ECHO Diabetes

Case Discussion

January 11, 2024

Clinical Questions

- Does shift work affect blood sugars/impact blood sugars?
  - If so, ideas to manage blood sugars in this population.
- Ideas on how to adjust medications after steroid bursts or cortisone injections.
- Other medication options if patient does not tolerate semaglutide/gastric emptying gets worse.

Very complex management challenges – challenging for endocrinologist…..

Shift Work & Diabetes

- Especially overnight work and/or varying shifts (~16% of workers):
  - Associated with an Increased risk of Metabolic Syndrome & Type 2 Diabetes - ~37% increased risk of T2D
  - Associated with difficulty managing diabetes

- Disrupted diabetes management due to both
  - Disrupted Circadian Rhythm / body clocks (tied to daylight & darkness)
    - cortisol, melatonin, insulin, etc.
    - Insulin resistance, reduced metabolic rate / altered sleep quality, satiety & hunger
  - Disrupted Lifestyle
    - Sleep cycles, timing, duration, quality - increased hyper and hypoglycemia
    - Food options (vending machines, snacking) – altered hunger, satiety
    - Activity - often less (unless job requires increased activity – more hypoglycemia)

Endocrine Society (2017 Annual Meeting)

Diabetes control is more difficult for night shift workers

- Study shows that people with type 2 diabetes have poorer control over their blood glucose levels when they work the night shift **- *independent of what workers ate or any sleep problems they had***.*[not just lifestyle]*
- Night shift workers
  - had an **average A1C of 8.2%**, significantly higher than the 7.6% A1C for daytime workers
  - **reported shorter sleep duration, higher daily intake of calories and higher BMI**
- *Even after the researchers* ***adjusted their statistical analyses for factors that could affect glucose metabolism, including sleep duration, dietary intake and BMI, the significant association between shift work and glycemic control remained.***
- PWD who work at night "should pay special attention to managing their disease through **healthy eating, regular exercise and optimal use of medications** prescribed by their physician,"
- Also, a need to **test interventions** that may improve glycemic control in this patient group, such as ***attempting to reduce the circadian misalignment*** (disruption in the sleep-wake cycle).

Impact beyond shift work: Recent studies on light & dark exposure

- Even a low level of *light at night* may disrupt blood sugar levels
  - TV or other lights left on
  - Streetlights

- "Alignment Between 24-h Light-Dark and Activity-Rest Rhythms Is Associated With Diabetes and Glucose Metabolism in a Nationally Representative Sample of American Adults" Diabetes Care 2023
  - Higher BGs when more out of alignment with natural light

Lifestyle Tips for Shift Workers – from the CDC

Eating Habits

- **Try to eat breakfast, lunch, and dinner at your normal times** as much as possible, even if you're working a late night or overnight shift. **Avoid large meals in the middle of the night** to reduce the chance of a spike in your blood sugar. [and can disrupt sleep]
- Grabbing convenience foods or other less healthy options can be tempting when working overnight. **Planning and prepping your meals and snacks in advance** is a great way to set yourself up for success and have healthy options any time of day. You ***won't have to rely on vending machines and other less healthy convenience foods.***

Sleep Schedule

- Try keeping track of your sleep to help you understand your patterns and how many hours you're getting. Take **short naps** when you're not working ***if you're not getting enough hours of sleep***.
- Some shift workers have trouble falling asleep or staying asleep. You can set up your sleeping area so it's dark and free from distractions. **Blackout curtains and sound machines** can create a comfortable environment to help you catch up on sleep after a late-night shift.
  - [Night shift workers might also consider **bright light therapy]** – the Sleep Foundation
- *Avoid caffeine toward the end of your shift*, so you'll be able to fall asleep and stay asleep.

Physical Activity

- If you're unable to be active on workdays, focus on being active on your days off.
  - Some people find that physical activity helps them sleep, while others find that it keeps them awake if done close to bedtime. Pay attention to how physical activity affects you as you plan your activity schedule.

Lifestyle Tips for Shift Workers – from the CDC

Blood Sugar Monitoring

- For people who work the day-shift, blood sugar taken first thing in the morning will be a fasting measurement (8 or more hours since last meal) - **FBS *not* first thing in AM** if you work overnight
  - [HCP needs to orient to glucose reports – mark when sleep, meals, work, etc.] [work vs non-work-days]
- Make sure you're **checking your blood sugar consistently** to help you stay within your target range throughout your shift, especially if your job requires you to move around.

Medication Schedule

- **Taking all medicines consistently at the same time every day*** is crucial to diabetes self-management. Working irregular hours may make it hard to stick to your schedule, so plan ahead.
  - **Having a plan** is especially important if you need to take **medicines with food during a shift**.
- Consider **setting a reminder,** like an alarm on your phone, so you don't miss any doses.
- Talk with your **doctor about your medication schedule if you need help figuring out a realistic plan** that will work for you.
  - *[problems with NPH, SU meds, etc. – favor Tresiba for basal insulin, once weekly GLP1 RA]

Stress and Fatigue

- Working overnight or rotating shifts can take a toll physically, emotionally, and socially. Some shift workers may feel added stress or fatigue from their unique work hours. It can be **more difficult to feel socially connected** if you work different hours from your family and friends.
  - Find time when you can for hobbies, self-care, and social time with loved ones to help manage your stress.

- Diabetes and Shift Work | CDC

Glucocorticoid (Corticosteroid) Therapy

- Impact on Diabetes
  - Hyperglycemia
  - Hypoglycemia as taper/ discontinue
  - Central adiposity/ muscle wasting
  - Dyslipidemia
  - Elevated BP
- Impact on the Hypothalamic - Pituitary - Adrenal (HPA) axis
  - HPA suppression
  - Secondary Adrenal Insufficiency (SAI)
  - Cushing's Syndrome (CS) (GC excess) – bone, infection/healing, skin, mood, eyes, GI, etc.

