Non-oral and Locally Injected Corticosteroids: Should we monitor for hyperglycemia?

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Objectives:
1. Review of corticosteroid synthesis, its physiological and pharmacological effects, routes of administration and common uses
2. Describe the mechanism of corticosteroid-induced hyperglycemia and clinical significance of topic
3. Evaluate current literature assessing hyperglycemia related to corticosteroids given by topical, intra-articular, inhaled routes and epidural routes
4. Discuss recommendations regarding hyperglycemia associated with the use of non-oral and locally injected corticosteroids given by topical, intra-articular, inhaled and epidural routes
INTRODUCTION

ADRENAL GLANDS

- Responsible for regulating the stress response through the synthesis of corticosteroids and catecholamines

Structure

- Consists of 2 endocrine glands:
  - Adrenal medulla (secretes catecholamines): Central core of the adrenal gland, surrounded by the adrenal cortex. Chromaffin cells of the medulla are the body's main source of the catecholamines
  - Adrenal cortex (secretes steroid hormones): Situated along the perimeter of the adrenal gland. Mediates the stress response through the production of mineralocorticoids and glucocorticoids. Synthesizes androgen (secondary site)

Regulation of Endogenous Level of Cortisol


CRH: corticotropin-releasing hormone
ACTH: Adrenocorticotropic releasing hormone
**Hypothalamic-pituitary-adrenal (HPA) axis is a feedback loop** (hypothalamus, pituitary and the adrenal glands)\(^2,4,5\)

- Cortisol’s effect on the hypothalamus completes the negative feedback loop
- Release of cortisol into circulation has multiple effects
  - Elevation of blood glucose for increased metabolic demand
  - Can have negative effects on the immune system and prevent release of immunotransmitters

**Physiological and Pharmacological Effects of Glucocorticoids** \(^6-9\)

1. Metabolic effects
2. Immune responses
3. Skeletal muscle wasting
4. Bone formation and resorption
5. Lipid metabolism
6. CNS
7. Cardiovascular system
8. Eye
9. HPA axis disturbance
10. Electrolyte and water balance

**Metabolic Effects**
- Increases nutrient availability by raising blood glucose, amino acid, and triglyceride levels.
- Increases blood glucose by antagonizing insulin action and by promoting gluconeogenesis in the fasting state.
- Increases levels of amino acids by muscle protein catabolism
- Increased levels of amino acids are utilized by the liver as fuels for gluconeogenesis.

**Immune Effects**
- Immunosuppression
  - Risk for infections

**Skeletal muscle wasting**
- **Steroid Myopathy.** Two distinct types: acute and chronic.
  - Chronic (or classic) form occurs after prolonged use of corticosteroids. The acute form is less common and is associated with rhabdomyolysis, and occurs abruptly with high-dose corticosteroids.
  - Characterized by weakness of proximal limb muscles. Myopathy of respiratory muscles in patients with asthma or COPD.
  - Recovery from steroid myopathy is slow and incomplete.
Osteoporosis
- Decreased osteoblast rebuilding and increased resorption by osteoclast

Lipid Metabolism
- Glucocorticoids cause a characteristic redistribution of fat, with peripheral wasting of adipose stores and central obesity
- Excessive fat deposition occurs on the back of the neck (buffalo hump) and face (moon face)

CNS
- Psychological and behavioral changes; aggravation of pre-existing psychiatric disorders
- Examples: Euphoria, depression and paranoid psychosis

Cardiovascular
- Fluid retention, edema, hypertension

Eyes
- Increased intra-ocular pressure and cataract formation
- Increased glucose levels and auto-oxidation in lens (diabetic retinopathy)

HPA axis disturbance
- Hypothalamic pituitary adrenal (HPA) axis disturbances are associated with disruptions in endogenous insulin secretion, insulin resistance and diabetes mellitus

Electrolyte and water balance
- Mineralocorticoids maintain electrolyte and water balance
- Aldosterone
- Enhance reabsorption of Na⁺ from the tubular fluid
Major complications attributed to chronic steroid use 7-9
- The rate of side effects associated with steroid use differs depending on the dose and long term use

<table>
<thead>
<tr>
<th>Duration</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term corticosteroid therapy</td>
<td>Electrolyte abnormalities, hypertension, hyperglycemia, pancreatitis, hematologic, immunologic and neuropsychologic effects</td>
</tr>
<tr>
<td>Long term corticosteroid therapy</td>
<td>Osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic and ophthalmologic effects, hyperlipidemia, growth suppression</td>
</tr>
</tbody>
</table>

- Information on the systemic effects of corticosteroids are well-defined but the effects on glucose metabolism are not well-known 10

Medications that can cause elevated blood glucose 11
- Interferon alfa, diazoxide, diuretics, glucocorticoids, nicotinic acid, oral contraceptives, phenytoin, beta-blockers, clozapine, olanzapine etc.

