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# Do Inhaled Corticosteroids Cause an Increased Risk for Developing or Worsening a Patient's Diabetes Mellitus?

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**Do inhaled corticosteroids cause an increased risk for developing or worsening a patient's diabetes mellitus?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

### OBJECTIVE

The objective of this selective EBM review is to determine whether or not inhaled corticosteroids (ICS) cause an increased risk for developing or worsening a patient's diabetes mellitus (DM).

### STUDY DESIGN

Review of three English language primary studies published in 1993, 2009 and 2010.

### DATA SOURCES

A nested case-control analysis, a randomized control trial and a prospective randomized, double-blind, double-dummy, placebo-controlled, crossover investigation comparing the onset and/or progression of diabetes mellitus in patients using ICS were found using Ovid MEDLINE, PubMed, and Cochrane databases.

### OUTCOMES MEASURED

Incidence or progression of diabetes was measured using a combination of oral glucose tolerance test, serum insulin levels, HgA1c levels, and fasting glucose levels.

### RESULTS

Faul had 70% of patients that experienced some increase in HgA1c levels, but none that were statistically significant. Kiviranta had very slight increases in blood glucose when compared to the patient's baseline measurements. Suissa had a 34% increase in the onset or progression to insulin use of diabetic patients.

### CONCLUSIONS

While all of the studies showed an increase in the incidence or progression of diabetes in patients taking ICS, none of the increases were significant enough to preclude diabetics from taking ICS as needed. Careful monitoring of a patient with diabetes needing an ICS is warranted to prevent loss of diabetes control. Additionally, a baseline HgA1c level on a patient newly prescribed an ICS might be beneficial.

### KEYWORDS

Inhaled corticosteroids, diabetes

## INTRODUCTION

According to Faul et al, the prevalence of Diabetes Mellitus (DM), chronic obstructive pulmonary disease (COPD), and asthma are increasing.<sup>1(p14)</sup> These last two conditions, along with others, require the use of inhaled corticosteroids (ICS). With these two facts in mind, the likelihood that a person will be given an inhaled corticosteroid while being at risk for, or having, DM increases at the same rate. A link between ICS use and DM incidence or progression could have vast, yet currently unrealized, implications, as this situation, where a patient needs an ICS and has, or is at risk for developing DM, becomes more and more common. It is likely that it will become vital for both patients and Physician Assistants to be familiar with the effects of ICS on blood glucose level control as it relates to DM prevention and treatment.

15% of adults have a condition, such as COPD or asthma, requiring ICS as treatment.<sup>2</sup> 25.8 million, or 8.3%, of people in the US have DM.<sup>3</sup> DM is a very costly disease with the most recent data from the CDC showing costs to the US of \$174 billion dollars for healthcare related to DM.<sup>3</sup> While a firm number of visits to healthcare providers is hard to establish, \$116 billion dollars were spent on direct medical costs of the above \$174 billion. Also, people with DM spent 2.3 times more on healthcare in 2007 than people without diabetes when variability between different ages and sexes are taken into account.<sup>3</sup> DM has a very real impact on the time patients spend seeking healthcare and how much money they have to spend on that care.

Usually, to treat DM, there are several options used: insulin, sulfonylureas, meglitinides, biguanides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, or DPP-4 inhibitors. To treat asthma or COPD, there are several inhaled corticosteroids available including flunisolide, triamcinolone acetonide, beclomethasone dipropionate, fluticasone propionate, or budesonide. Further, other

medications such as salmeterol, formoterol, albuterol, or levalbuterol can also be used to treat these conditions in conjunction with ICS.<sup>2</sup>

It is known that oral corticosteroids (OCS) impair insulin action, which can lead to hyperglycemia.<sup>4</sup> Further, both serum glucose and glycated hemoglobin (HbA1c) are used to distinguish between a disease state where a person has DM, is pre-diabetic, and when a person does not have DM. These same levels are also used to monitor the disease state once a person has a diagnosis of DM.<sup>2</sup> Since it is known that OCS can impact DM onset and control by affecting blood glucose levels, it stands to reason that inhaled corticosteroids could have a similar effect on insulin action. Given the rise in people being diagnosed with a condition requiring ICS, and that many people are facing rising risk factors for DM, due to the obesity epidemic in the United States<sup>5</sup>, is close glucose monitoring needed to prevent incidence and progression of DM in those using ICS?

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not inhaled corticosteroids (ICS) cause an increased risk for developing or worsening a patient's diabetes mellitus (DM).

## **METHODS**

The studies selected for this review focused on patients over the age of 18 who presented using ICS or with indications for use of ICS. This class of drug also served as the interventions for the studies and was compared to placebo and/or other medications. The outcomes measured were progression to diabetes, change in anti-diabetic medication, or use of insulin.