Glucocorticoid Induced Hyperglycemia

- The mechanisms by which corticosteroids cause hyperglycemia include both ***increased insulin resistance:***
  - increased hepatic gluconeogenesis
  - increases in central and visceral adiposity
  - greater lipolysis in peripheral fat stores and
  - a rise in glucagon
  - impaired endogenous GLP1 activity
- and ***impairment of insulin synthesis***:
  - direct effects on Beta cells to inhibit insulin production and secretion
    - Inflammation & injury of Beta cells
  - a reduction in the incretin effect

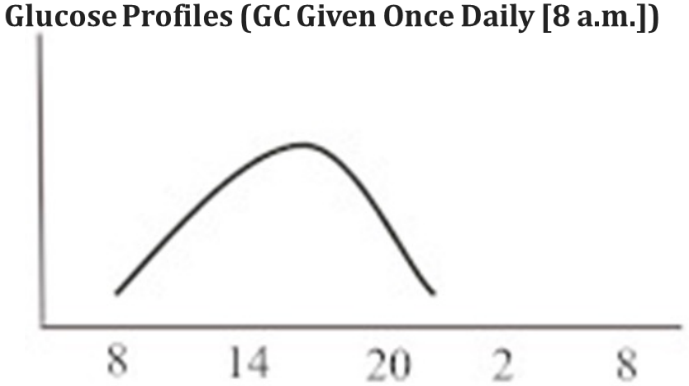
Glucocorticoid (GC) Therapy & Diabetes

- Glucocorticoids are the *“drug class with the highest risk of provoking the development of hyperglycemia and overt diabetes mellitus”*
- **Steroid Induced Hyperglycemia (SIHG)** is defined as *abnormally elevated blood glucose* associated with the use of GCs in patients *with or without pre-existing DM*
- Steroids may be administered by various regimes and in variable doses and may **cause hyperglycemia** when administered at **supraphysiological doses by any route** *(topical, oral, inhaled, intramuscular, intravenous, or intra-articular)* [**variable individual response to GCs]**
- The *glucose lowering agents* of choice should *match daily glucose profiles and the mechanism of action* should *fit to the corresponding GC agent*.

GCs in the outpatient population

- A single or short course of an oral GC (e.g., prednisolone) in the morning may be the *commonest mode* of administration.
  - In susceptible patients, this will often result in **a rise in blood glucose by late morning** that continues into the evening (**~4 to 8 hours following the administration of oral GCs**)
  - Overnight the blood glucose generally falls back, often to baseline levels the next morning.

  - *Fasting blood glucose* measurements can *underestimate* glucocorticoid-induced hyperglycemia and diabetes, particularly in intermediate-acting treatments that are administered in single morning doses.
    - Glucocorticoids cause predominantly *postprandial hyperglycemia*
    - ***Postprandial glycemia after lunch*** offers the greatest diagnostic sensitivity.

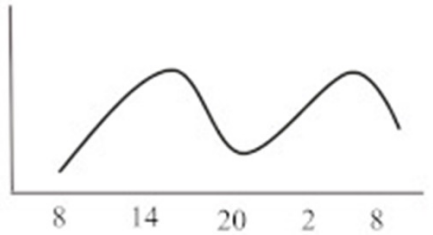


Insulin is usually the treatment of choice because of its efficacy and safety. Insulin provides:

- an immediate onset of action
- an unlimited hypoglycemic power
- can be easily titrated

Insulin therapies

- Morning administration of **basal human insulin (Humulin or Novolin N**) may closely fit the glucose excursion induced by a single dose of oral steroid in the morning.
  - E.g., 10 units of basal human (NPH) insulin with a daily dose increase of between 10% and 20%, titrated to the blood glucose level
    - dose increments of up to 40% have been shown to be required in some individuals
  - ADA – [with] "once-or twice-daily steroids, administration of **NPH is standard approach** (because NPH action peaks at 4-6h after administration it is best to give it concomitantly with steroids) – [NPH can be] administered *in addition to daily basal-bolus insulin or in addition to oral anti-diabetic medications*"



Estimation of the Initial Dose of Insulin in Glucocorticoid- Induced Hyperglycemia, According to the Type and Dose of Glucocorticoids

Prednisone dose, mg/day	Dexamethasone dose, mg/day	Insulin NPH, glargine/detemir dose, IU/kg/day
≥40	≥8	0.4
30	6	0.3
20	4	0.2
10	2	0.1

Another option – increase TDD of insulin

- *very little evidence available* – consider a *cautious* increase in total daily insulin dose (TDD) according to prednisolone (or prednisolone equivalent [PE]) dose:
  - PE of 20 mg → 10% increase in TDD
  - PE of 40 mg → 20% increase in TDD
  - PE of 60 mg → 30% increase in TDD

- *Basal analogue insulin* may be appropriate if hyperglycemia is present throughout the day and into the evening (especially for long-acting glucocorticoids such as dexamethasone & multidose or continuous glucocorticoid use)
  - Care should be taken to identify and **protect against nocturnal and early morning hypoglycemia** if insulin glargine, insulin detemir or insulin degludec are used in this context.

Newer Options

- **Incretin medications** *"should probably be the drug of choice because of their immediate onset of action, their predominant effect on postprandial glycemia, and their low risk of hypoglycemia related to glucose-dependent effects*". Endocrinol Metab (Seoul). 2017 Jun; 32(2): 180–189.
  - "With an inherently low predisposition to hypoglycemia and **quick onset of action**, they are potentially well suited to dealing with steroid-induced hyperglycemia." Morris D (2018) Diabetes & Primary Care 20: 183–7

- Case reports & variable results from studies of effectiveness of **SGLT2i meds**
  - "The mechanism of action of sodium–glucose cotransporter 2 (SGLT2) inhibitors (provided renal function allows) *suggests that they could be useful in dealing with hyperglycemia induced by steroids*, but firm evidence of their effectiveness is yet to be gathered" Morris D (2018) Diabetes & Primary Care 20: 183–7
  - "Dapagliflozin has shown to be **safe** in patients hospitalized for chronic obstructive pulmonary disease (COPD) developing SIHG but **did not improve glycaemic control or clinical outcomes**." Diabetes Obes Metab. 2018 May; 20(5): 1306–1310.
    - Some express concern about DKA with Beta-cell suppression by GC therapy

- Most suggest *continuing GLP1 RA & SGLT2i meds when start GCs*

Case Report Volume 8, Number 1, February 2018, pages 10-12

Steroid-Induced Hyperglycemia Successfully Treated With Once-Weekly Dulaglutide in an Old Patient With Type 2 Diabetes

Hidetaka Hamasakia et al

- Glucocorticoids induce hyperglycemia in case of pancreatic α- and β-cell dysfunction. Glucagon-like peptide-1 receptor agonists (***GLP-1RA) may prevent steroid-induced hyperglycemia by improving hyperglucagonemia and insulin secretion***.
- An 85-year-old man was treated with oral prednisolone for chronic hypersensitivity pneumonitis, and his glycemic control deteriorated after the initiation of steroid therapy.
- After the administration of **dulaglutide injection,** his **glycemic control was improved**, and we **could discontinue insulin therapy. Both fasting and postprandial plasma glucagon levels were significantly suppressed by a GLP-1RA, dulaglutide.**
- GLP-1RAs therapy may be a useful strategy for the treatment of steroid-induced hyperglycemia.

BMC Endocr Disord. 2020; 20: 58.