Glucocorticoids are the most common cause of drug-induced diabetes. The exact prevalence is unknown. 9,12 A recent population-based study determined that the relative risk of developing diabetes was amplified two fold in patients receiving steroids compared to those who did not. 9

Proposed mechanism of corticosteroid induced hyperglycemia 6,12-14
- Reduce glucose utilization
- Increase glucose production
- Inhibit the effects of insulin on myocytes and adipocytes
- Increase hepatic glucose release

![Figure 1. Pathophysiological mechanisms of glucocorticoid (GC)-induced diabetes. GC excess causes inhibition of insulin secretion by pancreatic β cells and reduces insulin sensitivity in liver, skeletal muscle and adipose tissue. NEFA, nonesterified free fatty acids; *, mechanisms involved in determining fasting hyperglycemia.](TRENDS in Endocrinology & Metabolism)
Corticosteroids\textsuperscript{3,15}
- Vary in potency and some may have more prominent effects on elevating blood glucose than others. Dexamethasone for example is 30x more potent than hydrocortisone\textsuperscript{15}

**Routes of Administration for Glucocorticoids\textsuperscript{15-16}**

**Local (Preferred)**
- Intra-articular
- Intrasynovial
- Intrarectal
- Topical
- Nasal
- Inhaled

*Can be administered at high doses, while minimizing systemic adverse effects*

**Systemic**
- Oral
- Intramuscular
- Intravenous
• Corticosteroids are given through various routes (intravenous, oral, inhaled, intra-articular, intramuscular and epidural routes) and have a broad range of indications
• Corticosteroids are the most important and frequently used class of anti-inflammatory drugs
• Corticosteroids have multiple uses for the treatment of inflammatory, autoimmune and endocrine disorder. It is also used as symptom control in cancer patients, as well as treatment for adrenal insufficiency, asthma, brain tumors, chronic obstructive pulmonary disease, connective tissue, rheumatic disorders (lupus, rheumatoid arthritis) and poison ivy etc.

**Common Corticosteroids Indications**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred Corticosteroid</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Hydrocortisone (plus fludrocortisone if additional mineralocorticoid activity needed)²³</td>
<td>Traditional replacement of choice.²³ Hydrocortisone provides both mineralocorticoid and glucocorticoid activity. However, prednisone or dexamethasone provide more physiologic (i.e., longer acting) glucocorticoid replacement.⁷</td>
</tr>
<tr>
<td>Asthma</td>
<td>Prednisone or prednisolone⁷</td>
<td>Commonly used. Less mineralocorticoid activity than hydrocortisone.⁴</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>Dexamethasone⁷</td>
<td>Long history of use, ease of use, clinical comfort.⁷</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Methylprednisolone, prednisone⁶</td>
<td>Mentioned in GOLD guidelines.⁸</td>
</tr>
<tr>
<td>Connective tissue and rheumatic disorders (e.g., lupus, rheumatoid arthritis)</td>
<td>Prednisone⁷</td>
<td>Well-absorbed, intermediate duration of action, cheap, variety of strengths and dosage forms. Can also use methylprednisolone or prednisolone.¹ Single morning dose mimics physiologic cortisol secretion and minimizes HPA axis suppression.⁷</td>
</tr>
<tr>
<td>Nausea and vomiting (radiation, chemotherapy, postoperative, pregnancy)</td>
<td>Dexamethasone</td>
<td>Most commonly used/studied.</td>
</tr>
<tr>
<td>Poison ivy/oak/sumac</td>
<td>Prednisone taper starting with 1 mg/kg/day or 30 to 60 mg per day (0.5 mg/kg/day for children), total therapy duration 14 to 21 days²⁶</td>
<td>Standard regimen.² Do not use pre-packaged corticosteroid taper; dose too low and duration of therapy too short.⁴</td>
</tr>
</tbody>
</table>

© in general, hydrocortisone is chosen only when sodium and water retention are desired (e.g., for treatment of adrenal insufficiency).¹ Intermediate-acting agents (prednisone, prednisolone, methylprednisolone) given once daily may minimize HPA-axis suppression.⁷ Prednisone is commonly used due to cost, available strengths, and clinical convention/comfort. Dexamethasone is used for certain indications based on clinical experience. Oral liquid prednisolone formulations are often used in children.

