Steroid Hyperglycemia

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Objectives

- Explain the pathophysiology of steroid induced hyperglycemia
- Understand different glucocorticoid duration of action and how that may affect medication choices
- Review inpatient management
- Discuss outpatient management and suggestions for treatment.

Defining the problem

- "Steroids"
  - Glucocorticoids (GCs): "A hormone that predominantly affects the metabolism of carbohydrates and, to a lesser extent, fats and proteins. Glucocorticoids are made in the adrenal cortex, and chemically classed as steroids. Cortisol is the major natural glucocorticoid. The term glucocorticoid also applies to equivalent hormones synthesized in the laboratory.
    - Prednisone, prednisolone, betamethasone, dexamethasone
  - Used to treat and control inflammatory conditions and induce immunosuppression
  - In people with cancer, GCs are often used as adjuvant therapy with chemotherapy
- From MedicineNet.com; https://www.medicinenet.com/script/main/art.asp?articlekey=4390.Retrieved 1/28/17
- Oyer, D.S., Shah, A., Bettenhausen, S. (2006). *How to Manage Steroid Diabetes in the Patient With Cancer*. Journal of Supportive Oncology. 4(9). 479-483.

- At supra-physiological doses, GCs:
  - Reduce synthesis of pro-inflammatory cytokines
  - Reduce T-cell function and antibody Fc receptor expression
    - Activate the anti-inflammatory and immunosuppressive processes.
  - Adverse effects
    - CHO metabolism, Insulin sensitivity, insulin secretion

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Corticosteroid Comparison Chart

	Equivalent Glucocorticoid Dose (mg)	Potency relative to Hydrocortisone: Anti-Inflammatory	Potency relative to Hydrocortisone: Mineral-Corticoid	Half-Life: Plasma (minutes)	Half-Life: Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	–

Reference: Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis. Facts and Comparisons, Inc.:122-128, 1997

Commonly Prescribed Replacement Steroid Equivalents

Prednisone		Cortisone		Dexamethasone		Hydrocortisone (Cortef)
5 mg	=	25 mg	=	0.75 mg	=	20 mg

Steroid comparison chart. Retrieved from: http://www.nadf.us/downloads/adrenalhormone.pdf

The Pathophysiology of GCs

- GCs antagonize the metabolic effects of insulin
- Induce insulin resistance
  - Interfere with GLUT-2 signaling in the pancreas
  - Interfere with GLUT-4 signaling in the muscle cells.
  - Catabolize proteins which releases amino acids which interfere with insulin signaling in the muscle cells
  - Induce lipolysis leading to elevated FFA and Tg levels leading to insulin resistance by reducing glucose disposal into muscle cells
  - Enhance counterregulatory hormones (glucagon, cortisol, epinephrine)

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The Pathophysiology of GCs

- Reduce Insulin secretion from beta cells
  - May induce cellular apoptosis
- Promote gluconeogenesis by direct hepatic stimulation
- Affect post meal blood sugar due to insulin resistance and impaired insulin secretion
- Blood sugar effects are temporal and depend on the type of GC (see previous slide)

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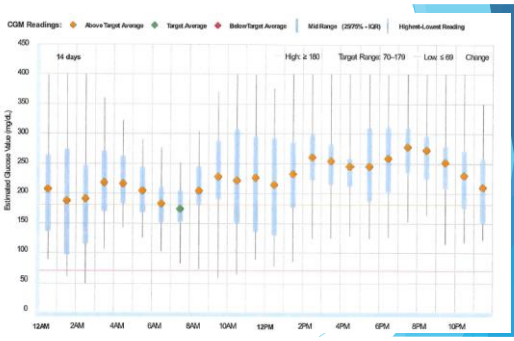