Dulaglutide improves glucocorticoid-induced hyperglycemia in *inpatient* care and reduces dose and injection frequency of insulin

- **Results:** Six-point blood glucose levels at pretreatment and discharge were comparable between the two groups. However, **daily injection frequency of injectable drugs and insulin dose were significantly lower in the Dula group than that in the non-Dula group.**
- **Conclusion: These findings suggest that Dula could provide glycemic control while reducing the insulin dose and injection frequency in inpatients with GC-induced hyperglycemia.**
  - The occurrence of adverse events such as gastrointestinal symptoms and hypoglycemia did not increase in the Dula-treated patients compared to those not treated, suggesting its safety.

“local-and-systemic-side-effects-of-corticosteroid-injections-for-musculoskeletal-indications”

- In patients with diabetes **Intra-articular corticosteroid injections** can ***significantly affect serum glucose levels*.**
- **Serum glucose levels typically peak 1-3 days after injection,** and a **postinjection level as high as 500 mg/dl has been reported.**
- A case report describes *hyperglycemic coma* occurring after a single 80-mg triamcinolone epidural steroid injection in a patient with *noninsulin-dependent diabetes* .

Impact of inhaled and intranasal corticosteroids on glucose metabolism and diabetes mellitus: A mini review.

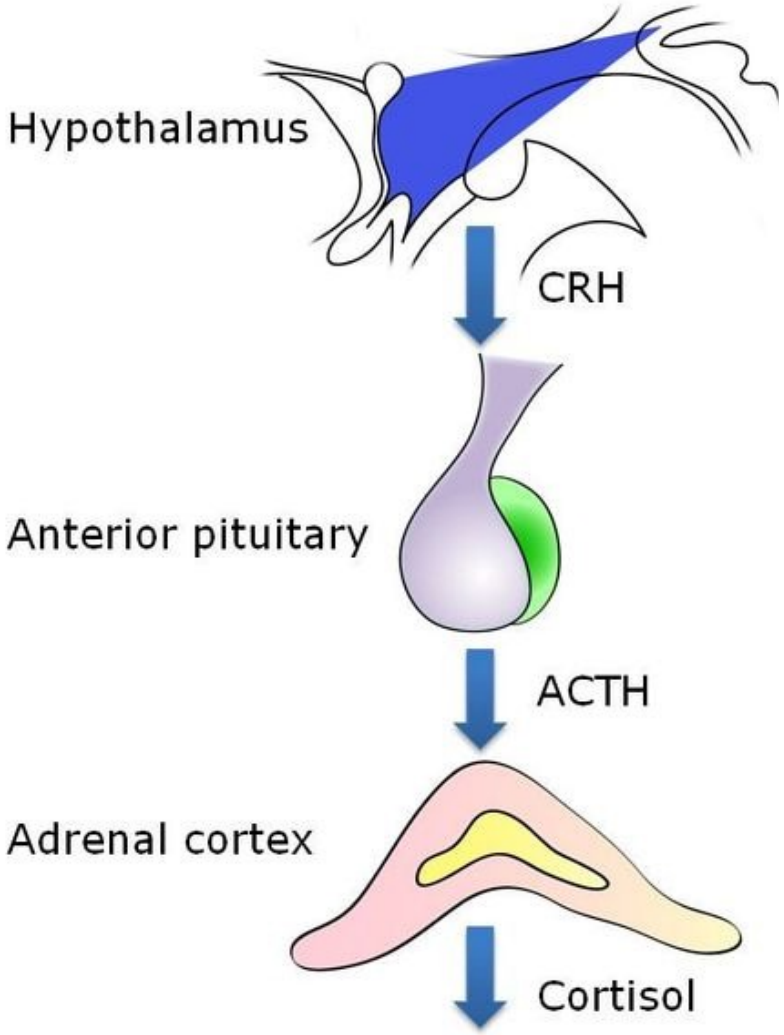
World J Diabetes 2023; 14(8): 1202-1211 [PMID: 37664474 DOI: 10.4239/wjd.v14.i8.1202]

- Multiple large observational studies suggest that ***high dose ICS*** is associated with increased incident DM and ***worsened DM control***
  - ***Increase in average BG by 86 mg/dl, higher A1c, increased need for insulin***
  - only two studies of INS (intranasal steroids) and DM, with both studies *demonstrating a short-term association of INS use with hyperglycemia.*
- ***High doses of ICS/INS should be avoided when possible***.
  - The following strategies for **ICS/INS dose minimization** can be considered:
    - Use of non-pharmacological measures (trigger avoidance, smoking cessation, vaccination to avoid infection)
    - control of comorbid conditions
    - use of non-ICS-containing medications
    - intermittent rather than regular ICS dosing
    - appropriate de-escalation of high ICS doses

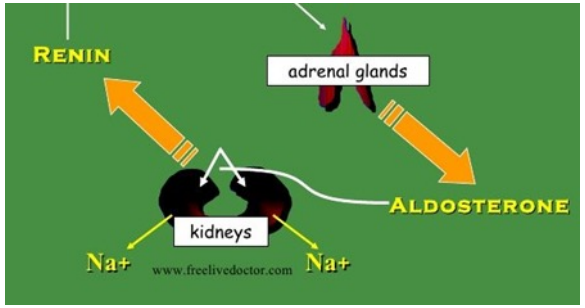
For our patient

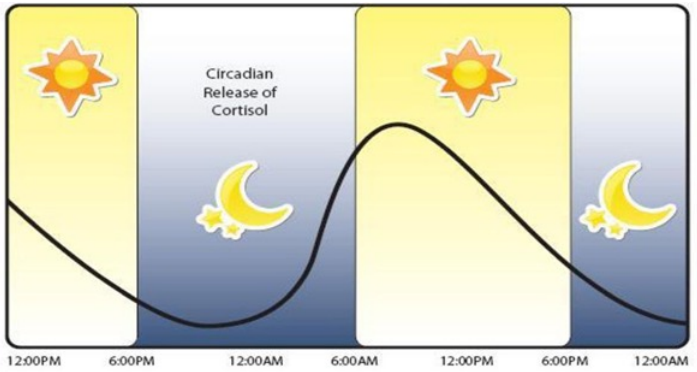
- Hyperglycemia could be aggravated by
  - Prednisone burst therapy – use NPH add-on therapy
  - Intraarticular GC injections
    - Check for BG increase 1-3 days following IA injection – can have prolonged effect
  - High dose fluticasone inhaled (+/- intranasal) therapy
    - Potential continuous effect depending on amount of systemic absorption
- GLP1 RA therapy might help reduce impact of ICS and maybe IAGC
  - Also increased basal insulin dose
- Continue metformin, SGLT2i (empagliflozin) & (?) glipizide
  - however, glipizide more unpredictable due to shift work – consider dc glipizide & increase long-acting basal insulin (this also simplifies a bit)
- Current basal insulin 14u/day = 0.146 u/kg – awaiting response to semaglutide 0.25 mcg dose –
  - could increase basal insulin dose during slow titration of GLP1 RA – then taper
  - improved glycemia might improve gastric motility

