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MINIREVIEWS

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

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Abstract

Inhaled corticosteroids (ICS) and intranasal corticosteroids (INS) are the mainstays of treatment for chronic respiratory diseases like asthma, chronic obstructive pulmonary disease, and allergic rhinosinusitis. In addition, these localized forms of steroid therapy are generally considered to have fewer systemic side effects compared to long-term oral corticosteroids. However, concern and controversy remain over the impact of ICS and INS on the incidence and control of diabetes mellitus (DM). Given the widespread use of ICS and INS, even small individual effects on DM could lead to large consequences for the global population. Multiple large observational studies suggest that high dose ICS is associated with increased incident DM and worsened DM control, though the contribution of other risk factors is less certain. In addition, only two studies were done to investigate the association of INS and DM, with both studies demonstrating a short-term association of INS use with hyperglycemia. While more research evaluating the risk of ICS/INS for DM-related adverse events is needed, 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, and appropriate de-escalation of high ICS doses.

Key Words: Beclomethasone; Budesonide; Fluticasone; Glucocorticoids; Glucose; Hyperglycemia

Core Tip: Inhaled corticosteroids (ICS) and intranasal corticosteroids (INS) are the mainstays of treatment for chronic respiratory diseases like asthma, chronic obstructive pulmonary disease, and allergic rhinosinusitis. Multiple large observational studies suggest that high dose ICS is associated with increased incident diabetes mellitus (DM) and worsened DM control, though the contribution of other risk factors is less certain. In addition, only two studies were done to investigate the association of INS and DM, with both studies demonstrating a short-term association of INS use with hyperglycemia.

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INTRODUCTION

Corticosteroids are important anti-inflammatory drugs that are widely used in respiratory disease. Inhaled corticosteroids (ICS) are the mainstay of treatment for patients with asthma[1]. ICS are also added to dual bronchodilators for patients with chronic obstructive pulmonary disease (COPD) who have frequent exacerbations and peripheral eosinophilia ≥ 300 cells/μL[2]. Like ICS for asthma and eosinophilic COPD, intranasal corticosteroids (INS) are the key medications to treat allergic rhinitis[3]. Given the high global prevalence of asthma, COPD, and allergic rhinitis, widespread use of ICS and INS is expected[4,5].

Diabetes mellitus (DM) is another disease with a high global burden[6]. Complications of uncontrolled DM include coronary artery disease, peripheral vascular disease, kidney failure, and eye disease, and can be a serious threat to both quality of life and survival[7]. As such, reducing both the development of DM, and the worsening of DM control, would be crucial in reducing the global burden of DM. Apart from antidiabetic drugs, prevention of chronic hyperglycemia would also be helpful. Therefore, long-term use of drugs that impair glucose metabolism, such as oral steroids, should be avoided[8]. However, it is uncertain if ICS and INS have systemic effects on glucose metabolism, and if ICS and INS increase the risk of incident DM (*i.e.,* development of new cases of DM) or worsen DM control. Therefore, this paper will use clinical data from human studies and review the impact of ICS and INS on DM incidence or control.

PHARMACOLOGY OF ICS AND INS

Corticosteroids are synthetic glucocorticoids, which differ in glucocorticoid receptor binding affinity and potency[9]. For ICS and INS, all corticosteroids are administered as active forms, except for beclomethasone dipropionate and ciclesonide, which are prodrugs requiring metabolism to active forms. The more potent agents used as ICS and INS are fluticasone furoate, mometasone furoate, fluticasone propionate, beclomethasone dipropionate (*via* its active metabolite beclomethasone monopropionate), and ciclesonide (*via* its active metabolite desisobutyryl ciclesonide). The less potent agents used as ICS and INS are budesonide, triamcinolone acetonide, and flunisolide. In general, the more potent glucocorticoids can be used in smaller doses to achieve the same anti-inflammatory effect as the less potent agents. In addition, given lower delivered doses, use of more potent glucocorticoids does not necessarily translate into more adverse effects.