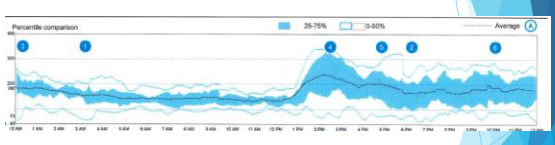

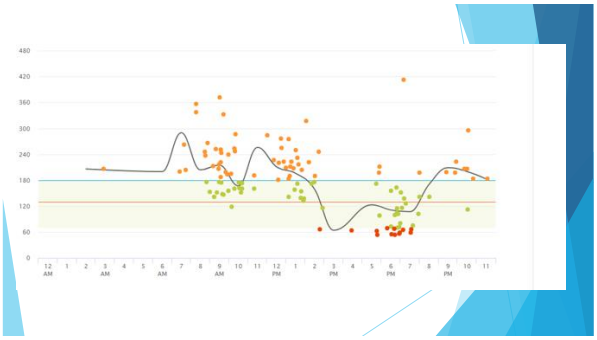

Why is this important?

- Even a few days of hyperglycemia can have deleterious effects on the immune system
- Acute hyperglycemia is associated with acute inflammation and endothelial dysfunction in patients with and without diabetes
  - Fluctuations in glucose associated with increased cardiovascular mortality
- May precipitate DKA or Hyperglycemic Hyperosmolar state.

- Clore, J.N. & Thurby-hay, L. (2009). Glucocorticoid-Induced Hyperglycemia. *Endocrine practice, 15 (5).* 496-474.
- Oyer, D.S., Shah, A., Bettenhausen, S. (2006*). How to Manage Steroid Diabetes in the Patient With Cancer.* Journal of Supportive Oncology. 4(9). 479-483.

Why is this important?

- May unmask indolent diabetes. There is no way of knowing if glucose will return to normal after GCs are stopped.
  - A1c prior to initiation
  - 7.2 million with undiagnosed DM. 84 million with pre-diabetes
- Control will ameliorate symptoms, reduce risk of acute complications and reduce infection risk.
- Odds ratio for risk of developing "steroid diabetes" with long term GC use for chronic conditions (ie: RA, COPD, Ulcerative colitis etc.) is 1.5-2.5.
  - Best test is 2h OGTT

- Statistics about Diabetes. (2017). American Diabetes Association. Retrieved from: http://www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.com/
- Clore, J.N. & Thurby-hay, L. (2009). Glucocorticoid-Induced Hyperglycemia. *Endocrine practice, 15 (5).* 496-474.
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Why is this important?

- 40-56% of all inpatient consults to endocrinology are for new or worsening diabetes due to steroids. $$
- 16% in-hospital mortality new hyperglycemia compared with 1.7% euglycemic.
- 3% in-hospital mortality if diabetic with hyperglycemia
- Longer stays, increased ICU admits, poor wound healing, higher infection rates
- Strong predictor of transplant graft failure
- Identify those at risk:
  - Pre-existing T1DM, T2DM
  - Increased risk for DM: +FHx, Obesity, Previous GDM, PCOS, Ethnicity, Pre-DM, previous hyperglycemia with steroids

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Treatment

- Limited clinical trials conducted to guide outpatient management
- Know the steroid type, frequency
  - Select therapy based on pharmacokinetics and pharmacodynamics of the GC.
  - IR can increase 60%-80% depending on the dose/type of GC used.
- Same glycemic targets: pre-prandial 80-130. 2h post prandial < 180. A1c < 7%
- Individualize care

- Roberts, A., James, J., Dhatariya, K. (2014). Joint British Diabetes Societies for inpatient care; Management of Hyperglycaemia and steroid (glucocorticoid) therapy. Retrieved from: http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf
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- Standards of Medical Care in Diabetes-2018. (2018). Diabetes Care. 41(1).