The HPA axis

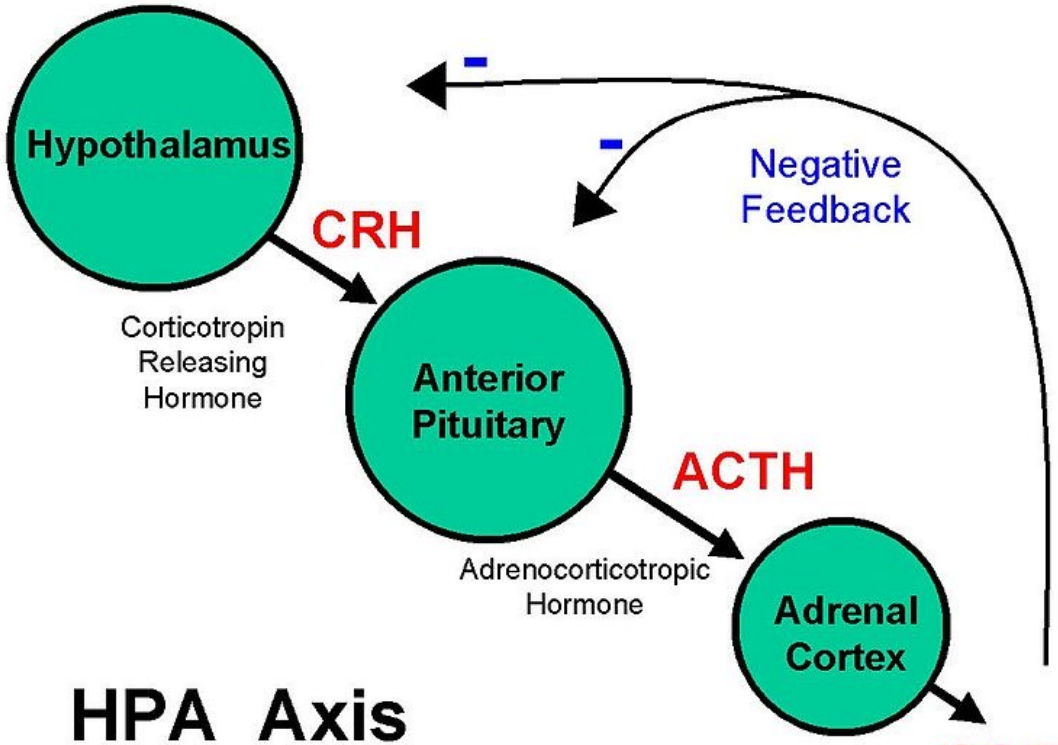


STRESS – stimulates
Increase in HPA activity
Independent of
Circadian rhythm

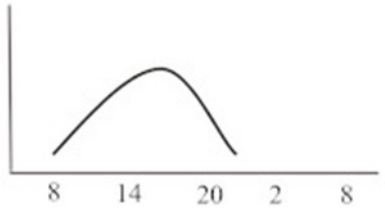


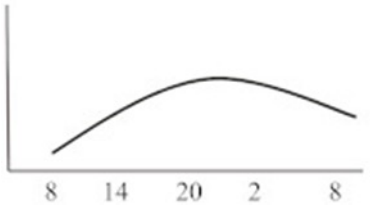


GC receptors, activation/inactivation processes
Individual (genetic) variation



HPA Axis





DHEA-S

Longer half-life
Low if suppressed
ACTH /cortex

CORT **Synthetic GC**

Suppressed CRH & ACTH
Adrenal cortical atrophy
Secondary Adrenal Insufficiency (SAI)
Unable to respond to
demands of stress (surgery,
Infection, injury, etc.)

Secondary Adrenal Insufficiency (SAI)

- Is the **most common form of adrenal insufficiency**, and it is commonly seen with ***exogenous steroid administration*** *and their subsequent withdrawal or superimposed physiologic stress*
- Is considered a *"master of disguise"* condition - Often *has non-specific symptoms* that can be attributed to the condition being treated and/or other medications – these include:
  - fatigue, weakness, malaise, *nausea*, dizziness, headache, *abdominal pain*, *musculoskeletal pain, myalgia, arthralgia*, poor weight gain and *hypoglycemia*
  - *hyponatremia* may be present secondary to inappropriate arginine vasopressin release [cortisol/GCs suppress AVP, if low on cortisol, excess AVP release]
    - hyperkalemia and hyperpigmentation - features that are associated with primary AI are *not* present with SAI [PAI – low aldosterone & cortisol, high ACTH]
- Can go unrecognized until a *physiological stress* (surgery, trauma, inter-current illness) precipitates an ***acute crisis:***
  - Symptoms of this acute crisis vary from hypotension, vomiting, hypovolemic shock, unexplained hypoglycemia, seizures, decreased level of consciousness, coma and even *death*

SAI after Intraarticular GC injections

- The incidence of adrenal insufficiency is **higher with intra-articular corticosteroid injections** [**52.2%** (95% CI, 40.5–63.6)] than with **oral corticosteroids** [**48.7%** (95% CI, 36.9–60.6)].
- The degree of adrenal suppression is directly proportional to the **steroid dose injected** (*increased systemic absorption*)
  - Also, more systemic absorption from *inflamed joints* & the same dose divided among *multiple joints* [or multiple joints injected at full dose]
- Although HPA suppression with IAGCs ***typically lasts for weeks***, the ***duration could be prolonged (****screening urine as far along as* ***nine months after the most recent steroid injection,*** *has detected the* ***presence of synthetic glucocorticoids*** *with the potential for* ***a long systemic duration of action even after a single depot injection*** → chronic ACTH suppression resulting in **atrophy of the zona fasciculata** with a ***decrease production of cortisol*** .
- Given some *uncertainty exists about the duration of suppression*, ***education*** regarding symptoms and management of adrenal insufficiency should be given to patients who are vulnerable to adrenal crises in ***times of stress or illness while the HPA is suppressed***.
  - https://www.hormones-australia.org.au/wp-content/uploads/2020/11/Sick-Day-Management-Plan-FINAL-fillable.pdf

For Inhaled GCs (ICS) - Fluticasone has a greater risk of systemic absorption & Adrenal Suppression (AS)

- A systemic review concluded that **fluticasone** exhibited a greater dose dependent effect on adrenal suppression compared with other ICS.
  - This is likely due to pharmacokinetic properties of fluticasone including its long half-life and high lipophilicity resulting in ***greater systemic retention***
- In the case of **COPD patients** who are on ICS, ***a total daily dose of ICS ≥1000 mcg of fluticasone propionate*** appears to be associated with higher risk of AS.
  - Treating physicians should keep an open mind to screen any COPD patients who are **on more than 400 mcg/day of fluticasone propionate** or its equivalent dosage.
  - the risk of AS appears to be greater in ***COPD patients*** who are exposed to the highest dose of ICS than those with asthma.
- Any patient who is on inhaled corticosteroids should be screened for AS if they have any signs or symptoms of AS regardless of the dosage.

