Current Perspectives on the Contribution of Inhaled Corticosteroids to an Increased Risk for Diabetes Onset and Progression in Patients with Chronic Obstructive Pulmonary Disease

Felix J.F. Herth a, b, Peter Bramlage c, Dirk Müller-Wieland d

a Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg, and b Translational Lung Research Center Heidelberg, Heidelberg, c Institute for Pharmacology and Preventive Medicine, Mahlow, and d Department of Internal Medicine, Endocrinology, Diabetes and Metabolism, Asklepios Klinik St. Georg, Hamburg, Germany

Key Words
Chronic obstructive pulmonary disease · Diabetes · Hyperglycemia · Inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD), which is characterized by progressive airflow limitation, is predicted to become the third leading cause of death globally in 2030 [1]. COPD results from long-term exposure to inhaled irritants (e.g., air pollution or smoking), which cause robust inflammatory responses in the lungs and several prominent symptoms, including shortness of breath, coughing, and sputum production. Moreover, COPD is known to be associated with several important chronic comorbid diseases [2]. In particular, recent evidence has supported that COPD may constitute an important risk factor for the development of type-2 diabetes [2, 3], and several studies have identified an increased prevalence of diabetes in COPD patients [4–8].

The treatment of COPD involves lifestyle modifications as well as various pharmacotherapies. In fact, due to the presence of inflammation in COPD, corticosteroids have been used for decades to treat acute exacerbations of COPD (AECOPD) [9]. Current estimates suggest that...
corticosteroids are administered to over 70% of COPD patients in the USA and Europe [10]. These drugs can be delivered either systemically or through the respiratory tract as inhaled corticosteroids (ICS). In this regard, the most commonly used ICS for the treatment of COPD are fluticasone propionate, budesonide, and beclometasone dipropionate. Although these corticosteroids are routinely employed and generally considered to be safe and effective for the short-term treatment of severe COPD-associated symptoms [11–13], it is known that prolonged exposure to corticosteroids can lead to substantial side effects [14]. Thus, there is ongoing controversy surrounding the use of ICS [10, 15, 16], especially at high doses, which are routinely used in the clinic for the treatment of COPD [17, 18].

Several recent studies have raised concern regarding potential adverse effects associated with the use of ICS, including enhanced susceptibility to pneumonia, influenza, cataracts, and fractures as well as tuberculosis [19–22]. In addition, investigations have supported the role of ICS in increasing the risk of hyperglycemia and type-2 diabetes in COPD patients [23, 24]. Nevertheless, this side effect of ICS therapy remains controversial [25, 26], and the mechanisms by which ICS may contribute to diabetes development remain ill defined. In particular, the roles of ICS pharmacokinetics and patient characteristics have not been thoroughly investigated.

In this review, we critically discuss current evidence regarding the relationship between ICS therapy in COPD patients and an increased risk for the incidence and progression of type-2 diabetes. In addition, we discuss therapeutic conditions (e.g. dosing and pharmacokinetics), clinical implications, and future perspectives related to this potential ICS-associated adverse effect in COPD patients.

**Methods**

**Systematic Search of the Literature**

Electronic literature searches were performed using PubMed in June 2014. To identify information related to the association between ICS use and diabetes in COPD patients, the term ‘inhaled corticosteroids’ was searched in combination with each of the following terms: ‘diabetes’ and ‘hyperglycemia’. Also, additional searches were performed to identify factors that might contribute to ICS-induced side effects, such as diabetes, in COPD patients. For this, the term ‘inhaled corticosteroids’ was searched in combination with each of the following terms: ‘chronic obstructive pulmonary disease’ and ‘COPD’. These systematic searches were then extended through manual screening of the references included in the selected papers in order to identify further supporting information.