Treatment

- Capillary blood sugar monitoring is paramount to guiding appropriate therapeutic interventions.
- If single am dose GC; check Bg prior to lunch when hyperglycemia is likely to be greatest
- Increase frequency of Bg checks if pre-prandial is not at goal
- If T1DM, check Bg ac and hs, prn
- Consider CGM

Treatment

- Short course may need no other intervention than increased monitoring
  - If FPG < 200, no previous history, low dose CS.
  - Tx: low carb diet, physical activity.
- Treat the post prandial first.
  - Studies with health subjects:
    - Stress dose hydrocortisone 240mg . FPG returned to normal within 1 day, plasma concentration of cortisol doubled.
    - IV hydrocortisone: 50% decrease in insulin sensitivity
    - Oral prednisone 30mg/day x 7 days, 60% reduction in insulin sensitivity.

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Treatment-Oral Medications

- Sulfonylureas
- Conflicting evidence
  - Secretagogue
  - inexpensive
  - Have been proposed due to their effect on prandial Bg
  - Extended release don't selectively target post prandial hyperglycemia
  - May increase hypoglycemia risk due to duration

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Treatment-Oral Medications

- Metiglinides
  - Shorter acting secretagogue
  - May be inexpensive
  - Shorter duration of action; focus on early phase insulin secretion, may miss peak of steroid
  - Need to dose prior to eating

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Treatment-Oral Medications

- Metformin
  - Limited published data on use and effectiveness.
  - Closely counteracts effects of GC (reduced hepatic output of glucose and insulin sensitizer)
  - Inexpensive, favorable weight profile
  - Risk for acidosis of low perfusion state, renal impairment
  - Does not target post prandial

- Wallace, M.D. & Metzger, N.L. (2018). Optimizing the Treatment of Steroid-Induced Hyperglycemia. *Annals of Pharmacology, 52 (1).* 86-90.

Treatment-Oral Medications

- TZDs
  - Improve insulin sensitivity via PPAR gamma agonism at skeletal muscle and adipose
  - Inexpensive
  - Impractical for short term GC use, long onset and offset 2+ weeks
  - May be beneficial with long term steroid
  - Risk for fluid retention (fluid retention risk also with GC)

- Oyer, D.S., Shah, A., Bettenhausen, S. (2006). *How to Manage Steroid Diabetes in the Patient With Cancer.* Journal of Supportive Oncology. 4(9). 479-483.
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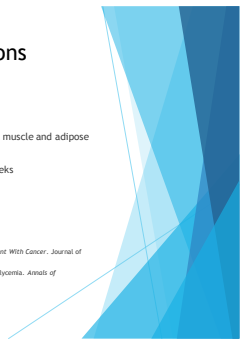
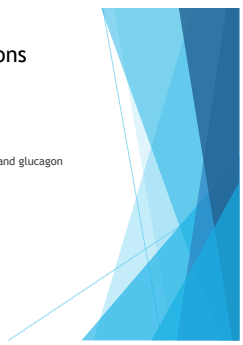


Treatment-Oral Medications

- DPP-4/GLP-1
- Limited data on use with steroid hyperglycemia
- Both lower post prandial Bg by first phase insulin secretion and glucagon inhibition
- Low risk for hypoglycemia
- Expensive, not practical for short term use



Treatment-Oral Medications

- SGLT-2s
- No published studies

Treatment-Insulin

- Insulin
- Preferred medication for steroid induced hyperglycemia
- type, dose, frequency will dictate regimen
- NPH is preferred for intermediate acting steroids (prednisone, prednisolone).
  - Dose in am with steroid dose
  - 0.1u/kg-0.4u/kg
  - Closely mimics prednisone

  Duration of action.
- If long acting GC, Lantus is preferred

Table 3
Suggested Dosages of NPH Insulin for Tapering Dosages of Glucocorticoids

Prednisone dosage (mg/d)	Insulin dosage (U/kg)
≥40	0.4
30	0.3
20	0.2
10	0.1

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Treatment-Insulin

- Insulin adjustments
  - Reduce or increase insulin 0.1u/kg for every 10mg reduction or increase (see previous slide) to a maximum of 0.4u/kg
  - Can also adjust based on percentage:
    - Percentage of insulin corresponds to ⅓ the percentage in steroid change.
    - For example if a steroid is increased or decreased by 50%, an increase of decrease of insulin by 25%
  - If pre-existing DM
    - Consider adding weight based once daily NPH to usual regimen
    - Consider increasing basal 10%-20%. Can adjust daily. Prandial / correction 40%-50%. Up to 100% may be needed for post prandial control.