Use of Oral GC (OCS) + ICS increases risk of SAI

- **OCSs are risk factors for adrenal insufficiency**
  - patients prescribed high doses of ICSs are likely to have ***more severe respiratory disease*** and to more commonly receive OCSs
  - **the risk was significantly greater among those exposed to a high dose of ICSs** (OR 1.84, 95% CI 1.16–2.90).
- For OCSs, the multivariable models showed that **each additional prescription of OCS** was associated with a **65% increased risk of adrenal insufficiency** (OR 1.65, 95% 1.52–1.82).
  - Along this line, when the independent effect of cumulative doses of OCSs in the prior year was studied**, each additional 1000 mg of OCS** was associated with a **5.2-fold time increase in risk of adrenal insufficiency** (OR 5.2, 95% CI 3.76–7.19).
- When we stratified the analysis by the presence of probable *COPD or asthma*, the **risk was significantly greater among patients with COPD exposed to the current highest daily dose of ICSs** (adjusted OR 2.13, 95% CI 1.11–2.07) *than those with asthma* (adjusted OR 0.73, 95% CI 0.25–2.07).
- Physicians caring for patients with respiratory disease taking ICSs, especially at daily doses equivalent to fluticasone ≥1000 μg per day, should be sensitive to the signs and symptoms of adrenal insufficiency in their patients.

Can be very confusing -

- Low Cortisol and low ACTH after an IA injection (& ICS)
  - Is there still synthetic GC "on board" (providing "GC coverage") (may not be enough for stress of surgery, etc.) *Or*
  - Is synthetic GC gone & patient has SAI & is unable to make endogenous cortisol due to low ACTH and adrenal cortical atrophy
    - Measure synthetic GC levels
  - AM cortisol level & Cosyntropin stim is going to be low in both situations
    - If AM cortisol >15 – good/adequate endogenous adrenal cortical function
    - AM cortisol 5-15 – "recovering" – coverage for symptoms of SAI &/or for stress (surgery, pneumonia, etc.)
    - AM cortisol <5 – either suppressed by remaining synthetic GC or SAI – depending on symptoms –
      - replacement doses if sxs of SAI [& no synthetic GC in urine or blood] - taper
      - hydrocortisone stress doses regardless if goes to ICU or surgery etc.
    - **Shift workers – AM cortisol level not accurate / reliable – disrupted diurnal rhythm -** consider measuring DHEA-S level – if suppressed (for age) – likely suppressed HPA axis

Stress Doses for Surgery or Critical Illness

- The consideration of the dose for supplemental stress doses depends on the basic understanding of endogenous cortisol production.
  - Normal cortisol production on average is 15–20 mg/day, which can increase to
    - 50 mg/day in response to minor procedures
    - 75–150 mg/day for moderate/major surgery
  - Thus, a dose of 1**00 mg/day of exogenous cortisol (hydrocortisone)** or glucocorticoid should be sufficient to sustain hemodynamics
- A rational regimen for **steroid supplementation in the perioperative** period is
  - administration of cortisol 25 mg iv, at the induction of anesthesia
  - followed by continuous infusion of cortisol 100 mg during the following 24 h
- In those instances, such as **burns or sepsis** which exaggerate the need for exogenous steroid supplementation
  - continuous infusion of cortisol, 100 mg every 12 h is sufficient.

For our patient

- Secondary Adrenal Insufficiency risk
  - **High dose Inhaled GC (fluticasone) + OCS**
    - Risk if missed doses or if ICS stopped, reduced or switched to another agent
      - Might need **transient replacement doses of HC**, tapered over time
    - Risk of inadequate stress response if illness, surgery, etc. - **stress coverage**
  - **Intraarticular GC injections**
    - Depends on dose, number of joints injected, frequency, individual genetic factors
  - Because of **shift work**/disrupted circadian rhythm - **AM Cortisol *not* reliable**
    - Cosyntropin test is not time dependent – more complicated but can be easily done
    - DHEA-S has long half-life (~ one day) – surrogate marker
      - If DHEA-S well into normal range for age – HPA suppression unlikely
      - If DHEA-S suppressed – assume at risk for SAI (especially if stress)

Gastroparesis – reduced gastric motility

- Diabetes – autonomic neuropathy (Vagal nerve damage)
  - Physiologic - hyperglycemia
- Collagen- Vascular disorders
  - Lupus, Scleroderma, etc.
- Surgery (vagal nerve damage)
- Viral infections
- Neurologic conditions
- Hypothyroidism
- Medications
  - Nicotine (also GERD, etc.)
  - Marijuana (hyperemesis syndrome)
  - ~ Glucocorticoids (also increased acid sxs, GERD, etc.)
  - ~ Metformin (maybe gastric delay, other GI sxs)

Glycemic values impact rate of stomach emptying (physiologic):

- **Hyperglycemia *delays*** stomach emptying*, nutrients are propelled more slowly for absorption at the intestinal level
- **Hypoglycemia *accelerates*** gastric emptying and increases the nutrient absorption speed, thus allowing for a prompter correction of glycemic levels

*If gastric emptying study done while patient hyperglycemic – will show physiologic delay

Medications that Slow Gastric Emptying

- I. Gastrointestinal Agents
  - Aluminum hydroxide Antacids
  - **H2 Receptor Antagonists** (e.g. Ranitidine)
  - **Proton Pump Inhibitors** (e.g. Omeprazole)
  - Sucralfate
  - Ondansetron (Zofran)
  - Phenothiazines (e.g. Chlorpromazine, Promethazine)
- II. Muscarinic cholinergic receptor antagonists.
  - Atropine (Atropine)
  - Belladonna alkaloids.
  - Benztropine mesylate (Cogentin)
  - Clidinium (in Librax).
  - Cyclopentolate (Cyclogyl)
  - Darifenacin (Enablex)
  - **Dicyclomine (Bentyl).**
  - Fesoterodine (Toviaz)

  [Clinidium (In Librax) and Dicyclomine (Bentyl) are two commonly used medications for Irritable Bowel syndrome (IBS). they may increase bloating, constipation, and ***delayed gastric emptying***.]
- III. Cardiovascular Medications
  - Beta-Adrenergic Receptor Agonists
  - Calcium Channel Blockers
- IV. Diabetes Medications
  - Incretin Mimetics or **GLP-1 Agonists**
  - Pramlintide (Symlin)
- II. Anticholinergic Medications
  - Diphenhydramine (Benadryl)
  - Tricyclic Antidepressants
  - Oxybutynin
- V. Miscellaneous
  - Alcohol
  - **Opioid Analgesics**
  - Interferon alfa
  - Levodopa
  - Cyclosporine (Sandimmune)
  - Lithium