Three types of studies were included in the review. One was a new-user cohort of patients and a nested case-control analysis. Next, a randomized control trial (RCT) was used. Finally, a

prospective randomized, double blind, double dummy, placebo-controlled, crossover investigation was utilized for the review.

All the studies for this review were found using the Ovid MEDLINE, PubMed, and Cochrane databases. The studies are all English language primary studies published between 1993 and 2010. The key words used in the searches were inhaled corticosteroids and diabetes. The articles were selected based on the following inclusion criteria: first, the studies were either RCTs or another form of primary research; second, the outcomes of the trials were found to be patient oriented evidence that matters (POEMS); third, the articles had been published in peer-reviewed journals; finally, the articles had not been used in a previously published systematic review (SR) or meta-analysis (MA). If the study had disease-oriented evidence (DOE) only, or had previously been used in an SR or MA, the study was excluded from this review. From these criteria, three studies were chosen for review: The effect of an inhaled corticosteroid on glucose control in type 2 diabetes (Faul et al)<sup>1</sup>; Effect of eight months of inhaled beclomethasone dipropionate and budesonide on carbohydrate metabolism in adults with asthma (Kiviranta et al)<sup>6</sup>; and Inhaled corticosteroids and the risks of diabetes onset and progression (Suissa et al)<sup>7</sup>.

The studies chosen for this review used the following statistics in reporting their data: mean change from baseline; p-value; relative risk increase; absolute risk increase; number needed to harm; median change from baseline; rate ratios; and confidence intervals.

Table 1: Table of Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion Criteria	W/D	Interventions
Faul, 2009	Prospective randomized, double-blind, double-dummy placebo-controlled, crossover investigation	14	52-76	≥18 yo, DM2 by fasting plasma glucose >126 mg/dl, physician dx either asthma or COPD	Tobacco use w/i 6mo; exacerbation of asthma/COPD w/i 3 mo; current insulin use; use of systemic corticosteroids or ICS, leukotriene receptor antagonists, or theophylline w/i 1mo; inability to read/complete diary card; inability to perform PEF/spirometry; inability to use MDI with spacer	2	Inhaled fluticasone propionate (440 µg twice daily) and oral montelukast (10mg/day)
Kiviranta, 1993	RCT	30 (15 with asthma, 15 control)	18-56	≥18yo, unstable asthma	Glucocorticoid use	0	Inhaled beclomethasone dipropionate and budesonide
Suissa, 2010	New-user cohort of patients and a nested case-control analysis	388,584	66 (±15)	Dispensed ≥3 prescriptions for respiratory medications in a 1-year period	Diagnosis of diabetes or dispensed a prescription for an anti-diabetic drug	0	Inhaled corticosteroids of any type

## **OUTCOMES MEASURED**

The studies focused on various aspects of monitoring blood sugars and medication use as related to the diagnosis and treatment of DM. The Faul et al study measured glucose control in type 2 diabetic patients to avoid diabetic treatment changes using HbA1c levels.<sup>1</sup> Kiviranta et al measured insulin resistance possibly leading to a diagnosis of diabetes and glucose intolerance possibly leading to a diagnosis of diabetes. This was done using the oral glucose tolerance test (OGTT).<sup>6</sup> Finally, Suissa et al measured incidence of diabetes and progression in severity of diabetes. Since the study was a nested case-control analysis, it measured when patients were advanced in their DM treatment or when anti-diabetic medication was initiated according to the patient's medical record.<sup>7</sup>

## **RESULTS**

Faul et al used ten people from an outpatient setting with concomitant DM and asthma or COPD broken into two groups. One received inhaled fluticasone propionate and oral placebo, the other oral montelukast and inhaled placebo for six weeks at the end of which, the groups were crossed over to the other treatment regimen for another 6 weeks. The inclusion criteria were: 18 years of age or older; type 2 DM; and a physician diagnosis of asthma or COPD on their medical records. Patients were excluded if they used tobacco within 6 months of enrollment in the trial, had an exacerbation of asthma/COPD within 3 months of the trial's start, were currently using insulin, used corticosteroids or leukotriene receptor antagonists or theophylline within 1 month of the trial, had an inability to read or write well enough to fill out the diary, were unable to perform pulmonary function tests, or had an inability to use a metered dose inhaler (MDI) with spacer.<sup>1</sup> ICS effect on glucose control was evaluated by this study as shown in Table 2. The primary outcome measured was the difference between patients' HbA1c levels after six weeks of