**Clinical significance of topics**

- Corticosteroids are used extensively in the treatment of multiple disease states and have major advantages
- Oral and intravenous steroids are well documented in affecting blood glucose metabolism but we have limited information available on the effects of non-oral and locally injected corticosteroids
Glucocorticoid induced hyperglycemia is a frequent problem which is undervalued in terms of diagnosis and treatment

Absence of clinical studies and specific recommendations for diagnosis and treatment

Corticosteroids, especially at higher doses, may be associated with an increased risk of requiring initial drug therapy for diabetes or increased risk of requiring insulin in patients already treated with oral anti-diabetic agents

Need to investigate how the use of steroids affects the co-existence of other chronic disease states

LITERATURE REVIEW

Article #1

Objective
To determine the effect of inhaled corticosteroids (ICS) therapy on glucose control in adults with type 2 diabetes mellitus and coexisting asthma or chronic obstructive pulmonary disease (COPD)

Methods
United States Department of Veterans Affairs Health Care System outpatient setting

3 week run in period (placebo inhaler, 2 puffs twice daily) after enrollment. On day 21, initial baseline data obtained (% HbA1c, randomization

Study Design
Prospective Randomized, double-blind, double-dummy placebo-controlled, crossover trial

Primary Outcome
Difference in %HbA1c after 6 weeks of use of ICS fluticasone propionate (FP) compared with 6 weeks use of oral montelukast

Secondary Outcome
Subject change in % HbA1c from baseline after each type of therapy

Subjects (N=12)
- Adults with diagnosis of type 2 diabetes (managed with oral hypoglycemic medication or without medication) and asthma or COPD
- 18 years or greater
- Type 2 diabetes confirmed by a fasting plasma glucose >126 mg/dl on a screening visit
- Physicians diagnosis of either asthma or COPD confirmed by electronic medical record review

Exclusion Criteria
- Use of tobacco within 6 months of enrollment
- History of exacerbation of asthma or COPD within 3 months of enrollment
- Current insulin therapy
- Use of systemic corticosteroids or ICS, leukotriene receptor antagonist, or theophylline within 1 month of enrollment
- Inability to read and complete a diary card
- Inability to perform spirometry, expiratory flow testing
- Inability to use metered dose inhaler with spacer
N=12 randomized to receive either inhaled FP (440 ug twice daily) & placebo, or inhaled placebo & oral montelukast (10 mg/day) for 6 weeks
- After 6 weeks, switched to opposite therapy for another 6 weeks
- 12 week trail of inhaled FP (440 ug twice daily) vs. oral montelukast (10 mg/day)
- Approved by the Stanford University Administrative Panel on Human Subjects Medical Research. Also, the Veterans Affairs Palo Alto Health Care System (VAPAHCS) Research and Development Committee
- Informed consent
- Albuterol meter-dose inhaler was prescribed on an as needed basis
- Subjects were allowed to take other prescribed medications (cholesterol, oral hypoglycemic etc.) during study and doses were not changed
- At randomization and after each 6 week treatment (day 63 & day 105)
  - Baseline demographics
  - Subjects underwent spirometry both before and again 20 minutes after administration of nebulized albuterol (lung function)
  - Fasting blood drawn for % HbA1c
- 6 subjects (oral hypoglycemic medication) recorded once daily self monitoring of blood glucose (SMBG)- after an overnight fast
- Those controlled with diet only, performed no daily SMBG
- Telephone contact of each participant once a week (drug compliance & assess adverse events)
- All subjects measured and recorded their daily peak expiratory flow rate (PEFR) in a diary cards
- Safety limit of study
  - Fall in PEFR by more than 20% or SMBG measurement of >300 mg/dl

### STATISTICAL ANALYSIS

| Statistical tests | Estimate a sample size n=16 with a crossover study design necessary to detect statistical significant difference
|                   | Two tailed t test (alpha =0.05, beta= 0.20)
|                   | Data presented as means (± standard deviation)

### RESULTS

| Results | 14 male subjects recruited, screened, and enrolled over 6 month period
|         | 2 subjects excluded – prior to randomization due to non-compliance
|         | 12 were randomized (2 excluded on day 21 of 1st treatment period for non-compliance)
|         | 10 subjects completed trial
|         | No study relevant adverse event
|         | Mean within-subject baseline to 6 week difference in % HbA1c was significantly greater after treatment with inhaled FP than after treatment with oral montelukast therapy (mean difference=0.25; P<0.025)
  |         | Mean % difference (0.25), smaller than 0.5% difference consider to be clinically relevant
<table>
<thead>
<tr>
<th>Variable</th>
<th>Change</th>
<th>% change</th>
<th>Change</th>
<th>% change</th>
<th>Difference</th>
<th>% change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgbA1c (%)</td>
<td>0.11 (0.17)</td>
<td>1.7 (2.6)</td>
<td>-0.14 (0.26)</td>
<td>-2.1 (3.6)</td>
<td>0.25 (0.29)</td>
<td>3.8 (4.3)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