**Evidence Linking ICS to Diabetes Risk in COPD Patients**

**ICS-Induced Hyperglycemia**

Recent evidence supports the association of ICS therapy with insulin resistance, hyperglycemia, and diabetes in COPD patients (table 1). In fact, patients with type-2 diabetes, who were predominantly taking ICS for lung-related conditions, were found to exhibit poorer glycemic control [i.e. higher glycated hemoglobin (HbA1c) levels] than those who did not receive ICS [27]. Furthermore, Slatore et al. [23] conducted a prospective cohort study involving 1,698 US veterans (approximately 85% with COPD) and found a dose-dependent effect of ICS therapy (beclometasone, flunisolide, and fluticasone) on serum glucose concentrations in patients with self-reported diabetes [23]. Notably, the mean ICS daily doses used in the study were 621 μg (SD = 555) and 610 μg (SD = 553) for subjects with and without diabetes, respectively (reported in triamcinolone equivalents). Among patients with diabetes, it was found that for each 100-μg increment in ICS dose there was an associated 1.82 mg/dl increase in serum glucose concentration. Moreover, subjects treated with antidiabetic drugs showed an increase of 2.65 mg/dl in serum glucose for every additional 100 μg of ICS. Thus, when considering published data regarding the conversion of serum glucose to HbA1c values (i.e. every 29 mg/dl increase in glucose equals a 1% rise in HbA1c) [28], these reported changes correspond to respective HbA1c augmentations of around 0.06 and 0.1% for every 100 μg of triamcinolone. Also, based on these findings it was estimated that subjects with diabetes taking 500 μg of fluticasone twice daily would experience an overall increase in serum glucose concentration of 72.8 mg/dl [23]. Strik-
ingly, this correlates with a 2.5% elevation in HbA1c [28]. Nevertheless, this study did not find similar ICS-associated blood sugar changes in nondiabetic patients. That being said, an investigation examining the effects of inhaled budesonide on insulin sensitivity in nondiabetics with asthma and COPD found that glucose rose significantly following ICS treatment in COPD patients [29]. In line with this, recent studies have also supported the notion that systemic corticosteroids can induce hyperglycemia in COPD patients in the absence of diabetes. Indeed, it was reported that prednisolone-treated COPD patients displayed a circadian cycle of hyperglycemia that occurred in the afternoon and evening [30]. Also, the Department of Veterans Affairs Cooperative Study Group found that hyperglycemia occurred significantly more often in subjects with AECOPD who were treated with sys-

Table 1. Key studies suggesting that ICS therapy can increase diabetes risk and/or progression

<table>
<thead>
<tr>
<th>Population</th>
<th>Principal findings</th>
<th>Reference</th>
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<tr>
<td>1,698 patients with and without diabetes (approximately 85% with COPD)</td>
<td>Dose-dependent effect of ICS therapy on serum glucose concentrations in patients with diabetes; each 100-μg increment in ICS dose led to a serum glucose increase of 1.82 mg/dl, while subjects treated with antidiabetic drugs showed an increase of 2.65 mg/dl for every 100 μg of ICS; no ICS-related blood sugar changes were found in nondiabetic patients</td>
<td>23</td>
</tr>
<tr>
<td>388,584 patients treated for respiratory disease (i.e. asthma and COPD patients), of whom 30,167 developed diabetes during the 5.5-year follow-up period</td>
<td>Dose-dependent effect of ICS therapy on diabetes risk and progression; 34% increased risk of diabetes onset with ICS and 64% increase with high-dose ICS (fluticasone-equivalent doses ≥1,000 μg/day). Also, ICS therapy led to a 34% increased likelihood of progression to insulin use, whereas high-dose ICS therapy led to a 54% increase</td>
<td>24</td>
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<tr>
<td>18,226 subjects with diabetes, of whom 5.9% had COPD (67.2% were given corticosteroids during the 12 months after study entry)</td>
<td>Patients with both diabetes and COPD who received a total corticosteroid DDD of ≥0.83/day displayed a 94% increased risk for diabetes-related hospitalization compared to those who did not receive corticosteroids; lower corticosteroid doses (DDD &lt;0.83/day) were not associated with an increased risk of diabetes-related hospitalization</td>
<td>33</td>
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emic glucocorticoids compared to controls [31]. In this regard, investigations have begun to elucidate the mechanisms by which corticosteroids might induce hyperglycemia, including direct effects on hepatic gluconeogenesis [32]. Taken together, these data suggest that hyperglycemia could represent an adverse effect associated with the use of high-dose ICS treatments in COPD patients, especially when type-2 diabetes is comorbid.