GLP1 RA medications

- Most common side effects are GI (nausea, vomiting, diarrhea)
  - Initiate therapy with the lowest dose & titrate *slowly* to avoid GI side effects
    - Okay to back down on dose/remain on lower dose if tolerated (nausea is dose-dependent)
    - Most GI side effects diminish over time
    - Long-acting GLP-1 RAs linked to less nausea and vomiting but more diarrhea than the short-acting GLP-1 drugs
    - Down titrate doses of insulin / sulfonylureas to avoid hypoglycemia
    - Counsel patients to stop medication with severe nausea, vomiting and diarrhea to avoid dehydration & potential Acute Kidney Injury (AKI)
  - If does ***not tolerate one GLP-1 agonist, another might be tried.***
  - Use of ***metformin*** is associated with more nausea and vomiting in those taking GLP-1 receptor agonists – consider reducing the dose of metformin
  - Counsel patients on how to **adjust diet** after initiation

- If has *incomplete* gastroparesis – GLP1 RA will worsen/ complete – not worsen

Counselling on nausea & diet (foods & volume)

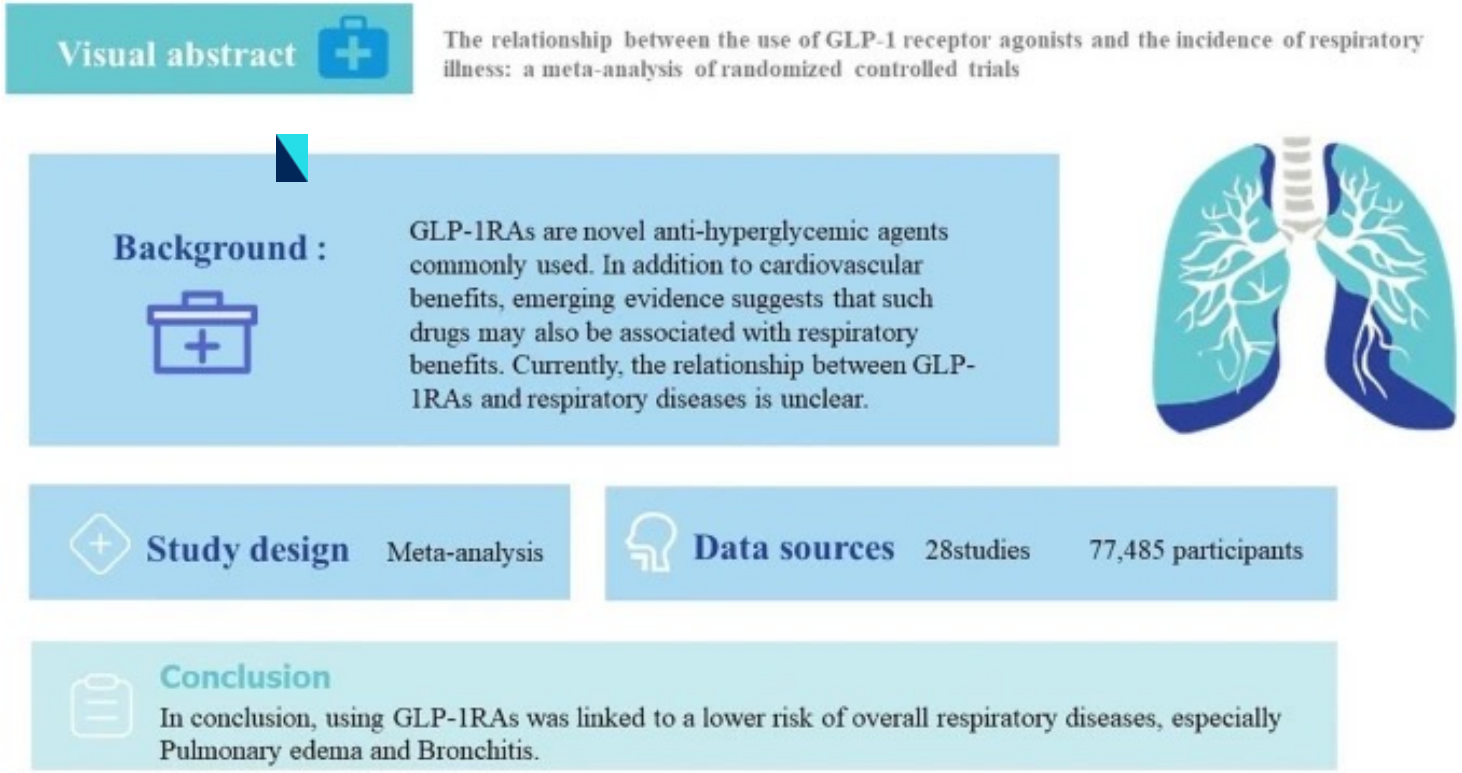
- There appears to be an association between nausea during GLP-1 RA therapy and both the ***fat*** content and ***size of meals***;
  - limiting or avoiding greasy, fatty or fried foods and eating smaller portions at mealtimes may help to prevent the feeling of nausea.
  - also limit soda (fizzy beverages) and foods such as onions, peppers (select more bland foods)
  - patients should be encouraged to eat slowly while undistracted and to pay careful attention to the amount and the pace at which that they eat.
    - Patients might be told **to eat less and to eat slower** than they ever have before**.**
    - **STOP EATING when feel full (satiety).**
- Patients may obtain some relief from nausea by consuming ginger (e.g., fresh ginger, ginger tea), soda crackers, or rice crackers. Slowly sipping hot water or sucking on sugar-free mints also may ease nausea.

Suggestions for reducing symptoms of Gastroparesis

- Gastroparesis can cause *erratic changes in blood sugar levels*.
  - These variations in blood sugar make diabetes worse.
  - In turn, *poor control of blood sugar levels* makes *gastroparesis worse*.
- Reduce symptoms with the following actions:
  - Keep ***blood sugar levels as close to their target range*** as possible.
  - Eat frequent, small meals that are low in fat and fiber.
    - **Fat, fiber, and large meals can delay stomach emptying** and make symptoms worse.

For our patient:

- Consider reducing/deprescribing some of the medications contributing to delayed gastric motility
- Attention to diet to reduce symptoms
- Continue to work at reducing hyperglycemia
- Tobacco cessation (multiple impacts)
- May not be a candidate for GLP1 RA due to GI issues but potential for otherwise benefiting from GLP1 RA effects
  - If GI symptoms are mild
    - Attention to diet
    - Consider reducing dose of metformin
    - Slow titration
    - Try another GLP1 RA (? Tirzepatide)
  - If GI symptoms severe - dc



A population-based cohort study (involving 56,243 participants) discovered that **GLP-1 receptor agonists reduce the incidence of severe exacerbation of COPD**. Compared with sulfonylureas, GLP-1 receptor agonists were associated with a ***30% decreased risk of severe exacerbation*** (3.5 v 5.0 events per 100-person years).