- Change in %HgbA1c
  - Inhaled FP therapy: 7 subjects with increase in % HgbA1c > baseline, 2 reduction and 1 unchanged
  - Oral montelukast therapy: 2 subjects with increase in % HgbA1c > baseline, 6 subjects had reductions and 2 were unchanged

**CONCLUSION**

Authors’ Conclusions

- Moderately high dose (ICS for treatment of asthma and COPD) is associated with small disturbances in glucose control after a relatively brief period of therapy in diabetic subjects relative to oral montelukast therapy
- The changes are detectable but smaller than those that would be considered clinically significant, therefore changing or stopping therapy is not necessary
- Careful monitoring of blood glucose when ICS therapy is initiated

**COMMENTS**

Limitations
- Small sample size
- Only male subjects

Strengths
+ First prospective, randomized double-blind, placebo controlled trial to compare the effects of anti-asthma medications on glucose metabolism (type 2 diabetes and coexisting asthma
+ Practical to real life setting (multiple diagnosis, allowed to take all other medications, etc.)
+ Participants contacted by telephone to ensure compliance
+ Safety limit set

**Recommendation inhaled corticosteroids**\(^{10,19}\)

- If hyperglycemia develops in patients receiving inhaled corticosteroids, stopping therapy is not necessary but careful monitoring is needed to determine when to consider lowering the inhaled corticosteroid dose and adding other non-corticosteroid therapies (leukotriene inhibitors, beta agonist etc.)
- In diabetics use of steroids may warrant adjusting or increasing dose of anti-diabetic therapy.

**Article #2**


**Objective**
Investigate an association between intense, longstanding topical corticosteroid use and diabetes mellitus

**METHODS**

**Study Design**
Nested case control study within a retrospective cohort of users of topical corticosteroids
<table>
<thead>
<tr>
<th>Study Site:</th>
<th>Database of drug dispensing records and hospital records (3 million individuals) in Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Study cohort</td>
</tr>
<tr>
<td></td>
<td>- New users of topical corticosteroids between Jan 1st 1992-December 31st 2004, with follow up of at least 4 years.</td>
</tr>
<tr>
<td></td>
<td>- Without diabetes in the 1 year period before the start of topical corticosteroids use</td>
</tr>
<tr>
<td></td>
<td>- No use of anti-diabetic drugs, insulin or analogues, blood glucose lowering drugs or diabetes related hospitalization</td>
</tr>
<tr>
<td></td>
<td>- New users</td>
</tr>
<tr>
<td></td>
<td>- Not been dispensed a topical corticosteroid during at least 1 year prior to their 1st dispensed topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td>- Followed from the start of topical corticosteroid use until the earliest onset of diabetes, transferring to a different pharmacy or end of the study period</td>
</tr>
<tr>
<td></td>
<td>Cases and control</td>
</tr>
<tr>
<td></td>
<td>- Classified as diabetic case</td>
</tr>
<tr>
<td></td>
<td>- Prescribed anti-diabetic drugs, followed by a second prescription within 1 year (date of anti-diabetic drug prescribing was defined as date of diagnosis &amp; was classified as the index date)</td>
</tr>
<tr>
<td></td>
<td>- Index date was preceded by at least 4 years in the cohort</td>
</tr>
<tr>
<td></td>
<td>- At least 2 topical corticosteroid dispensed before the index date</td>
</tr>
<tr>
<td></td>
<td>- Each case matched by age (± 2 years) and sex to 4 controls</td>
</tr>
<tr>
<td></td>
<td>- Controls were selected from all cohort members who were present on the case’s index date, did not have diabetes, had at least 2 topical corticosteroid dispensing before the cases index date and same duration of follow up as cases</td>
</tr>
<tr>
<td></td>
<td>- 58% of cases &amp; controls were female, 59% were ≥ 65 years</td>
</tr>
<tr>
<td>Methods</td>
<td>Data obtained from PHARMO record linkage system (linked drug dispensing and hospital records)</td>
</tr>
<tr>
<td></td>
<td>- Records included</td>
</tr>
<tr>
<td></td>
<td>- Dispensing drug, type of prescriber, dispensed date, amount dispensed, prescribed dose regimen and the duration of use of drug</td>
</tr>
<tr>
<td></td>
<td>- Hospital records: detailed information on primary and secondary diagnosis, procedures and date of hospital admission and discharge</td>
</tr>
<tr>
<td></td>
<td>- Non diabetic patients who were users of topical corticosteroid use during 1992-2004 (≥2 topical corticosteroid dispensing &amp; ≥ 4 yrs follow up)</td>
</tr>
<tr>
<td></td>
<td>- Diabetes onset (1st occurrence of anti-diabetic prescription or hospitalization for diabetes)</td>
</tr>
<tr>
<td></td>
<td><strong>Topical Corticosteroid exposure</strong></td>
</tr>
<tr>
<td></td>
<td>- Timeline</td>
</tr>
<tr>
<td></td>
<td>- Current users: Having at least one topical corticosteroid dispensing during the 2 year period before the index date</td>
</tr>
<tr>
<td></td>
<td>- Recent users: Having a prescription within the 4 year period before, but not during the 2 year period before the index date</td>
</tr>
<tr>
<td></td>
<td>- Past users: Used topical steroids only before the 4 year period before the index date</td>
</tr>
</tbody>
</table>
Average potency
- ATC-4 code D07AA: weak potency (score 1)
- ATC-4 code D07AB: moderate potency (score 2)
- ATC-4 code D07AC: potent (score 3)
- ATC-4 code D07AD: very potent (score 4)