**ICS and an Increased Risk for Incidence and Progression of Diabetes**

In addition to the possible short-term danger of ICS-induced hyperglycemia, Suissa et al. [24] recently conducted a population-based cohort study to examine whether ICS use and dose could increase the risk of developing diabetes in COPD patients. Overall, the cohort included 388,584 subjects treated for respiratory disease (i.e. asthma and COPD patients), and 7.8% were found to develop diabetes during the 5.5-year follow-up period. It was determined that treatment with ICS (i.e. beclometasone, budesonide, triamcinolone, fluticasone, and flunisolide; all doses converted to fluticasone equivalents) was associated with a 34% increased risk of diabetes onset, as defined by initiation of an oral antidiabetic medication. Moreover, the diabetes risk was greatest in those patients treated with high ICS doses. Indeed, there was a 64% increased risk upon administration of fluticasone-equivalent doses ≥1,000 μg/day. Moreover, the effect of ICS therapy on diabetes progression was examined among a subset of patients with respiratory disease and newly diagnosed diabetes treated with oral hypoglycemic agents [24]. Notably, ICS therapy was associated with a 34% increased likelihood of progression to insulin use, whereas high-dose ICS led to a 54% increase. Therefore, ICS treatment may not be ideal for patients with diabetes due to the potential for dose-dependent augmentation of blood glucose levels, an increased risk of diabetes progression, and a requirement for initiation/intensification of diabetes treatments [23, 24]. In this respect, it currently remains unclear whether ICS therapy in patients with COPD and diabetes might also worsen long-term diabetes-related complications, such as microvascular and macrovascular events.

**ICS and Diabetes-Related Hospitalization**

Furthermore, ICS-mediated effects on serum glucose levels may contribute to diabetes-related hospitalizations. Indeed, a recent retrospective study of claims data from the Australian Government Department of Veterans’ Affairs examined whether there was a dose-dependent risk of diabetes complications in patients with both diabetes and COPD who were treated with corticosteroids (systemic and inhaled) [33]. A total of 18,226 subjects with diabetes were examined, of whom 5.9% had COPD. Among these COPD patients, 67.2% were given corticosteroids during the 12 months after study entry. It was found that subjects with both diabetes and COPD displayed an increased risk of diabetes-related hospitalization upon high-dose corticosteroid therapy. In fact, there was a 94% increase in the likelihood of hospitalization for diabetes-related complications in those who received a total corticosteroid defined daily dose (DDD) of ≥0.83/day in comparison to those who did not receive corticosteroid therapy. In contrast, lower corticosteroid doses (DDD <0.83/day) were not associated with an increased risk for diabetes-related hospitalization. Therefore, it was suggested that routine use of high-dose corticosteroids might need to be avoided in individuals with COPD and comorbid diabetes, and when corticosteroids are used they should be administered in the context of close blood glucose monitoring. Also, it was proposed that efficacy should be reviewed within 4–8 weeks after commencing ICS therapy in patients with COPD and diabetes.

**Controversy Surrounding the Role of ICS in Diabetes**

In spite of the above findings, major clinical trials examining the safety and efficacy of various ICS therapies in COPD patients did not report increased rates of diabetes [17, 18, 34, 35]. However, it has been suggested that this may be due to the fact that these trials were not large enough to detect the increased diabetes risk based on the reported incidence of diabetes in COPD patients (14.2/1,000/year) [24]. In addition, a recent retrospective analysis of double-blind control trials indicated that ICS therapy in patients with asthma or COPD was not associated with the increased risk of new onset diabetes or hyperglycemia [26]. Furthermore, while another study reported that elderly patients given oral corticosteroids showed an increased risk of diabetes, ICS users did not [36]. Similarly, a further investigation observed no link between ICS and diabetes risk in elderly patients [25]. That being said, studies analyzing data from the 1990s do not allow for the assessment of very high ICS doses (i.e. similar to those currently used to treat COPD) [24]. Nevertheless, a more recent small randomized trial examining whether inhaled fluticasone propionate (440 μg twice daily for 6 weeks) led to changes in HbA1c levels in patients with type-2 diabetes and asthma or COPD also observed no effect of ICS treatment [37]. Finally, another small study investigating the effects of inhaled beclometasone...
sone dipropionate (2,000 μg/day for 2 weeks) on normal and elderly subjects found no effects on glucose metabolism [38].