For ICS, the delivered dose enters the systemic circulation *via* two routes[10]. The first route is *via* the gastrointestinal tract, where 60%-90% of the delivered dose is deposited in the oropharynx, swallowed into the stomach, absorbed through the intestines, and metabolized by the liver. Hepatic metabolism renders most of the systemically absorbed ICS inactive, even for corticosteroids with significant oral bioavailability (*e.g.,* beclomethasone dipropionate, budesonide, triamcinolone acetonide, and flunisolide). The second route by which ICS enters the systemic circulation is *via* the lungs, where the remaining 10%-40% of the delivered dose passes directly into the systemic circulation. ICS absorbed *via* the lung bypasses hepatic first-pass metabolism, and exerts greater systemic impact compared to ICS absorbed *via* the gastrointestinal tract.

For INS, the drug is sprayed as an aqueous suspension into the nose, with a relatively short dwell time of < 1 h[3]. Given rapid nasal ciliary clearance, much of the drug runs off after some absorption into the nasal mucosa. As such, systemic effects, if any, would arise from entry *via* the gastrointestinal tract. Like swallowed ICS, swallowed INS would also undergo first-pass metabolism in the liver with oral bioavailability depending on the type of corticosteroid.

EFFECT OF ICS AND INS ON GLUCOSE METABOLISM AND DM

Glucocorticoids drive hyperglycemia *via* increased hepatic gluconeogenesis and decreased hepatic/adipocyte glucose uptake, mediated by the glucocorticoid receptor in the cytoplasm of peripheral tissues (primarily liver, skeletal muscle, and adipose tissue)[11-13] (Figure 1) and possibly by hepatic activation of Krüppel-like factor 9[14]. Risk factors for hyperglycemia involve patient factors and drug factors. Patient factors include age and diseases that predispose to