Many GLP1 receptors in lung tissue

- May reduce airway hyperresponsiveness
- Mediate tracheal relaxation
- Reduce Inflammation

The relationship between the use of GLP-1 **receptor agonists and t…**
dmsjournal.biomedcentral.com/articles/10.1186/s13098-023-01118-6

Summary of Considerations

- Consider dc glipizide & increase long-acting basal insulin (glargine or degludec)
  - Less unpredictable with shift changes + simplification of meds
  - Continue empagliflozin & metformin
- Many potential benefits to patient from GLP1 RA therapy if she can tolerate
  - Slow-titration, attention to diet (especially fat & size), optimize basal insulin
  - Consider reducing metformin – reduce/deprescribe other meds that reduce gastric motility
  - If unable to tolerate – optimize basal insulin & step-wise mealtime insulin
- Add on NPH insulin for burst prednisone (OCS) therapy
- Assess glycemic response to IACS in days following IA injection - ? Spike on CGM
  - may need short term coverage (correction insulin vs increased basal dose)
  - Please feel free to reach out to me for assistance
- Patient at risk for adrenal suppression & adrenal crisis if surgery, illness, injury, etc.
  - Educate patient/ med-alert card & bracelet/ ? Measure DHEA-S level to confirm
  - Consider modification of steroid therapy – may need temporary GC replacement
- Continue to encourage/provide support for tobacco cessation (not scare tactics)

References & Resources

Cortisol Replacement Therapy

- Replacement doses: 6-10 mg/M2 in divided doses
  - e.g., 10 mg first thing in AM & 5 mg ~ 4 PM [>4 hours before bedtime]
  - remember different sensitivities – many people end up “over-replaced”
  - Case patient ~ 2 M2 – could start with 10 mg ***upon awakening*** (vs “morning”) & 5 mg ***at least 4 h before bedtime***
- Stress doses in cases of illness with fever:
  - For fever up to 103 degrees, double-up on regular steroid dose.
    - E.g., 20 mg upon awakening & 10 mg at second dose
  - For fever over 103 degrees, use triple dosing.
  - If the fever is less than 103 but the person is lethargic, use triple doses.
  - Alert your doctor
- GI illness – solu-Cortef rescue pen or vial – home injection kit

References

- London J Prim Care (Abingdon). 2015; 7(5): 103–106. Published online 2015 Sep 28. doi: 10.1080/17571472.2015.1082344; PMCID: PMC4606815 PMID: 26550039 *Steroid-induced hyperglycaemia in primary care* Edouard Mills and Senan Devendra
- Joint British Diabetes Societies guidelines https://www.diabetes.org.uk/resources-s3/2017-09/JBDS%20management%20of%20hyperglycaemia%20and%20steriod%20therapy_0.pdf
- Endocrinol Metab (Seoul). 2017 Jun; 32(2): 180–189.Published online 2017 May 29. doi: 10.3803/EnM.2017.32.2.180 PMCID: PMC5503862 PMID: 28555464 *Glucocorticoid-Induced Diabetes Mellitus: An Important but Overlooked Problem* Sunghwan Suh and Mi Kyoung Park
- Standard of Medical Care in Diabetes 2021, Diabetes Care Vol 44, supplement 1, s216
- DynaMed Plus
- Endocr Pract 2016 Feb;22(2):180-9. doi: 10.4158/EP15818.OR. Epub 2015 Oct 22. *HOSPITAL INSULIN PROTOCOL AIMS FOR GLUCOSE CONTROL IN GLUCOCORTICOID-INDUCED HYPERGLYCEMIA* Bethany Grommesh, Mamie J Lausch, Anna J Vannelli, Deborah M Mullen, Rich M Bergenstal, Sara A Richter, Lisa H Fish PMID: 26492541 DOI: 10.4158/EP15818.OR
- Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Minambres I, Gomez-Huelgas R. *Glucocorticoid-induced hyperglycemia*. J Diabetes. 2014;6:9–20.

- J Clin Med. 2021 May; 10(10): 2154. A Practical Guide for the Management of Steroid Induced Hyperglycaemia in the Hospital Felix Aberer, Daniel A. Hochfellner, Harald Sourij, and Julia K. Mader https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8157052/

J Clin Med. 2021 May; 10(10): 2154.

A Practical Guide for the Management of Steroid Induced Hyperglycaemia in the Hospital

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8157052/

Felix Aberer, Daniel A. Hochfellner, Harald Sourij, and Julia K. Mader

- In a pragmatic approach, insulin dose can be adjusted by half the percentage of the GC dose change.
  - For example, **when GCs are increased or tapered by 50%,** insulin dose is suggested to be **increased or reduced by 25%,** respectively.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7203793/

- BMC Endocr Disord. 2020; 20: 58.
- Published online 2020 May 7. doi: 10.1186/s12902-020-0542-5
- PMCID: PMC7203793
- PMID: 32381085
- Dulaglutide improves glucocorticoid-induced hyperglycemia in inpatient care and reduces dose and injection frequency of insulin
- Hiroyuki Uchinuma,# Masashi Ichijo,# Noriyuki Harima, and Kyoichiro Tsuchiyacorresponding author

- https://diabetes.medicinematters.com/hyperglycemia/medications/corticosteroid-treatment-diabetes-consequences/20006642

- BMC Endocr Disord. 2020; 20: 58.
  Dulaglutide improves glucocorticoid-induced hyperglycemia in inpatient care and reduces dose and injection frequency of insulin https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7203793/

- https://www.redsonoguide.com/wp-content/uploads/2019/10/Intra-articular-glucocorticoid-injections-and-their-effect-on-hypothalamicpituitaryadrenal-HPA-axis-function_.pdf

- https://www.kch.nhs.uk/wp-content/uploads/2023/01/pl-1098.1-adrenal-insufficiency-%E2%80%93-how-to-stay-safe-on-steroids.pdf

- https://www.parentprojectmd.org/care/care-guidelines/by-area/steroids/risk-for-adrenal-crisis/

- https://www.hormones-australia.org.au/wp-content/uploads/2020/11/Sick-Day-Management-Plan-FINAL-fillable.pdf

Omeprazole causes delay in gastric emptying of digestible meals

L Benini 1, G Castellani, E Bardelli, C Sembenini, M T Brentegani, S Caliari, I Vantini

Abstract

- We have studied gastric emptying of a solid, realistic meal (800 cal, 15% protein, 45% fat, 40% carbohydrate) in 21 healthy subjects twice, with and without a four-day pretreatment with 40 mg omeprazole. The last dose of the drug was taken 24 hr before the test, to avoid hypothetical nonsecretory side effects of the drug . Gastric emptying was measured by ultrasound of antral diameters. The results show that basal and maximal postprandial antral cross-sectional areas were the same during the two tests. A greater residual distention of the antrum was present throughout the study after the omeprazole treatment, the difference being significant at time 120 and 240.
- Omeprazole induced a highly significant delay in gastric emptying [control 199.6 (12.6) vs omeprazole 230.9 (12.7) min, mean (1 SEM); $P<0.003$]. The delay was not due to a prolonged lag phase, but rather to an effect on the slope of the emptying curve.
- This study shows that in normal subjects **omeprazole delays gastric emptying of a digestible solid meal.**

Shift Work, Night Shifts and Diabetes

- Shift work can affect people with type 1 diabetes and type 2 diabetes in a number of ways. Factors such as the times you eat, stress and changes to your body clock can all be significant.

