ECHO Diabetes

Steroid Induced Hyperglycemia

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How Do You Guide Your Patients with Diabetes (or risk of diabetes) when they are Treated with Steroids (glucocorticoids)?

- First, it is important to evaluate the
  - degree of pre-existing glucose intolerance
  - the patient's clinical condition (note that acute illness may result in "*stress hyperglycemia*" independent of steroid administration)
  - the degree of hyperglycemia
- Second, it is essential to determine the type, dose, and frequency of administration of the corticosteroid compound.
- Third, differentiate between ***temporary*** and ***indefinite*** treatment with glucocorticoids (e.g., Medrol dose pack vs Prednisone QD for RA)
- Fourth, recognize the mechanism of action, pharmacokinetics, and pharmacodynamics of various hypoglycemic drugs.

All these aspects influence the selection and schedule of hypoglycemic measures, as well as the goals set in terms of glycemic control.

Guidelines for Management of Steroid-Induced Hyperglycemia / Diabetes

- There is little *evidence* to guide how patients with hyperglycemia related to steroid use should be managed –
  - Guidance based on pathogenesis, pharmokinetics and clinical experience
- Short courses of steroids resulting in minimal periods of hyperglycemia *may not warrant intervention*.
- Higher dose steroids for longer periods may result in significant symptomatic hyperglycemia including fatigue, polyuria and polydipsia with the *potential for acute complications related to hyperglycemia* (DKA, Hyperosmotic Syndrome, increased infection)

Glucocorticoid (Steroid) Induced Hyperglycemia or Diabetes

- The use of steroid treatment in people with *preexisting diabetes* will undoubtedly result in worsening glucose control; this may be termed **steroid induced hyperglycemia**.
  - This will warrant temporary additional and more active glycemic management.
- A rise in glucose, related to steroid therapy occurring in people *without a known diagnosis* of diabetes is termed **steroid induced diabetes**.
  - Steroids can ***unmask undiagnosed diabetes*** mellitus or may ***precipitate the appearance*** of GIDM (Glucocorticoid Induced DM)
  - This may or may not resolve when the steroids are withdrawn.

Mechanisms of Glucocorticoid-Induced Hyperglycemia /Diabetes Mellitus

Reduced peripheral insulin sensitivity and/or promotion of weight gain - **increased insulin resistance**

Increase in glucose production through promotion of hepatic gluconeogenesis – **increased hepatic glucose output**

Destruction of pancreatic cells, leading to β-cell injury (inflammation)

β-Cell dysfunction

Impaired insulin release

Inhibited glyceroneogenesis

Increase in fatty acids

Increase in insulin resistance with increased glucose production and inhibition of the production and secretion of insulin by pancreatic β-cells

Risk Factors for Glucocorticoid-Induced Diabetes Mellitus

Higher dose of glucocorticoid treatment (prednisolone >20 mg, hydrocortisone >50 mg, dexamethasone >4 mg)

Longer duration of glucocorticoid treatment

Advanced age

High body mass index

Previous glucose intolerance or impaired glucose tolerance

Personal history of gestational diabetes or previous glucocorticoid-induced hyperglycemia

Family history of diabetes mellitus

Hemoglobin A1c ≥6%

any supraphysiological dose of steroid, approximating a dose of prednisolone > 5mg (or equivalent dose of the alternative synthetic glucocorticoids

Use of Steroids (glucocorticoids)

- In the outpatient population,
  - 40% of steroid use is for *respiratory disease*[e.g., asthma, COPD], with most of the rest being used in *musculoskeletal* [e.g., RA, SLE] and *cutaneous diseases*, and conditions requiring *immunosuppression* [and chemotherapy]
  - 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*)
  - Most steroid use is for *less than 5 days*, but 22% is for *greater than 6 months* and 4.3% for *longer than 5 years*
    - A single or short course of [oral] steroid (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 steroids**)
      - Overnight the blood glucose generally falls back, often to baseline levels the next morning.