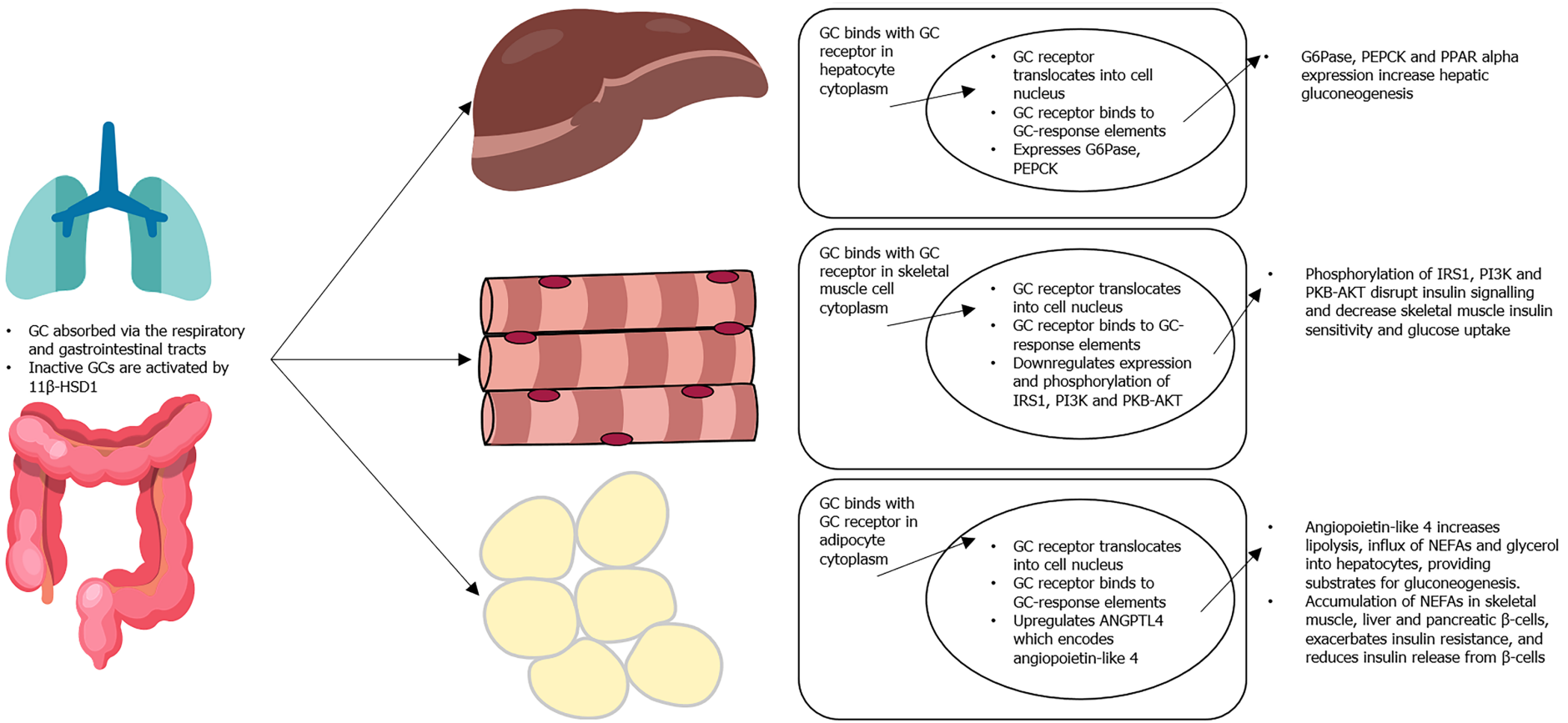

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Figure 1 Molecular signaling pathway of glucocorticoid-induced hyperglycaemia. GC: Glucocorticoid; G6Pase: Glucose-6-phosphatase, encoded by G6PC1; HSD1: Hydroxysteroid dehydrogenase type 1; IRS: Insulin receptor substrate; NEFA: Non-esterified fatty acid; PEPCK: Phosphoenolpyruvate carboxykinase, encoded by PCK1; PI3K: Phosphatidylinositol 3-kinase; PKB-AKT: Protein kinase B; PPAR: Peroxisome proliferator-activated receptor. Open-source clipart images from freesvg.org and scidraw.io.

hyperglycemia such as obesity. Drug factors include ICS/INS dose, corticosteroid formulation/potency, regular *vs* intermittent use of ICS/INS, and medications that inhibit cytochrome P450 3A4 and therefore hepatic metabolism of systemically absorbed ICS/INS. When hyperglycemia becomes chronic, DM and its complications may develop. Biochemically, chronic hyperglycemia can be reflected as elevations of fructosamine (indicates average serum glucose concentration over the preceding 2-3 wk)[15] and, more commonly, glycated hemoglobin (HbA1c).

Clinical studies investigating the association of ICS/INS have differing results. Some show no worsening of glucose metabolism or DM (Table 1), while others show worsening (Table 2). Multiple study designs from case reports to

Table 1 Studies showing no worsening of glucose metabolism/diabetes mellitus by inhaled corticosteroid/intranasal corticosteroid