Cumulative load:
- Total amount dispensed (grams) X potency score
- Summed up all topical corticosteroid load over the 4 year period prior to the index date

Covariates
- Co-medication with systemic corticosteroids and inhaled corticosteroids was considered
- Age of index, sex, year of index date, follow up duration, number of all hospitalizations during the 1 year period before the index date and co medication use in the 4 year period before the index date

STATISTICAL ANALYSIS

Statistics
- Association between topical corticosteroids use & new onset diabetes was studied using univariate and multivariate conditional logical regression
- Multivariate regression analyses were adjusted for co-medication and comorbidity

RESULTS

- 192,893 subject who met criteria for study, 7862 developed diabetes
- 2212 cases developed diabetes and had 4 years or greater of follow up since the start of topical steroids use and at least 2 topical corticosteroid dispensed before they developed diabetes
- An association of 1.24 fold increase risk of diabetes (odds ratio 1.24, 95% CI 1.11 to 1.40) was noted with current use of topical corticosteroids
- Higher duration of use of topical corticosteroid was associated with a higher risk of new onset diabetes.
- When used for >180 days it yields a 1.32 fold risk in the development of diabetes (odds ratio 1.32, 95% CI 1.14 to 1.54)
- Using a higher cumulative load of topical corticosteroids was also associated with a statistically significant risk of new onset diabetes

Timeline of topical corticosteroid use

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>OR adj (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Past</td>
<td>499</td>
<td>22.5</td>
<td>2219</td>
<td>25.8</td>
</tr>
<tr>
<td>Recent</td>
<td>462</td>
<td>20.9</td>
<td>1852</td>
<td>21.6</td>
</tr>
<tr>
<td>Current</td>
<td>1251</td>
<td>56.6</td>
<td>4511</td>
<td>52.6</td>
</tr>
</tbody>
</table>

Cumulative duration of topical corticosteroid use (days)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>OR adj (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>499</td>
<td>22.5</td>
<td>2219</td>
<td>25.9</td>
</tr>
<tr>
<td>1-60</td>
<td>831</td>
<td>37.6</td>
<td>3299</td>
<td>38.4</td>
</tr>
<tr>
<td>Parameter</td>
<td>Cases</td>
<td>Control</td>
<td>OR (95% CI)</td>
<td>OR adj (95% CI)</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>499</td>
<td>22.6</td>
<td>2219</td>
<td>25.9</td>
</tr>
<tr>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-90</td>
<td>343</td>
<td>15.5</td>
<td>1464</td>
<td>17.1</td>
</tr>
<tr>
<td>1.05 (0.90-1.23)</td>
<td>1.03 (0.88-1.21)</td>
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<tr>
<td>91-180</td>
<td>260</td>
<td>11.8</td>
<td>1106</td>
<td>12.9</td>
</tr>
<tr>
<td>1.04 (0.88-1.24)</td>
<td>1.04 (0.87-1.23)</td>
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<td></td>
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</tr>
<tr>
<td>181-365</td>
<td>371</td>
<td>16.8</td>
<td>1299</td>
<td>15.1</td>
</tr>
<tr>
<td>1.29 (1.11-1.50)</td>
<td>1.27 (1.09-1.49)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>366-730</td>
<td>303</td>
<td>13.7</td>
<td>1084</td>
<td>12.6</td>
</tr>
<tr>
<td>1.26 (1.07-1.48)</td>
<td>1.25 (1.06-1.47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>731-1460</td>
<td>238</td>
<td>10.8</td>
<td>736</td>
<td>8.6</td>
</tr>
<tr>
<td>1.44 (1.21-1.72)</td>
<td>1.38 (1.15-1.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1460</td>
<td>198</td>
<td>9.0</td>
<td>674</td>
<td>7.9</td>
</tr>
<tr>
<td>1.33 (1.10-1.60)</td>
<td>1.21 (0.99-1.47)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**CONCLUSION**

**Authors’ Conclusions**
Increased risk of new onset diabetes may be an important consideration when patients are treated with topical corticosteroids, especially when there is already an increased risk of diabetes and when intense skin treatment is needed.