fluticasone and when they had been on oral montelukast for six weeks. The second outcome measured was the change from baseline of a patient after each therapy. Mean change from baseline was +0.11 with fluticasone (SD 0.17). 20% of patients experienced an increase in HbA1c with oral montelukast while 70% of patients experienced some increase in HbA1c with fluticasone. The absolute risk increase was 50% with a number needed to harm of 2. While the difference in changes of HbA1c were not statistically significant (p-value <0.025), the researchers highly recommend close monitoring of type 2 diabetes patients needing inhaled steroid treatment due to the large percentage of trial patients who experienced some change in their HbA1c levels. Also prompting the recommendation was the low number needed to harm (NNH), which, in this study, refers to the number of patients who experienced a change in their HbA1c while taking ICS. Two patients were removed for non-compliance before randomization of the subjects. Additionally, two patients were removed for non-compliance after the trial began, one from each arm of the trial, so their data were simply excluded since the number of subjects in both arms remained the same. Phone contact was made weekly with the subjects to ensure their compliance with treatment throughout the trial.<sup>1</sup>

Table 2: Faul - Higher HgbA1c after 6 weeks of therapy<sup>1</sup>

CER <sup>a</sup>	EER <sup>b</sup>	RRI <sup>c</sup>	ARI <sup>d</sup>	NNH <sup>e</sup>	p-value
20%	70%	2.5	50%	2	<0.025

a = CER (Control Event Rate) = % of patients with higher HbA1c on oral montelukast

b = EER (Experimental Event Rate) = % of patients with higher HbA1c on inhaled fluticasone propionate

c = RRI (Relative Risk Increase), d = ARI (Absolute Risk Increase), e = NNH (Number Needed to Harm)

Kiviranta et al studied the effects on carbohydrate metabolism in adults of both inhaled beclomethasone dipropionate and budesonide at low doses for five months, followed by high

doses of these drugs for three months. Fifteen individuals with unstable asthma were matched with fifteen healthy controls for the study. Patients were included if they had currently unstable asthma, and excluded if they had a previous history of glucocorticoid use. This study primarily evaluated the control of asthma, but as a secondary outcome, blood glucose and insulin sensitivity were also measured.<sup>6</sup> This aspect of the study was measured using median change from the baseline blood glucose and serum insulin levels of each patient. At the onset of the study, patients were admitted to a hospital to establish a baseline for measuring their blood glucose and serum insulin levels. Table 3 shows that the median fasting blood glucose decreased from 4.8 mmol/L to 4.5 mmol/L at 1 month, rose to an average of 4.8 mmol/L at 5 months, and dropped to 4.7 mmol/L at 8 months ( $p < 0.05$ ). Median change from baseline with fasting serum insulin levels increased from 8 mU/L to 10 mU/L with beclomethasone and decreased from 9 mU/L to 7 mU/L with budesonide at 1 month. Values for both medications leveled off around 8 mU/L for the remaining reported values at 5 and 8 months (beclomethasone –  $p < 0.005$  and budesonide –  $p < 0.01$ ). The reported statistics could not be converted to dichotomous data.<sup>6</sup> No mention was made of how the compliance of patients was followed within the article.

Table 3: Kiviranta – Median change in blood glucose and serum insulin from baselines<sup>6</sup>

	Baseline		1 Month		5 Months		8 Months	
	BDP <sup>a</sup>	BUD <sup>b</sup>	BDP	BUD	BDP	BUD	BDP	BUD
Fasting Blood Glucose <sup>c</sup>	4.8 (4.6-5.4)	4.8 (4.2-5.3)	4.5 (4.1-4.9)	4.5 (4.0-5.4)	4.7 (4.3-5.6)	4.9 (4.2-5.3)	4.7 (4.5-5.0)	4.7 (4.1-5.4)
Fasting Serum Insulin <sup>d</sup>	8 (6-15)	9 (6-22)	10 (5-15)	7 (5-20)	8 (4-35)	8 (5-24)	7 (5-10)	8 (6-25)

c,d = p-values: Fasting Blood Glucose  $< 0.05$ , Fasting Serum Insulin  $< 0.05$  (BDP) and  $< 0.01$  (BUD)

Ranges in parentheses, a = BUD = Budesonide, b = BDP = Beclomethasone Dipropionate  
Fasting Blood Glucose in mmol/L, Fasting Serum Insulin in mU/L