Ref.	Study design	Patient population	ICS or INS exposure	Outcomes reported
Blackburn *et al* [18], 2002	Population-based cohort study	38441 elderly (≥ 66 years old) ICS users versus 53845 non-ICS users	Types and doses of ICS not stated	Over 3 yr, no association of ICS with incident DM
Borsi *et al*[36], 2018	Non-randomized trial	35 non-diabetic adults with mild to moderate asthma	BUD ICS 320 mcg every 12 h	Over 2 mo, ICS had no effect on HbA1c, insulin level and insulin sensitivity (HOMA-IR)
Canis *et al*[37], 2007	Non-randomized trial	Non-diabetic adults (12 asthma, 6 COPD)	BUD ICS 400 mcg twice daily	Over 8 wk, ICS had no effect on glucose, insulin level and insulin sensitivity (HOMA-IR)
Dendukuri *et al* [38], 2002	Nested case-control study	Adults aged ≥ 65 yr. 1494 cases of incident DM versus 14931 controls	Various types and doses of ICS	No increased risk of incident DM
Ebden *et al*[39], 1989	Prospective observational study	14 normal and 24 diet controlled DM subjects	BDP 2000 mcg/d for 2 wk	Over 2 wk, ICS did not worsen glucose tolerance test results or insulin levels
Faul *et al*[40], 2009	Crossover RCT	12 DM patients with asthma or COPD	FP ICS 440 mcg twice daily versus no ICS	Over 6 wk, no difference in HbA1c
Flynn *et al*[41], 2014	Record linkage study	4305 patients with COPD in Scotland	Various types and doses of ICS	Over at least 2 yr of follow-up, ICS did not increase incident DM or worsen pre-existing DM control
Giep *et al*[42], 1996	RCT	19 ventilator-dependent neonates < 1500 g birthweight	BDP ICS 1 mg/kg/d *via* ventilator circuit	No effect on blood glucose
Kiviranta and Turpeinen[20], 1993	Prospective observational study	15 adults with uncontrolled asthma; 15 healthy controls	Up to 2000 mcg/d of BDP ICS, and up to 1600 mcg/d of BUD ICS	Over 8 mo, no change of fasting glucose and insulin
Lee *et al*[33], 2016	Nested case-control study using South Korean claims database	Pregnant women who delivered between 1 January 2009 and 31 December 2011. 34190 GDM cases and 170934 control subjects	Various types and doses of ICS	ICS use was not associated with increase in the risk of GDM
Lempp *et al* [43], 2022	Electronic medical records study	127 patients aged 18 to 80 with COPD and type 2 DM on at least 2 oral anti-glycemic medications from 1 January 2000 to 31 December 2017	ICS (64 patients) versus no ICS (63 patients). Various types and doses of ICS	Over 5 yr, no difference in rate of DM worsening to HbA1c > 10% (threshold chosen as add-on insulin would be considered)
O'Byrne *et al* [21], 2012	Pooled analyses of RCTs	44528 patients with asthma (60 trials) or COPD (8 trials)	BUD and fluticasone ICS at various doses	Over a mean follow-up of 210 d in asthma trials and 268 d in COPD trials, no association between ICS use and hyperglycemia or incident DM
Pauwels *et al* [19], 1999	RCT	1277 adults with COPD and continued smoking	BUD ICS 400 mcg/d for 3 yr versus placebo	No increase in incident DM by BUD ICS 400 mcg/d
Pu *et al*[44], 2021	Systematic review of 17 RCTs which reported glucose/DM data	43430 adults with COPD	Various types and doses of ICS	No difference in glucose level, DM control or incident DM between the ICS group and the control group with follow-up ranging from 12-96 wk
Rogala *et al* [45], 2020	Cross-sectional study	6763 adult patients with asthma and/or diabetes	Various types and doses of ICS	No association with increased fasting glucose
Rogliani *et al* [46], 2014	Cross-sectional study	493 outpatients with COPD, seen between 2010-2012	Types and doses of ICS not stated	No association between ICS use and DM diagnosis
Rahman *et al* [47], 2021	RCT	70 patients with asthma, but no DM	Fluticasone ICS (at low to high doses) *versus* no ICS	Over 3 mo, no difference in fasting plasma glucose, 2 h after 75 g oral glucose intake, and in HbA1c
Slatore *et al* [48], 2009	Prospective cohort study	1698 adults with COPD	Various types and doses of ICS	No change of serum glucose in subjects without diabetes
Turpeinen *et al* [49], 1991	Prospective observational study	9 children with asthma	400-800 mcg/m^2/d of BUD ICS	Over 5 mo, no change of fasting glucose and insulin
Yucel *et al*[50], 2009	Case-control study	141 children with asthma (cases), 52 children without asthma (controls). All children did not have DM	75% of children were using on BUD ICS, and 25% of children were using FP ICS, at various doses	No significant association between cumulative dose of ICS and HbA1c

BDP: Beclomethasone dipropionate; BUD: Budesonide; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; FP: Fluticasone propionate; GDM: Gestational diabetes mellitus; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance;

ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; RCT: Randomized controlled trial.

randomized control trials have been employed, with the largest studies tapping on population registries. All the studies explored ICS as the exposure variable, while only two studies focused on INS[16,17].