**COMMENTS**

**Limitations**
- Age was not part of the eligibility criteria
- The pattern of use is not known and was variable
- Adherence to use after dispensed date
- Skin types and rate of absorption would vary
- No information on family history of diabetes and body mass index
- Netherlands population, culture, diet etc. compared to other countries
- Inclusion of patients from only one country

**Strengths**
+ Large sample size and data base
+ Adjusting for other covariates (use of both systemic and/or inhaled corticosteroids) to see if that would affect the results of the odds ratio and it did not
+ Accounted for confounding variables such as use of medication known to influence glucose metabolism etc.
+ Data collection from daily practice in an open access healthcare system
+ No information bias (using routinely recorded data)
+ Diverse spectrum of patients

**Recommendations regarding topical corticosteroids**
- There is an association between the development of hyperglycemia and the use of topical corticosteroids
Particularly in patients using topical corticosteroids in high concentration, dose and for a prolonged duration. Closer monitoring of blood glucose concentrations is necessary.

**Article #3**


<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate prospectively the effect of methylprednisolone acetate (MPA) injection at the knee joint in patients with controlled diabetes and osteoarthritis of the knee (OAK)</th>
</tr>
</thead>
</table>

**METHODS**

<table>
<thead>
<tr>
<th>Study Design:</th>
<th>Prospective study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Site:</td>
<td>Nazareth hospital</td>
</tr>
<tr>
<td></td>
<td>&gt; Approved by Helsinki committee of hospital and informed consent was signed by all patients</td>
</tr>
<tr>
<td>Subjects N=9</td>
<td>9 Patients (7 females and 2 male) with controlled diabetes (HgA1C &lt;7), use of a modern blood glucose monitoring device, knee pain due to osteoarthritis of the knee (OAK) for more than 3 months without sufficient response to non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy</td>
</tr>
<tr>
<td>Methods:</td>
<td>▪ Subjects who met criteria were administration 50 mg of methylprednisolone acetate (MPA) administered at the knee joint</td>
</tr>
<tr>
<td></td>
<td>▪ Patients were asked to monitor their blood glucose levels before and 2 h after breakfast, lunch and supper every other day for 1 week prior to injection and daily for 4 days, then every other day for 10 days following the injection using the same glucose monitoring devices</td>
</tr>
<tr>
<td></td>
<td>▪ Patients were asked to continue their same daily regimen of physical activity, diet and anti-diabetic treatment</td>
</tr>
</tbody>
</table>

**STATISTICAL ANALYSIS**

| Statistics | Increase in blood glucose level was considered significant if glucose levels were greater by 2 SD when compared to mean glucose levels before the injection |

**RESULTS**

▪ After the administration of intra-articular steroid injection there was a significant increase in blood glucose levels shown in all patients  |
▪ A significant increase 2-4hrs after injection was seen in 4 patients and within 12-24hrs an increase was seen in all other patients  |
▪ 3 patients were able to attain peak levels after 5hrs, while others subjects reached peak levels within 17, 24, 32, 48 and 84 h  |
▪ A peak of about 300 mg/dl was recorded in most patients and one patient had a peak of 500 mg/dl.  |
▪ The rise in blood glucose lasted for about 2-3days after the use of IASI and in some patients lasted up to 5 days
The effect of oral or intravenous steroid treatment on glucose metabolism is well known. The use of IASI of MPA at the knee joint will most probably increase blood glucose levels in patients with controlled diabetes and osteoarthritis of the knee. The pattern of increase in blood glucose levels is variable but temporary and lasts only for few days.

### Comments

- Very small sample size
- More studies needed
- No explanation to how adherence was measured
- Short duration of follow up
- Other medication that could cause diabetes, health history etc.

### Strengths

- One of the first studies to show that IASI may increase blood glucose levels
- Subjects were encouraged to continue their daily routine activities
- Helps give a better understanding of what may happen to diabetic patients using such treatment

### Table 1: Time relation of glucose levels following intra-articular steroid injection (IASI)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Time to earliest significantly increased glucose level, h</th>
<th>Earliest significantly increased glucose level, mg %</th>
<th>Time to peak glucose levels, h</th>
<th>Peak glucose levels, mg %</th>
<th>Time to return to baseline levels, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>330</td>
<td>5</td>
<td>375</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>160</td>
<td>5</td>
<td>310</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>184</td>
<td>17</td>
<td>283</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>227</td>
<td>32</td>
<td>463</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>134</td>
<td>5</td>
<td>314</td>
<td>70</td>
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<tr>
<td>6</td>
<td>26</td>
<td>249</td>
<td>84</td>
<td>282</td>
<td>96</td>
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<tr>
<td>7</td>
<td>12</td>
<td>255</td>
<td>48</td>
<td>500</td>
<td>104</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>154</td>
<td>24</td>
<td>181</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>150</td>
<td>48</td>
<td>165</td>
<td>58</td>
</tr>
</tbody>
</table>

### Conclusions

- The use of IASI of MPA at the knee joint will most probably increase blood glucose levels in patients with controlled diabetes and osteoarthritis of the knee.
- The pattern of increase in blood glucose levels is variable but temporary and lasts only for few days.