Taken together, recent evidence indicates that high-dose ICS therapy in COPD patients can lead to an increased risk for insulin resistance and hyperglycemia, as well as diabetes incidence and progression. However, this topic remains controversial and will require further investigation. Nevertheless, there is reason to consider the dangers associated with high-dose ICS in COPD patients in the clinical setting. In fact, in order to reduce the risk of potential ICS-related side effects, the efficacy and pharmacokinetics of these drugs at low/moderate doses may need to be more thoroughly evaluated.

**ICS Dosing and Diabetes Risk**

Although ICS therapies are widely used to treat COPD, optimal doses and lengths of treatment regimens remain to be adequately defined. This issue has recently become a focus due to increased awareness regarding the substantial risk for side effects associated with the use of high-dose ICS [19–24]. Dosing and pharmacokinetic properties (e.g. oral bioavailability, lung retention, and clearance) play a critical role in the clinical efficacy and safety of ICS therapies. Although the use of high-dose ICS (i.e. ≥500 μg, twice daily) has become routine in the clinic, there is evidence to support the efficacy of more moderate ICS doses in the treatment of COPD [39]. For example, recent randomized clinical trials have already evaluated the safety and efficacy of various doses of inhaled budesonide and fluticasone propionate (in combination with the β₂-adrenergic agonists formoterol and salmeterol) in COPD patients and have not observed large differences with regard to reductions in acute exacerbations with lower ICS doses (table 2). Also, data suggest that high-dose fluticasone (500 μg, twice daily) was not found to be advantageous in terms of lung function and quality of life when compared to a 250-μg dose [17, 34, 40–42]. Moreover, both high- and low-dose budesonide/formoterol (320/9 or 160/9 μg; twice daily) improved pulmonary function and reduced AECOPD symptoms over a 1-year period in patients with moderate to severe COPD [43, 44]. Therefore, future validation and implementation of such reduced doses could eliminate potential ICS-related effects on hyperglycemia and diabetes risk. Thus, systematic identification of the lowest possible effective ICS doses may represent a priority in improving therapeutic safety in COPD patients. For this, head-to-head comparisons of low and high doses for existing and emerging treatment strategies will be required.

**ICS Pharmacokinetics and Diabetes Risk**

**ICS Activity and Bioavailability**

The ICS dose is not the only variable that should be taken into account with regard to diabetes risk. Indeed, distinct ICS therapies for COPD also display significant differences in their pharmacokinetic profiles, which can impact their efficacy and safety. For example, budesonide and fluticasone, which are commonly used in COPD treatment, have different oral bioavailabilities and lung retention times. These differences can influence the systemic exposure and potential for systemic side effects, including hyperglycemia and diabetes. Understanding these pharmacokinetic properties is crucial for optimizing ICS therapy in COPD patients, particularly in the context of diabetes risk management.
variability in key pharmacokinetic properties (table 3), which can result in differential activity or a risk for systemic side effects (fig. 2). In general, although different ICS are rapidly cleared from the body, they display varied levels of glucocorticoid receptor binding, oral/lung bioavailability, and absorption rates [45, 46]. For example, considering the receptor binding of drugs commonly used to treat COPD, fluticasone propionate shows a high relative receptor affinity, whereas budesonide and flunisolide show intermediate and lower affinities, respectively [46]. However, this factor alone does not determine the efficacy of a given ICS and can even contribute to systemic side effects. Indeed, a high pulmonary bioavailability is also required for these drugs to function locally, and it has been reported that pulmonary residence times are high for fluticasone propionate but short for budesonide and flunisolide [47]. In addition, variability in lung retention and mean absorption times must also be considered in relation to adverse effects (e.g. fluticasone propionate and budesonide show absorption times of 4.9 and 1.8 h, respectively) [46].