Among the studies showing no worsening of glucose metabolism/DM by ICS/INS (Table 1), patients with both asthma and COPD were followed up for as long as three years[18,19]. The doses of ICS/INS range from intermediate to relatively high doses (up to 2000 mcg/d of beclomethasone dipropionate ICS, and up to 1600 mcg/d of budesonide ICS) [20]. Some studies, though large, did not collect DM-related adverse events purposefully, which can lead to false negative findings (*i.e.*, finding no association when a real association is present). For instance, in a pooled analysis of 68 randomized trials for ICS (60 for asthma; 8 for COPD), the number of DM-related adverse events relied on spontaneous adverse event reports only, without formal biochemical validation of DM[21].

Among the studies showing worsening of glucose metabolism/DM by ICS/INS, the smaller studies generally use relatively high doses of ICS (up to budesonide ICS 2000 mcg daily and fluticasone propionate ICS 2000 mcg/d) and demonstrated laboratory abnormalities related to hyperglycemia (*e.g.*, increased HbA1c, glycosuria). Both studies involving INS demonstrated hyperglycemia[16,17]. The case report involving INS suggests that dose matters, as off-label use of high-dose INS in an infant with type 1 DM resulted in hyperglycemia, which resolved when the INS was switched to a standard low-dose formulation[17].

Nonetheless, laboratory abnormalities do not necessarily translate into DM. Development of new DM has only been uncovered in large observational studies[22-27]. Within these large datasets, the risk factors for incident DM associated with ICS/INS use are not always obvious, though some studies have ascribed increased DM risk with higher ICS doses [25-29]. For example, using a Canadian health insurance database, Suissa *et al*[27] studied 388584 patients with respiratory disease, and found that current use of ICSs had a 34% increase in the incidence rate of DM [rate ratio (RR) = 1.34; 95% confidence interval (CI): 1.29-1.39] and a similar increase in the incidence rate of worsening DM control (RR = 1.34, 95%CI: 1.17-1.53). The RRs were greatest for the highest ICS doses, equivalent to at least 1000 mcg/d fluticasone: RR for incident DM 1.64, 95%CI: 1.52-1.76; RR for worsening DM control 1.54, 95%CI: 1.18-2.02. However, apart from ICS dose, and the possible role of increased bioavailability of triamcinolone INS contributing to hyperglycemia[16], other patient-specific or corticosteroid-specific risk factors have not been well-studied.

REDUCING THE IMPACT OF ICS AND INS ON GLUCOSE METABOLISM AND DM

From existing studies, the impact of ICS/INS on glucose metabolism and DM is inconsistent, though the reasons for inconsistency are not completely apparent. Nevertheless, ICS dose has been repeatedly identified as a risk factor in large observational studies, which would have adequate power to uncover significant associations between dose and incident DM. In addition, in the only 2 studies focused on INS, high INS doses were associated with hyperglycemia. Therefore, it is prudent that ICS/INS doses are minimized to obtain benefit while avoiding potential hyperglycemia and DM.

Strategies to minimize ICS and INS doses are outlined in Table 3. In general, non-pharmacological measures should be used to optimize disease control and reduce the reliance on high dose ICS/INS formulations. These non-pharmacological measures include trigger avoidance, smoking cessation, and vaccination to avoid infection. Holistic management of environmental triggers and comorbid conditions such as obesity, obstructive sleep apnea, cardiac dysfunction, anxiety, and depression can be considered as part of a "treatable traits" approach to improve the care of patients with chronic respiratory disease, further reducing the need for high dose ICS/INS. Using this approach, physiological, biochemical, psychosocial, microbiological, and comorbidity traits are targeted with both pharmacological and non-pharmacological interventions[30].

Additionally, non-ICS-containing medications may also be used to improve disease control, *e.g.*, use of long-acting bronchodilators in asthma and COPD[2]. If ICS/INS are needed, dosing strategies such as intermittent dosing can be employed. For asthma, compared to regular ICS use, intermittent dosing with ICS-formoterol has proven to be as effective for prevention of exacerbations in patients with mild asthma, with reduced cumulative exposure to ICS[31]. Finally, de-escalation of high ICS/INS doses should be considered when following up patients with well-controlled disease. Apart from clinically directed de-escalation, biomarkers such as blood eosinophil count can guide clinicians when reducing ICS exposure in COPD[2]. Similarly, exhaled nitric oxide may guide clinicians when reducing ICS exposure in asthma[32].

