Steroid Hyperglycemia
Chris Lewis, ARNP, BC-ADM, CDE

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, to a lesser extent, fats and proteins. Glucocorticoids are made in the adrenal cortex, and chemically classified 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

References:
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


The Pathophysiology of GCs

- GCs antagonize the metabolic effects of insulin
- Induce insulin resistance
  - Interferes with GLUT 3 signaling in the pancreas
  - Interferes with GLUT 4 signaling in the muscle cells.
- Catalyze proteins which release 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)

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)

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.


Why is this important?

- May unmask undiagnosed 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.


Why is this important?

- 40-56% of all inpatient consults to endocrinology are for new or worsening diabetes due to steroids. $SS$
- 16% 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, ABO, Ethnicity, Pre-DM, previous hyperglycemia with steroids

References:

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

References:

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 elevated.
  - IV hydrocortisone: 50% decrease in insulin sensitivity.
  - Oral prednisone 30mg/day x 7 days, 60% reduction in insulin sensitivity.


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.


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.

Treatment - Oral Medications

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


- 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)


- 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).
    - Give in am with steroid dose
    - 0.1u/kg-0.4u/kg
    - Closely mimic prednisone duration of action.
  - If long-acting GC, Lantus is preferred

<table>
<thead>
<tr>
<th>Prednisone Change (mg)</th>
<th>Insulin Change (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>30</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- Preferred Insulin for Steroid Induced Hyperglycemia

- 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 ½ the percentage in steroid change.
      - For example, if a steroid is increased or decreased by 50%, an increase or decrease of insulin by 25%
    - If pre-existing DM
      - Consider adding weight-based once daily NPH to usual regimen

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: 1:30, 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


Special cases

- Inpatient
  - Goal 140-180
  - Tight control reduces hospital related complications
  - Use dosing for steroids like outpatient
  - If BG > 180, insulin drip
  - SWMC: inpatient diabetes service, Caret count correction
  - Clear DC plan if new regimens or tapering steroids
    - If steroid hyperglycemia expected with no previous diagnosis, ordered screening IBGUTT in wards post discharge
  - Diabetes education for SWMC

- Long term steroids
  - Transplant
    - Can use combination of oral medications or insulin regimens.
    - If renal failure, insulin is recommended
    - Metformin + steroids has a multiplicative effect on blood sugars.
    - Need plan for adjusting at home
  - COPD, Rheum
    - Interim insulin tapering superimposed on daily administration

Special cases

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.


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 4%.
- Potency and duration increase risk
- Application to open, irritated, or large surface of skin a risk

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