### References

Monitor blood glucose before and 2hrs after breakfast, lunch, and supper every other day during 1 week prior to injection and daily for 4 days, then every other day for 10 days following the injection and also 1 hr after the injection.

- Serum fructosamine levels were obtained just prior to and 2 weeks following the IASI.

- Patients were asked to continue normal daily routine (physical activity, diet, anti-diabetic medication).

### STATISTICAL ANALYSIS

**Statistics**

Blood glucose level higher by at least 2 standard deviations (SD) after injection (significant)

Wilcoxon’s test: used to compare serum fructosamine levels obtained 2 weeks following the injection to those obtained just prior to injection.

### RESULTS

- No reports of patients adding or stopping medication during study. Also no reports of symptoms/signs suggesting infection.
- Significant increase in blood glucose levels only involved both pre and post prandial measurement of all meals.
- Return to baseline levels similar to those prior to the IASI was observed within approximately 2 days.
- The use of celestone injection at the knee joint resulted in rapid significant increase in blood glucose levels in all patients within 1 hr and returned to baseline levels (before injection) in most patients within 2 days.
- No significant difference was found between fructosamine levels obtained 2 weeks following the IASI compared to those obtained prior to the injection.

**Table 2** Time relation of glucose levels following IASI of Celestone Chronodose and fructosamine levels prior and following IASI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time to earliest significantly increased glucose level (h)</th>
<th>Earliest significantly increased glucose level (mg%)</th>
<th>Time to peak glucose levels (h)</th>
<th>Peak glucose levels (mg%)</th>
<th>Time to return to baseline levels (h)</th>
<th>Fructosamine level before IASI</th>
<th>Fructosamine level after IASI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>198</td>
<td>6</td>
<td>339</td>
<td>18</td>
<td>259</td>
<td>286</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>180</td>
<td>34</td>
<td>251</td>
<td>34</td>
<td>321</td>
<td>335</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>207</td>
<td>6</td>
<td>313</td>
<td>46</td>
<td>332</td>
<td>297</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>298</td>
<td>2</td>
<td>351</td>
<td>46</td>
<td>410</td>
<td>351</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>201</td>
<td>32</td>
<td>430</td>
<td>72</td>
<td>287</td>
<td>290</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>226</td>
<td>2</td>
<td>251</td>
<td>25</td>
<td>323</td>
<td>303</td>
</tr>
</tbody>
</table>

### CONCLUSION

**Authors’ Conclusions**

The observed outcome of increased blood glucose levels after the use of IASI can help give some indication of what will happen to many diabetic patients who receive IASI treatment.

**Limitations**

- Very small sample size
- More studies needed
- No explanation to how adherence was measured
- Short duration of follow up
- Other medication that could cause diabetes, health history etc.

**Strengths**

+ Subjects were encouraged to continue their daily routine activities.
+ Helps give a better understanding of what may happen to diabetic patients using such treatment

**Recommendation for intra-articular injections**¹⁹,²¹,²²
- Following the administration of intra-articular injections with corticosteroids, hyperglycemia can be observed approximately 2-5 days after injection
- The increase although minimal can be significant in diabetic patients so closer monitoring of blood glucose levels is warranted and adjustments in therapy should be made when necessary

**Article #5**


**Objective**
To investigate potential systemic effects of glucocorticoid injections into the epidural space or shoulder in patients with or without diabetes

**METHODS**

**Study Design**
Prospective study

**Subjects**
N=29
- Enrolled 29 patients
  - 18 women and 11 men
  - Mean age 38 years
  - Each received 3 local injections of 1.5ml cortivazol at 3 day intervals
  - Injected in epidural space 18 patients (disk related sciatica) & intra-articular in 11 patients (frozen shoulder)
  - 17 non-diabetic & 12 had type 2 diabetes (controlled with hypoglycemic agent n=9, diet alone n=1, insulin n=2)
  - No history of local or systemic glucocorticoid therapy within the last 2 months