Although not supported by specific studies, given the pharmacology of ICS, avoidance of strong CYP450 3A4 inhibitors (*e.g.*, clarithromycin, itraconazole, ketoconazole, voriconazole) can preserve the high first-pass metabolism and hepatic inactivation of swallowed ICS and INS. Furthermore, it will be prudent to avoid other causes of hyperglycemia and DM, such as regular, high-dose oral corticosteroids.

FUTURE DIRECTION

Some systemic absorption of ICS/INS is inevitable, and systemic effects would be proportional to the dose of delivered. Apart from dose, other potential risk factors require further elucidation. Nevertheless, even if risk factors have for susceptibility to ICS/INS-related DM are identified, it is unknown how patients who receive ICS or INS should be

Table 2 Studies showing worsening of glucose metabolism/diabetes mellitus by inhaled corticosteroid/intranasal corticosteroid

Ref.	Study design	Patient population	ICS or INS exposure	Outcomes reported
Ajmera *et al* [22], 2017	Retrospective study of Medicaid claims (2005-2008)	15287 adults with newly diagnosed COPD, who were diabetes free at baseline	Types and doses of ICS not stated	Over 1 yr, ICS use associated with greater risk of new-onset diabetes (adjusted OR = 1.23, 95%CI: 1.07-1.47)
Ben-Dov *et al* [17], 2023	Case report	9-mo-old female with type 1 DM	Off-label use of otic ciprofloxacin 0.3%/dexamethasone 0.1% drops in the nasal passage for choanal obstruction with granulation tissue	Over 7 d, average daily blood glucose increased by 86 mg/dL. Hyper-glycemic spikes resolved within 2 d after switching to mometasone furoate 0.05% spray
Faul *et al* [51], 1998	Case report	67-year-old asthmatic man	FP ICS 2000 mcg/d	Over 40 wk, patient developed glycosuria with rise of HbA1c to 8.2%. Glycosuria resolved and HbA1c fell to 7.0% with reduction of FP ICS to 500 mcg/d
Faul *et al* [52], 1999	Case report	67-year-old asthmatic man	BUD ICS 2000 mcg/d	Over 20 wk, patient developed glycosuria with rise of HbA1c to 8.2%. Glycosuria resolved and HbA1c fell to 7.2% with reduction of BUD ICS to 800 mcg/d
Gayle *et al* [23], 2019	Nested case-control study	220971 adults with COPD and previous smoking registered at a United Kingdom Clinical Practice Research Datalink practice (January 2010-December 2016)	Types and doses of ICS not stated	Increased incident DM (OR = 1.73, 95%CI: 1.65-1.82), adjusted for smoking status, deprivation, BMI, hypertension, coronary heart disease and heart failure
Kruszynska *et al*[53], 1987	Prospective observational study	9 normal adults aged 21-44 yr	BDP ICS 500 mcg twice daily	Over 4 wk, ICS use associated with increased peak blood glucose (7.1 *versus* 6.7 mmol/L, $P < 0.01$) after 75 g oral glucose load. No effect on fasting blood glucose or HbA1c
Lelii *et al* [54], 2016	Case report	2-year-old boy with recurrent wheezing	FP ICS 100 mcg twice daily for 2 mo before presentation with whining, agitation, and diuresis	Transient symptomatic hyperglycemia (10 mmol/L). FP ICS then replaced with montelukast
Lund *et al* [24], 2023	Case-only symmetry analysis of Danish national registries	348996 individuals > 40 yr with a first-ever prescription for any antidiabetic drug 1996-2018	Inhaled β2-agonists combined with glucocorticoids	Increased risk of incident diabetes (SR = 1.35, 95%CI: 1.28-1.42 and SR = 1.14, 95%CI: 1.06-1.22 in replicate analyses)
Metsälä *et al* [25], 2020	Nationwide, register-based case-cohort study	Children who were born January 1, 1995, through December 31, 2008, in Finland and diagnosed with type 1 DM by 2010 (n = 3342), compared with 10% random sample from each birth-year cohort (n = 80909)	Beclomethasone, BUD, fluticasone. Dose not stated	Over a median of 7.9 yr, increased risk of type 1 DM after adjusting for other anti-asthmatic drugs, asthma, sex, and birth decade (HR = 1.29, 95%CI: 1.09-1.52), if patients received high-dose ICS (> 800 mcg budesonide equivalent dose)
Mizrachi *et al* [16], 2012	Retrospective observational study	1768 DM patients treated with INS, with 245 patients providing HbA1c data and 163 patients providing fasting glucose data	BUD, FP, triamcinolone acetonide INS. Dose not stated	Over 3 mo, triamcinolone acetonide associated with increased fasting glucose but not with HbA1c. Other INS had no association with either glucose or HbA1c changes
Price *et al* [28], 2016	Matched cohort study	682 adults (≥ 40 years old) with COPD prescribed ICS in two large United Kingdom databases (1983-2016)	Types and doses of ICS not stated	Over 12-18 mo of follow-up, ICS prescription associated with increased HbA1c, with adjusted difference 0.16% (95%CI: 0.05%-0.27%) in all COPD patients, and 0.25% (95%CI: 0.10%-0.40%) in mild-to-moderate COPD patients. ICS prescription also associated with more diabetes-related general practice visits and more frequent glucose strip prescriptions. Associations were stronger for higher cumulative ICS doses (> 250 mg FP equivalent), compared to ≤ 125 mg
Price *et al* [26], 2019	Matched cohort study	18774 adults (≥ 40 years old) with COPD initiating ICS or long-acting bronchodilator in two large United Kingdom databases (1983-2016)	Types and doses of ICS not stated	Over a median follow-up at least 3.5 yr, ICS use associated with increased risk of incident DM (HR = 1.27, 95%CI: 1.07-1.50). ICS use also worsened DM control for high-dose ICS (mean daily dose ≥ 500 mcg FP equivalent)
Saeed *et al* [55], 2020	Cohort study using Danish health databases	50148 adults with COPD	Predominantly BUD (about 50%) and fluticasone (about 45%) ICS, at various doses. Other ICS (< 5%) used included beclomethasone, ciclesonide and	Over 7 yr, ICS use was associated with an increased risk of DM (HR = 1.16, 95%CI: 1.01-1.32) for high-dose ICS use (≥ 970 mcg BUD equivalent) and BMI < 30 kg/m^2