DX -Glucocorticoid (Steroid) Induced Hyperglycemia or Diabetes

- Defined as an ***abnormal increase in blood glucose associated with the use of glucocorticoids*** in a patient with or without a prior history of diabetes mellitus.
- The diagnosis of GIDM is set according to the criteria established by expert committees based on the current criteria for diagnosing diabetes:
  - an 8-hour fasting blood glucose level ≥126 mg/dL
  - a 2-hour post-75 g oral glucose tolerance test (OGTT) ≥200 mg/dL
  - a hemoglobin A1c (HbA1c) percentage ≥6.5%
  - in patients with symptoms of hyperglycemia, a random plasma glucose reading ≥200 mg/dL
- In patients treated with most glucocorticoids, measuring ***fasting blood glucose*** 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.**

DX -Glucocorticoid (Steroid) Induced Hyperglycemia or Diabetes

- HbA1c may be a suitable method for *diagnosis* in patients treated with corticosteroids for >2 months, but it is not useful for patients whose treatment has been initiated more recently.
  - An HbA1c *prior to the commencement* of steroids in patients perceived to be at high risk of steroid induced diabetes and in those with known diabetes may be *informative*.
- At the commencement of corticosteroid therapy in people considered *at risk* of steroid induced diabetes, capillary blood glucose (CBG) testing should be initiated once daily.
  - This should be **prior to or following lunch or evening meal** when the hyperglycemic effects of morning steroid dosing is likely to be greatest.
- 50% of the time, GIDM occurred between the *2nd and 4th week* on glucocorticoid therapy (important to continue monitoring)

Transient or Temporary Corticosteroid Use

- One of the most common schedules of treatment
- Characterized by 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. This hyperglycemia is temporary according to the duration of corticosteroid treatment.
- **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.
  - Most available oral hypoglycemic drugs have a slow onset of action and the action profile of oral hypoglycemic drugs throughout the day does not usually coincide with the pattern of glucocorticoid-induced hyperglycemia.
- 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.***

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) – [can be] administered *in addition to daily basal-bolus insulin or in addition to oral anti-diabetic medications"*
- **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.
- ADA- "For higher doses of glucocorticoids, increasing doses of **prandial & correction insulin**, often in extra-ordinary amounts, are often needed in addition to basal insulin"

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

Non-insulin Therapies

- Preference should be given to agents that target postprandial hyperglycemia and have a *rapid onset* of action.
- The use of ***oral hypoglycemic drugs*** is reserved for the treatment of **mild glucocorticoid-induced hyperglycemia** (glycemia <200 mg/dL) in patients without known diabetes or with diabetes adequately controlled by lifestyle measures or oral hypoglycemic drugs.
  - In the absence of studies comparing different strategies, the choice of the oral hypoglycemic drug should depend on the type and schedule of the corticosteroid and on the potential advantages and disadvantages of oral hypoglycemic drugs.

T2DM patients who are well controlled with **lifestyle** measures or with **oral hypoglycemic drugs** that **exacerbate their hyperglycemia during corticosteroid treatment**

- May require an oral hypoglycemic agent or if already on an oral hypoglycemic regimen may require
  - dose intensification,
  - addition of an alternative agent or
  - initiation of insulin if despite these measures, blood glucose levels persistently remain >180 mg/dL.
    - On starting insulin, the dose of sulfonylureas should be reduced to prevent hypoglycemia, while other oral hypoglycemic agents can be continued.
    - With sulfonylurea there is a risk of hypoglycemia when corticosteroid doses are reduced, and this risk is very high when a nocturnal dose of corticosteroids is removed.
    - Patients on agents that can cause hypoglycemia need to **check their blood glucose levels more frequently than usual 1 to 3 days after a glucocorticoid dose reduction**, because it may take this amount of time for the glycemic effect of the glucocorticoid to diminish and for them to adjust their diabetes medication to the appropriate dose

Non-insulin Medication options for people taking steroid therapy

- **Sulphonylureas** promote insulin release from pancreatic beta cell
  - A *short acting sulphonylurea*, such as glipizide, taken once daily may manage the glucose excursion associated with a once daily oral steroid treatment, with dose titration while monitoring for hypoglycemia (usually dose at same time)

- Shorter-acting agents (**Glinides**), such as nateglinide (Starlix) or repaglinide(Prandin) have an *immediate onset of action and a short effect duration (*allows adaptation to the hyperglycemic profile of the corticosteroids and reduces the risk of hypoglycemia in the morning)
  - For patients with mild hyperglycemia who are unable or unwilling to perform injections of insulin, a trial of short-acting secretagogues such as nateglinide or repaglinide taken before meals could be considered.
    - Their major disadvantage is the requirement for multiple daily doses.