With regard to nonlung absorption, increased oral bioavailability (i.e. the proportion of the dose that is swallowed) can lead to heightened systemic exposure and the potential for side effects. However, when considering bioavailability, measuring the systemic exposure to an inhaled drug can be challenging and requires a temporal comparison of corticosteroid plasma concentrations for inhaled

Table 3. Key pharmacokinetic characteristics of several ICS commonly used to treat COPD

<table>
<thead>
<tr>
<th>ICS</th>
<th>Key pharmacokinetic properties</th>
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<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>High relative receptor binding (1,800)</td>
</tr>
<tr>
<td></td>
<td>Low oral availability (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>Absorption rate (4.8 h)</td>
</tr>
<tr>
<td></td>
<td>High half-life (14 h)</td>
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<tr>
<td>Budesonide</td>
<td>Intermediate relative receptor binding (935)</td>
</tr>
<tr>
<td></td>
<td>Intermediate oral availability (11%)</td>
</tr>
<tr>
<td></td>
<td>Absorption rate (1.9 h)</td>
</tr>
<tr>
<td></td>
<td>Intermediate half-life (2.8 h)</td>
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<tr>
<td></td>
<td>Lipid conjugated</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Low relative receptor binding (53)</td>
</tr>
<tr>
<td></td>
<td>High oral availability (15%)</td>
</tr>
<tr>
<td></td>
<td>Low half-life (0.1 h)</td>
</tr>
<tr>
<td></td>
<td>On-site activation in lungs</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Low/intermediate relative receptor binding (180)</td>
</tr>
<tr>
<td></td>
<td>Intermediate oral availability (7%)</td>
</tr>
<tr>
<td></td>
<td>Low half-life (1.6 h)</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Low/intermediate relative receptor binding (223)</td>
</tr>
<tr>
<td></td>
<td>High oral availability (23%)</td>
</tr>
<tr>
<td></td>
<td>Low half-life (2.0 h)</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>High relative receptor binding (2,200)</td>
</tr>
<tr>
<td></td>
<td>Low oral availability (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate half-life (4.5 h)</td>
</tr>
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</table>
dosing with those obtained after intravenous dosing. Also, the administered doses need to be large enough to produce measurable plasma concentrations (i.e. within the limit of reliable detection) [48]. In this regard, peak plasma levels of budesonide occurred much earlier and were approximately 20-fold higher than those of fluticasone propionate [49]. In addition, ICS plasma concentrations can vary significantly based on the type of delivery system used (e.g. dry powder vs. metered-dose inhalers) [50]. Nevertheless, it has been demonstrated that ICS display a wide range of oral bioavailability, with fluticasone propionate showing <1%, budesonide having 11%, and beclometasone monopropionate being the highest at 26% [46]. Thus, beclometasone monopropionate may be more likely to induce adverse effects based solely on the level of systemic exposure. However, that being said, factors such as drug metabolism can also influence bioavailability and the likelihood of an ICS producing negative effects. In this regard, ICS are generally thought to be inactivated and metabolized via the cytochrome P450 system [51]. Interestingly, inflammation has been found to be associated with the downregulation of cytochrome P450 enzymes, which could lead to prolonged ICS activity in COPD patients [52].

ICS Half-Life and Modification

Half-life also represents an important ICS characteristic. A low-dose ICS present for a prolonged period of time is more likely to have a better safety profile than a high-dose ICS with a short half-life. In this regard, fluticasone propionate shows a relatively long half-life (14 h) compared to other ICS, while the newer fluticasone furoate displays a half-life of 17–24 h [53]. For this reason, recent clinical trials have begun to evaluate the efficacy and safety of fluticasone furoate for the treatment of COPD [54, 55]. Additionally, some ICS require bioactivation processes in the lung, which can contribute to their safety profiles by locally restricting their activity [56]. Finally, it is known that certain ICS have the potential to become lipid modified within the lung, which can facilitate retention and slow release from the target tissue, thereby reducing systemic side effects. In this respect, budesonide can be lipid conjugated [57, 58], while fluticasone propionate cannot [58].

Taken together, consideration of these various pharmacokinetic properties might help to optimize the ICS therapy for COPD patients (fig. 2). Indeed, efficient systemic clearance, a high receptor affinity, a low oral bioavailability, a high lung deposition, a long pulmonary residence time, a long half-life, and lipid modification might contribute to the enhanced efficacy and safety of an ICS.

