaluating Risks versus Benefits

- Rosuvastatin's JUPITER study
  - RR: 28% increase in DM compared to placebo
  - Absolute risk: 1.2% in placebo, 1.5% in rosuvastatin 20 mg arm
  - Study enrolled patients at high risk for DM (but not diagnosed with DM at baseline)
  - In patients ***with*** ≥1 DM risk factors, 134 CV events or deaths were avoided for every 54 new cases of DM
  - In patients ***without*** a major DM risk factor, 0 new cases of DM diagnosed, 86 total CV events or deaths prevented

Ridker PM et al. *Lancet* 2012; 380:565-71.

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HMG-CoA Reductase Inhibitors

Evaluating Risks versus Benefits

- In non-diabetic patients with risk factors for diabetes
  - The absolute risk increase is small
  - The benefits on CVD reduction still outweigh the risk of diabetes in most patients
  - Monitor non-diabetic patients on statin therapy for development of diabetes

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HMG-CoA Reductase Inhibitors

Evaluating Risks versus Benefits

- In diabetic patients
  - There may be a slight worsening of glycemic control
  - The benefits on CVD reduction in most patients outweigh the risk of hyperglycemia
  - Monitor glucose and A1c (as usual) and adjust therapy accordingly (as usual)
- Statin therapy is recommended by both the ADA and AACE/ACE guidelines in diabetic patients to prevent ASCVD

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Pentamidine

- Mechanisms of drug-induced hyperglycemia
  - Direct cytolytic effects on pancreatic beta cells
    - causes hypoglycemia initially
  - Effect may be irreversible
  - Pancreatitis

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Assessment and Management

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Preventive Strategies

- Avoid/minimize administration of more than one drug that can induce hyperglycemia
- Avoid/minimize administration of drugs that may have pharmacokinetic or pharmacodynamic drug interactions with suspected drug
- Use lowest dose for the shortest duration if possible

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Preventive Strategies

- Obtain baseline fasting plasma glucose (FPG) prior to initiation of therapy
- Monitor FPG and ppBG as clinically indicated
- Monitor for symptoms of hyperglycemia
- Monitor weight at each office visit

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Management

- Discontinue or reduce dose if possible
- Minimize duration of use
- Administer antidiabetic medications if patient develops diabetes mellitus
- Dietary changes
- Exercise
- Monitor for and management long-term complications of DM

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Patient Education

- Relative risks versus benefits of medication(s)
- Importance of monitoring and follow-up testing
- More frequent blood glucose monitoring (if already with diabetes)
- When to discontinue medication(s)
- Signs and symptoms of hyperglycemia

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Signs and Symptoms of Hyperglycemia

- Mild to moderate
  - Excessive thirst and polydipsia
  - Polyuria
  - Blurry vision
  - Increased fatigue
  - Unexplained weight loss
  - Polyphagia

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Signs and Symptoms

- Severe
  - Nausea and vomiting
  - Lethargy
  - Obtundation
  - Abdominal pain
  - Breath with fruity odor
  - Dehydration
  - Metabolic acidosis
  - Coma

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