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Impact of inhaled and intranasal corticosteroids on glucose metabolism and diabetes mellitus

See KC. Inhaled and INSs

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

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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.

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. 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[1]. Like ICS for asthma and eosinophilic COPD, intranasal corticosteroids (INS) are the key medications to treat allergic rhinitis[2]. Given the high global prevalence of asthma, COPD, and allergic rhinitis, widespread use of ICS and INS is expected.

Diabetes mellitus (DM) is another disease with a high global burden. 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. 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. 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[3]. 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[4]. 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[2]. 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)[5-7] (Figure 1) and possibly by hepatic activation of Krüppel-like factor 9[8]. Risk factors for hyperglycemia involve patient factors and drug factors. Patient factors include age and diseases that predispose to 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)[9] 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 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[10,11].

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[12,13]. 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)[14]. 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[15].

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[10,11]. 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[11].

Nonetheless, laboratory abnormalities do not necessarily translate into DM. Development of new DM has only been uncovered in large observational studies[32-37]. 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[35-39]. For example, using a Canadian health insurance database, Suissa *et al*[37] 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[10], 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 "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[45].

Additionally, non-ICS-containing medications may also be used to improve disease control, *e.g.*, use of long-acting bronchodilators in asthma and COPD[1]. 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[46]. 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[1]. Similarly, exhaled nitric oxide may guide clinicians when reducing ICS exposure in asthma[47].

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 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[23].

Also, only two studies involving INS have been done to investigate its relationship with hyperglycemia[10,11]. 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[5]. 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[51]. Another approach is to enhance insulin signaling and mitigate hyperglycemia *via* 11β-hydroxysteroid dehydrogenase type 1 inhibition[52].

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.

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