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Treatment-Insulin

- Other "schemes" which may be useful
- Prandial
  - Low/medium/high protocols:
  - 5 units, 10 units, 15 units with meal or 1:10g CHO.
  - ISF: 1:50, 1:40, 1:30 respectively.
- Prandial
  - Using Regular for those who eat and snack or have delayed gastric emptying; Rapid insulin analogue for those who don't snack or eat high CHO
  - 0.1u/kg/meal to start
  - 0.4u/kg/meal if BG control is 200-300
  - 0.8u/kg/meal for those with BG control > 300

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Special cases

- Inpatient
  - Goal 140-180.
  - Tight control reduces hospital related complications
  - Can dose for steroids like outpatient
  - If BG > 300, insulin drip
  - SHMC: inpatient diabetes service. Carb count/correction
  - Clear DC plan if new regimen or tapering steroids
    - If steroid hyperglycemia inpatient with no previous diagnosis, recommend screening 2h OGTT 6 weeks post discharge
    - Diabetes education for DSME

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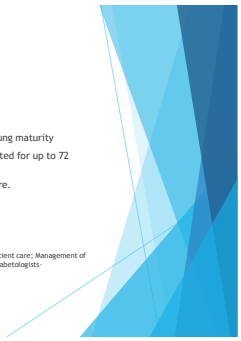
Special cases

- Long term steroids
  - Transplant
    - Could use combination of oral medications or insulin regimen.
    - If renal failure, insulin is recommended
    - Tracrolimus + steroids have a multiplicative effect on blood sugars.
    - Need plan for adjusting at home
  - COPD, Rheum
    - Interimittent steroid tapers superimposed on daily administration

Special cases

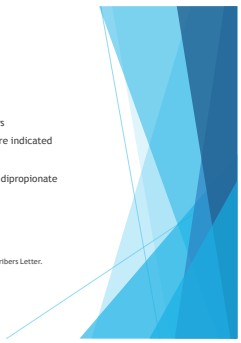
- Preg
  - Betamethasone is usually given in two doses to promote fetal lung maturity
  - Betamethasone has a 26-54 hour half life, Bg may remain elevated for up to 72 hours with each injection
  - May need to increase meal/correction dose by up to 40% or more.
  - "Sweet success" program
  - Questions? Alyson Blum PharmD, CDE at this WADE conference.
  - Roberts, A., James, J., Dhatariya, K. (2014). Joint British Diabetes Societies for inpatient care; Management of Hyperglycaemia and steroid (glucocorticoid) therapy. Retrieved from: http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf



Special cases

- Injectable:
  - Wide spread use; data on Bg effect sparse
  - Elevated bg between 5 and 84 hours, typically elevated 2-3 days
  - If type 1, more frequent Bg monitoring and dose adjustments are indicated
- Topical
  - Wide bioavailability. Mometasone less than 1%. Betamethasone dipropionate approximately 44%.
  - Potency and duration increase risk
  - Application to open, irritated, or large surface of skin a risk

Hyperglycemia Associated with Non-oral and Locally Injected Corticosteroids. (2011). The Prescribers Letter.



Special cases

- Inhaled
  - Small risk of developing diabetes. Odds ratio 1.34.
  - Dose and potency dependent
  - No blood sugar elevations with intranasal steroids
- Epidural
  - Elevated blood sugars for up to 2 weeks.
  - More pronounced and longer duration in pt. with diabetes compared to people without
  - Recommendation is for more monitoring, dose adjustments

Hyperglycemia Associated with Non-oral and Locally Injected Corticosteroids. (2011). The Prescribers Letter.