**Methods:**
- Lab test done at baseline (before injection) & at 3 post treatment visits (1,7 and 21 days after the 3rd injection)
- Lab test:
  - Plasma level cortisol and ACTH at 8am
  - Potassium, total cholesterol and triglycerides, fasting and postprandial blood glucose levels, urine free cortisol excretion in 24hrs
  - Systolic & diastolic blood pressures were recorded at baseline and at each visit
  - Diabetics with fasting blood glucose ≤10 mmol/l (n=9) continued their usual treatment. Those with > 10 mmol/l (n=2), insulin was started

**STATISTICAL ANALYSIS**

**Statistics**
- Wilcoxon’s test for paired variables
- Mean at baseline compared to mean at post visits
- P <0.05 considered statistically significant

**RESULTS**
- Plasma cortisol, ACTH and urinary free cortisol showed large decreases at post visit day 1 and 7 compared to baseline, and a smaller decrease at day 21
- Significant increase noted in post prandial glucose levels
  - Higher increase in patients with diabetes than those without
Conclusions

Authors’ conclusions:

- Local glucocorticoid injections may cause loss of glucose control in patients with diabetes. Blood glucose should be monitored closely. Glucose level elevations may persist for 2 weeks.
- Increase in postprandial glucose levels is more significant and lasts longer in patients with diabetes than those without.
- Need to achieve glucose control before these injections and also closer monitoring of blood glucose levels several weeks after these injections are warranted.

Changes in the 12 diabetic patients (D) & the 17 non-diabetic patients (ND) after three cortivazol injections into the shoulder or epidural space

<table>
<thead>
<tr>
<th></th>
<th>D₀ D/ND</th>
<th>D₁ D/ND</th>
<th>D₇ D/ND</th>
<th>D₂₁ D/ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPBG (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₀</td>
<td>9.4 ± 3.3/</td>
<td>14.2 ± 5.5*/</td>
<td>13.9 ± 4.8 */</td>
<td>12.1 ± 5/</td>
</tr>
<tr>
<td>D₁</td>
<td>6.2 ± 1.7/</td>
<td>7.2 ± 3*/</td>
<td>6 ± 2.4/</td>
<td>5.9 ± 2.1/</td>
</tr>
</tbody>
</table>

PPBG: postprandial blood glucose
D₀: Baseline; D₁: Day 1; D₇: Day 7; D₂₁: Day 21
* P<0.05

CONCLUSION
**COMMENTS**

| Limitations          | - Findings may not apply to other glucocorticoids  
|                      | - Large increase in postprandial blood glucose level in group with diabetes may be attributed to poor glucose control  
|                      | - Small sample size  
| **Strengths** | + Good comparison of both diabetic and non-diabetic patients post prandial blood glucose levels  
|                      | + One of 1st studies to look into epidural glucocorticoids injections  
|                      | + Good evidence to support proper glucose control before injections are administered  

**Recommendation for epidural injection**

- Hyperglycemia after injection with epidural injection can occur in patients receiving steroid & especially those who are already diabetic. Elevated blood glucose levels can persist for up to 2 weeks, so glucose monitoring is recommended.

**DISCUSSION**

**Non-orally and locally injected corticosteroids: Should we monitor for hyperglycemia?**

- **Inhaled corticosteroid’s**
  
  Stopping therapy is most likely not necessary but careful monitoring is needed to consider when to lower dose and add alternative therapy. In diabetic patients, may need to increase dose of their anti-diabetic medication.

- **Topical corticosteroid’s**
  
  Monitoring needed for patients using a high concentration, dose and for a prolonged period especially when using for greater than 6 weeks. Different skin types may also vary in corticosteroid absorption.

- **Intra-articular corticosteroid’s**
  
  Hyperglycemia more prominent within the first 2-5 days after injection. Minimal increase in non-diabetics but more significant in diabetics, therefore closer monitoring needed.

- **Epidural corticosteroid injections**
  
  Hyperglycemia has been documented and can persist for approximately 2 weeks, so close monitoring during this period, especially in diabetics.
CONCLUSION

- Hyperglycemia is a side effect to monitor for in patients receiving non-orally and locally injected steroids based on currently available evidence-based literature.
- The degree of increase in blood sugar level is variable.
- Patient should be warned and educated about the symptoms of diabetes when starting glucocorticoid treatment.
- The exact duration of time to monitor and treat for hyperglycemia with non-orally and locally injected steroids, varies based on multiple factors:
  - Method of administration (inhaled vs. topical vs. articular vs. epidural).
  - Concentration, dose and duration of use.
  - Pre-existing factors for impaired glucose metabolism (diabetes, metabolic syndrome, family history, other medications elevating glucose levels etc.)
- Therefore, the decision on how to monitor and when to treat should be made on a case by case basis.
- More randomized studies, with larger sample sizes needed in future research.

REFERENCES