- Shift work can alter the body's circadian rhythms, internal body clocks that respond to natural daylight and darkness. Consequently, blood sugar levels can be affected: altering sleep times can lead to greater problems with hyperglycemia (too high blood sugar) and hypoglycemia (low blood sugar).
- If you are susceptible to hypoglycemia, you should keep fast-acting glucose on you at all times and be aware of how to manage hypos at work

- Changes in sleep or shift times can also affect when you feel hungry during the day. This can make it more challenging to eat healthily and avoid snacking on the wrong foods.

Case Rep Endocrinol. 2022; 2022: 4798466.

Development and Resolution of Secondary Adrenal Insufficiency after an Intra-Articular Steroid Injection

Jia Wei Tan and Sachin K. Majumdar

- SAI is the most common form of adrenal insufficiency, and it is commonly seen with exogenous steroid administration and their subsequent withdrawal [5]. Cortisol exhibits negative feedback on the release of corticotropin-releasing hormone (CRH), ACTH, and ADH [6]. Exogenous corticosteroids can result in suppression of the HPA axis that may last after the offending agent is discontinued, and since cortisol levels may remain low, the usual suppressive effect on ADH may also be absent. Therefore, ADH levels can be elevated in adrenal insufficiency resulting in diminished free water excretion and predisposition to hyponatremia, particularly when water is consumed in excess, as occurred with our patient. Cortisol secretion is diurnal, and a low morning cortisol level is indicative of adrenal insufficiency. However, levels at other times lack diagnostic utility and might be difficult to interpret on their own. An ACTH level would differentiate between primary and secondary adrenal insufficiency [7]. A low-normal ACTH points towards SAI and warrants an MRI of the hypothalamic-pituitary area to rule out hypothalamic or pituitary lesions such as craniopharyngioma, metastasis, and pituitary adenoma [8]. DHEA-S, which is an ACTH-responsive hormone, has a long half-life (about 20 h) and less diurnal variation than cortisol [9] and can serve as an adjunct measure in the diagnosis of adrenal insufficiency. A middle to upper range of normal reference value of DHEA-S indicates that the underlying pathology is less likely due to SAI.

W Intra-articular glucocorticoid injections and their effect on hypothalamic–pituitary–adrenal (HPA)-axis function
Philip C. Johnston • M. Cecilia Lansang Endocrine (2015) 48:410–416
DOI 10.1007/s12020-014-0409-5

- IAGC can result in a sharp decline in cortisol to low or undetectable levels within the first days after administration. HPA-axis suppression can typically last up to four weeks after a single injection, although recovery of HPAaxis to baseline can take longer depending on the dose and frequency of injections. Considering the widespread use of intra-articular steroid injections and their clinical effectiveness, physicians who administer these need to be aware of the potential risks of HPA-axis suppression and/or iatrogenic Cushing syndrome. Guidelines for the frequency of dosing in addition to defined time intervals between each injection should be clear. High risk populations have the potential to be screened for adrenal suppression and could include those who receive high doses and multiple injections particularly within the previous six months. Patients who are undergoing scheduled surgery and who have received an intra-articular glucocorticoid injection within the previous month could potentially undergo testing for adrenal suppression, and if present supplemented with oral steroids as a bridging measure

- https://www.redsonoguide.com/wp-content/uploads/2019/10/Intra-articular-glucocorticoid-injections-and-their-effect-on-hypothalamicpituitaryadrenal-HPA-axis-function_.pdf
- The purpose of IAGC is to provide a high synovial fluid concentration and thus *act locally* at the joint to reduce pain and inflammation, while at the same time *limiting systemic absorption*
    - **systemic absorption has been widely recognized** as evidenced by the beneficial effects on other joints that have not been injected
- A recommendation of **up to three glucocorticoid injections per year with a minimum of thirty days between injections** has been advocated due to the concern regarding **hypothalamic–pituitary–adrenal (HPA)-axis suppression.**
- **Synthetic glucocorticoids** are lipophilic and possess **higher glucocorticoid receptor binding affinity compared to the endogenous form and are thus more potent**. – most commonly used preparations are:
    - Triamcinolone acetonide (TA) (‘Kenalog)’ and triamcinolone hexacetonide (TH), (‘Aristospan’) as well as methylprednisolone acetate (MPA), and ‘Depo-medrol’ typically at doses of 40–80 mg
- IAGC are are typically retained in the *IA cavity for 2–3 weeks* after a single injection. However, **screening urine as far along as nine months after the most recent steroid injection**, has detected **the presence of synthetic glucocorticoids** → the potential for a long systemic duration of action even after a single depot injection

Fluticasone – greater risk of systemic absorption

- A systemic review concluded that fluticasone exhibited a greater dose dependent effect on adrenal suppression compared with other ICS.
- This is likely due to pharmacokinetic properties of fluticasone including its long half-life and high lipophilicity resulting in greater systemic retention
- AI secondary to ICS is due to a number of mechanisms.
  - Firstly, subgroups of these patients have a genetically predetermined propensity to develop AS.
  - Secondly, the underlying chronic disease for which they are on these inhaled steroids it-self has varying effect on HPA axis response.
  - Thirdly, the variable safety profile of the inhaled steroid (and other concomitant drugs) that is used has an impact on HPA axis.
  - Finally, there is a dose dependent AS in these patients.

Transient or Temporary Corticosteroid Use

- One of the most common schedules of treatment is ***high initial doses and a gradual reduction*** as the underlying disease ameliorates
  - can lead to **initial moderate to severe hyperglycemia** with **rapid changes in glycemia** in response to changes in the glucocorticoid dose.
- **Insulin** is usually the ***treatment of choice*** because of its efficacy and safety.
  - Insulin provides an *immediate* onset of action, an unlimited hypoglycemic power, and can be *easily titrated*.
- Changes in the dosage of glucocorticoids require parallel and proportional adjustments of the insulin dose.
  - In the outpatient setting, it is ***essential to instruct*** *the patient and/or the patient's family regarding* ***how to adjust the dose of insulin according to glycemia and changes in the dose of glucocorticoids.***