			mometasone	
Schou and Wolthers [15], 2011	Crossover RCT	17 children with asthma	BUD ICS 400 mcg daily for 1 wk	Over 1 wk, ICS use increased serum fructosamine compared to no ICS use (228.1 μmol/L *versus* 223.1 μmol/L, $P = 0.02$)
Slatore *et al* [48], 2009	Prospective cohort study	1698 adults with COPD, among United States veterans enrolled in 7 primary care clinics between February 1997 and December 1999	Various types (*e.g.*, beclomethasone, flunisolide, fluticasone) and doses of ICS	Over 2-4 yr, among diabetics only, there was a 1.82 mg/dL (95%CI: 0.49-3.15) increase in serum glucose, for every 100-mcg triamcinolone equivalent/d increase in ICS dose
Ställberg *et al* [29], 2020	Cohort study	7078 Swedish patients with COPD using data from real-world, primary care settings	Types and doses of ICS not stated	Over at least 6 mo, ICS use, especially at high dose (≥ 640 mcg/d BUD equivalent), was associated with incident type 2 DM
Suissa *et al* [27], 2010	Nested case-controlled study using a Canadian health insurance database	388584 patients with respiratory disease	Various types of ICS (beclomethasone, BUD, triamcinolone, fluticasone, flunisolide), at various doses	Over 5.5 yr of follow-up, 34% increased rate of initiation of an anti-diabetic agent, especially in patients receiving high dose ICS (≥ 1000 mcg/d FP equivalent). In diabetics on oral hypoglycemic agents, ICS use increased risk of progression to insulin

BMI: Body-mass index; BUD: Budesonide; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; OR: Odds ratio; FP: Fluticasone propionate; HR: Hazard ratio; ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; RCT: Randomized controlled trial; SR: Sequence ratio.