Suissa et al formed a cohort of 388, 584 adult patients who were treated in Quebec's health system for respiratory disease. These patients were followed using data gleaned from the records of patients from health insurance databases. The patients were studied until the year 2007, or until they experienced diabetes onset/progression. The authors of the study formed a cohort of people who had received a prescription for medication for a respiratory condition at any point during a one-year period. Patients were excluded from selection if they had a diagnosis of diabetes or had taken anti-diabetic medication before the beginning of the study. Once patients had progressed to the point of diabetes, those patients who were given a prescription for an anti-diabetic medication during the period of study were grouped into a sub-cohort. Patients that were given insulin as their first anti-diabetic medication were excluded from this sub-cohort. Ten random records matched for age to the patients of interest in the study were selected to serve as controls for each case followed by the study.<sup>7</sup> The study focused on whether or not ICS use would cause DM onset or speed progression to insulin use in patients with DM. As Table 4 shows, Dichotomous data were not presented, but rather rate ratios were calculated for incidence of diabetes (34%) and progression from oral hypoglycemic agents to insulin (34%). The increased rate of incidence of diabetes was 34% (Rate Ratio of 1.34) with a 95% confidence interval (CI) of 1.29-1.39. Oral hypoglycemic to insulin progression was increased at a rate of 34% (Rate Ratio of 1.34) as well, with a 95% CI of 1.17-1.53.<sup>7</sup> Since the study was done only using medical records, there was no way of ascertaining compliance during the time period studied.

Table 4: Suissa – Rate Increase in Incidence and Progression of DM with ICS use<sup>7</sup>

	Rate Increase	Rate Ratio	95% CI
Incidence <sup>a</sup>	34%	1.34	1.29-1.39
Progression <sup>b</sup>	34%	1.34	1.17-1.53

a = Incidence refers to new incidence of DM

b = Progression refers to change from oral anti-diabetes medication to insulin

Neither the Faul et al, nor the Kiviranta et al trials had any adverse effects reported during their studies. Suissa et al did not report on adverse effects in their nested case-control study because the data was collected purely from medical records, making it difficult to directly link any potential adverse effects to a single intervention.<sup>7</sup>

## DISCUSSION

ICS are widely used to treat asthma and COPD.<sup>7</sup> ICS are first-line treatments for persistent asthma and are given to any age patient.<sup>8</sup> While used for COPD, ICS are only useful in limited situations when a patient has frequent exacerbations and in those cases are prescribed in high doses.<sup>9</sup> “ICS have been shown to have systemic effects, but their effect on glucose metabolism in patients with type 2 diabetes has not been well defined. Although considered a safe therapy, there are concerns about the systemic effects of ICS.”<sup>1(p14)</sup> OCS have clearly been shown to cause an increased risk of DM, and since ICS are inhaled versions of the same class of drugs, albeit with a different delivery, a similar set of reactions may occur with their use, prompting the concerns about systemic effects.

The studies by Faul et al and Kiviranta were limited in size with ten and thirty subjects respectively. Faul et al were limited in the length of time patients were treated with fluticasone in their study. The 6-week period of treatment was shorter than may have been needed to see the full effects of the medication, since the study measured HbA1c and red blood cells have a half-life of sixty days. This could have affected the validity of measuring the effects of the fluticasone

treatment using HbA1c.<sup>1</sup>

## CONCLUSION

Faul et al concluded that glucose control was affected by therapy with ICS, but to a degree smaller than would usually be clinically relevant. However, since the diseases are all increasing in prevalence, initiating a patient on ICS should prompt the clinician to consider monitoring his or her blood glucose levels more closely than otherwise might be needed, especially if the patient is diabetic.<sup>1</sup> Kiviranta et al determined that an early decrease in insulin resistance occurs, but with prolonged therapy, a slight decrease in insulin sensitivity prevails.<sup>6</sup> Suissa et al related high doses of ICS to an increased risk of incidence of DM.<sup>7</sup> Also, patients with DM were more likely to progress to needing treatment with insulin.<sup>7</sup>

The evidence demonstrates that receiving inhaled corticosteroids increases a patient's risk for developing DM or worsening a patient's existing DM. The risk is small according to two of the three studies, which leads to the conclusion that while the risk exists, it should not preclude initiation of treatment, nor prompt discontinuation of treatment. Close monitoring, however, is strongly supported by the evidence within the studies analyzed.

Two of the three studies did not strongly differentiate between asthma and COPD, so disease specific studies for both asthma and COPD would be excellent areas for further study. Since the dosing and length of time a person is exposed to an ICS is different between the two diseases, studying each disease separately may yield different conclusions from when they were combined.<sup>8,9</sup> Also, the weight of patients was not factored into the calculations done by the studies. While this is not directly linked to either COPD or asthma, it is related to an increased risk for DM. Further, obese patients may have difficulty breathing due to their excess weight,

which may worsen coexisting asthma or COPD.<sup>10</sup> It therefore bears further research to specifically evaluate obese patients using ICS. Lastly, since the peak age of asthma onset is 3 years old,<sup>8</sup> it would be of benefit to study the effects of ICS use in children and adolescents. In the studies used for this review, only adults were considered. In addition, long term use of ICS in patients who have reached adult age and have used an ICS continuously since childhood or adolescence would give insight into the potential long-term risks for DM onset or progression of the most common population to have prolonged ICS exposure.<sup>2</sup>

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