Non-insulin Medication options for people taking steroid therapy

- **Metformin** is an attractive option because it enhances insulin sensitivity; thus, preventing metabolic side effects during systemic glucocorticoid therapy.
  - In patients requiring *long-term glucocorticoid use*, metformin could be a reasonable choice given acceptable renal function.
- **Pioglitazone** may improve diabetes-related parameters by antagonizing the pathways of glucocorticoid-induced insulin resistance and by reversing the adverse effects of glucocorticoids on β-cell function but *can take a number of weeks to achieve maximal effect*.
  - Pioglitazone is an option providing there are no contraindications (e.g., heart failure and fluid retention, particularly when used in conjunction with insulin, macular oedema, risk of fractures, unexplained macroscopic hematuria).

The usefulness of metformin and pioglitazone in the treatment of *transient* corticosteroid-induced hyperglycemia is *limited* due to their *slow onset of action*

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** [cg – exenatide ER (Bydureon) –not as quick onset], 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 **SGLT-2 inhibitors**
  - "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 did *not* improve glycemic control in patients with *prednisone-induced hyperglycemia* during Acute Exacerbation of COPD. In future studies, it would be interesting to study its effect in patients with less severe hyperglycemia caused by lower-dose chronic glucocorticoid treatment." Diabetes Obes Metab. 2018 May; 20(5): 1306–1310.

Type 2 diabetes and steroid treatment – General Guidance

- Set target for Capillary Blood Glucose (CBG) (e.g., 100-180)
- Consider increasing monitoring to 4 times daily
- Refresh diabetes education with patient
- If hyperglycemia on non-insulin therapies
  - Glipizide – titrate dose with maximum (largest) dose in the morning
  - Metformin – titrate to maximum of 1g BD
- If on evening once daily human insulin (NPH) consider switch to morning dosing
- If uncontrolled hyperglycemia or multiple daily dosing of steroid, consider switch to basal analogue insulin (or alternative regimen) and involve diabetes team
- Beware of nocturnal and early morning hypoglycemia

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Extra Slides

Predisposing factors leading to increased risk of hyperglycemia with steroid therapy

- Pre-existing type 1 or type 2 diabetes
- People at increased risk of diabetes (e.g., obesity, family history of diabetes, previous gestational diabetes, ethnic minorities, polycystic ovarian syndrome)
- Impaired fasting glucose or impaired glucose tolerance, HbA1c 6.0-6.5%
- People previously hyperglycemic with steroid therapy

- The length of time on glucocorticoids, the relative potency of the glucocorticoid and the absolute dose all play a role in the occurrence of GIDM

Therapeutic goals in patients with GIDM

- Treatment of corticosteroid-induced hyperglycemia be considered when the preprandial and postprandial capillary glucose levels are ≥140 and ≥200 mg/dL, respectively.
- In the case of chronic treatment with glucocorticoids at fairly stable doses, the control goals and the need for drug treatment can be based on the recommended control aims for most patients with diabetes mellitus: preprandial glycemia <130 mg/dL, postprandial glycemia <180 mg/dL, and HbA1c <7%.
- The selection strategy for hypoglycemic drugs should prioritize those with a mechanism of action that fits with the pathophysiology of the process and the patient's hyperglycemic profile.
  - In the *posttransplant* setting, as more studies will be conducted with these and other agents, it is essential to focus attention to on *drug—drug interactions* is essential.
- For patients with persistent significant hyperglycemia with glucose levels >300 mg/dL, more aggressive insulin therapy is indicated, such as intravenous insulin infusion, a higher dose of insulin, or more frequent correction with rapid-acting insulin

From DynaMed Plus

- consider glucocorticoid timing, dose, and duration of action when determining insulin treatment regimens
  - for patients on short-acting glucocorticoids (such as prednisone)
    - patients on morning doses of glucocorticoids have high blood glucose during the day but often reach normal levels overnight
    - standard approach may include prandial insulin dosing (often using intermediate-acting NPH insulin)
  - for patients on long-acting glucocorticoids (such as dexamethasone, or multidose or continuous glucocorticoid therapy) or high doses of glucocorticoids
    - long-acting or basal insulin may be required to control fasting blood glucose
- increasing doses of prandial and correctional insulin may be required for high-dose glucocorticoid therapy, often in addition to basal insulin
  - regardless of antihyperglycemic regimen, anticipate frequent adjustments based on changes in glucocorticoid dosing and point-of-care glucose testing