Table 3 Methods to reduce the impact of inhaled corticosteroid and intranasal corticosteroid on glucose metabolism and diabetes mellitus

Strategy	Methods
Minimize ICS doses	Use non-pharmacological measures (*e.g.*, trigger avoidance, smoking cessation, vaccination to avoid respiratory infections) to optimize disease control and reduce the need for high dose ICS[2]
	Manage comorbid conditions to optimize disease control (*e.g.*, management of obesity, OSA, heart failure, anxiety, depression) and reduce the need for high dose ICS. Consider using the "treatable traits" approach for holistic management of chronic respiratory diseases[30]
	Use long-acting bronchodilators to reduce the need for high dose ICS[2]
	Ensure good inhaler technique (or use valved holding chamber) to improve lung delivery and effectiveness of ICS, reducing the need for high dose ICS[2]
	Consider intermittent formoterol-ICS therapy rather than regular ICS for asthma[31]
	Actively step-down regular ICS dosing, including changing regular to intermittent ICS use, by clinical assessment[31]
	Actively step-down regular ICS dosing by measuring FENO in asthma[32]
	Actively step-down or step-off ICS if peripheral eosinophil count < 300/μL in well-controlled COPD[2]
Minimize INS doses	Use non-pharmacological measures (*e.g.*, trigger avoidance, smoking cessation, vaccination to avoid respiratory infections) to optimize disease control and reduce the need for high dose INS[56]
	Use non-steroidal medications like intranasal antihistamines to reduce the need for high dose INS[56]
	Ensure good intranasal delivery technique to improve effectiveness of INS, reducing the need for high dose INS
	Actively step-down regular INS dosing, including changing regular to intermittent INS use, following clinical assessment, *e.g.*, as-needed intranasal corticosteroids for seasonal allergic rhinitis[57]
Maintain hepatic inactivation of ICS and INS	Avoid strong CYP450 3A4 inhibitors like clarithromycin, itraconazole, ketoconazole, and voriconazole[3,9]
Minimize risk of hyperglycemia	Avoid long-term oral corticosteroids[18]
	Weight management for overweight and obese patients[58]
	Ensure good glycemic control for diabetic patients[58]

COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; FENO: Fractional exhaled nitric oxide; ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; OSA: Obstructive sleep apnea.

screened or monitored. Therefore, future studies need to address both risk factors for DM-related complications of ICS/INS as well as mitigation of DM-related risk. In addition, special populations such as pregnant women require more study[33].

Also, only two studies involving INS have been done to investigate its relationship with hyperglycemia[16,17]. Although the studies demonstrate an adverse association of INS with fasting glucose levels, a more chronic effect is not apparent given the lack of association with HbA1c level. More research for INS is therefore required. These studies need to be large enough to uncover small but significant associations, and long enough to identify chronic hyperglycemia leading to incident DM.

Efforts to disentangle the desired anti-inflammatory effects and diabetogenic consequences of glucocorticoids have led to the discovery of several candidate pharmacological compounds[11]. Selective glucocorticoid receptor agonists and selective glucocorticoid receptor modulators can preserve anti-inflammatory function and minimize induction of hyperglycemia. For instance, caesaldekarine is a promising plant-derived compound that has selective glucocorticoid receptor modulator-like properties[34]. Another approach is to enhance insulin signaling and mitigate hyperglycemia *via* 11β-hydroxysteroid dehydrogenase type 1 inhibition[35].

CONCLUSION

Overall, the association of ICS/INS with DM cannot be ignored, especially given multiple large observational studies demonstrating a positive association and dose-response. As ICS/INS are widely used, even a small individual effect of ICS/INS on DM would be clinically significant on a population basis. To avoid under-recognition of DM-related adverse events, these events should be deliberately collected and validated in future observational cohorts and randomized trials involving ICS/INS. Meanwhile, although ICS/INS are critical agents for control of chronic respiratory diseases, harm minimization should be undertaken by patients and high doses avoided whenever possible.

FOOTNOTES

Author contributions: See KC collected the data, wrote the paper, read and approved the final manuscript.

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