Intersubject Variability

In addition to the unique pharmacokinetic characteristics of the various ICS, it has also been suggested that interindividual variability may exist with regard to ICS pharmacokinetics (e.g. rate of systemic lung absorption). Notably, these differences could also contribute to ICS dosing requirements and side effects. Indeed, as part of a small randomized clinical study, 9 normal subjects were administered high-dose budesonide and fluticasone propionate (1,600 and 1,000 μg, respectively; both twice daily) [59]. Blood samples were sequentially collected prior to and at various times after the delivery of an ICS dose in order to determine plasma drug concentrations and pharmacokinetics. Notably, it was demonstrated that there was considerable intersubject variability with regard to the rate of lung absorption for both drugs. Also, some individuals displayed a more sustained plasma drug level than would be predicted for budesonide and higher-than-expected plasma drug concentrations in the morning compared to the evening for fluticasone propionate. Nevertheless, these results may need to be interpreted with care as it has been suggested that the study of ICS absorption rates and systemic effects of budesonide and fluticasone propionate in healthy individuals may not be relevant to diseased subjects [49, 60].

Overall, current evidence indicates that the standard of care could be effectively altered in order to reduce the ICS dose, thereby diminishing therapeutic side effects. Considering the unique pharmacokinetic properties of each ICS may help to determine which drugs are less likely to contribute to the development and/or progression of diabetes and other adverse effects in COPD patients.

Clinical Implications and Future Perspectives

Strikingly, recent ICS use rates for the treatment of COPD have been reported to be over 70% [10, 39]. However, these rates do not coincide with treatment guidelines, which only recommend the use of ICS in late-stage disease (approximately 20% of patients) [13]. In line with this, it was suggested that at least 25% of COPD patients given ICS therapies could be considered as overtreated [61]. Indeed, a recent study analyzing 10,711 COPD patients found an inappropriate ICS use rate of 18% and reported that this lack of adherence to the recommended criteria for ICS therapy led to a lower self-reported patient health status and higher healthcare costs [62]. Thus, current clinical practices regarding the use of ICS therapy for...
the management of COPD may be contributing to unnecessary increases in ICS-related adverse event rates. Therefore, efforts may be required to raise awareness among healthcare professionals regarding recommendations for ICS use when treating COPD patients. Notably, such modifications in the management of COPD patients have the potential to reduce not only costs related to the administration of ICS therapies but also those associated with subsequent requirements that might arise for oral antidiabetic medications [24].

In this regard, adequate analysis of risk-to-benefit ratios and increased selectivity of patients receiving ICS therapy has been encouraged [63]. However, future studies will be required to firmly establish which patient characteristics might be associated with an increased risk for specific ICS-related side effects. Although it remains unclear whether unique factors contribute to the susceptibility for an increased risk of diabetes incidence and progression upon ICS therapy, current evidence may support avoidance of the routine use of high-dose corticosteroids in individuals with COPD and comorbid diabetes. Indeed, it has already been suggested that high-dose corticosteroids be used in the context of close blood glucose monitoring in these patients [33]. However, a further understanding of the mechanisms that contribute to ICS-related effects on glycemic control could allow for informed selection and improved monitoring of at-risk patients, ultimately improving the safety and efficacy of ICS treatment of COPD.

Moreover, the addition of certain add-on therapies may prove to be useful for diminishing hyperglycemia in ICS-treated patients. For example, the phosphodiesterase-4 inhibitor roflumilast is an anti-inflammatory medication that appears to enhance lung function in COPD patients. Interestingly, roflumilast treatment was also found to improve fasting blood glucose and HbA1c levels in subjects with comorbid type-2 diabetes [64]. Therefore, this drug could be beneficial with regard to glycemic control in ICS-treated COPD patients. Nevertheless, clinical studies are only now underway to assess combination therapies involving roflumilast and ICS for the management of COPD [65]. Thus, emerging therapeutic strategies could also be pivotal for reducing the risk of diabetes onset and progression in COPD patients.

Taken together, the overuse of ICS therapy regimens, the lack of patient selectivity, and inadequate treatment options may all contribute to ICS-related side effects. Therefore, improved clinical management based on current therapeutic options as well as the future development and incorporation of novel treatment strategies could effectively reduce potential ICS side effects, such as diabetes, in COPD patients.

Conclusion

Although recent studies have suggested that high-dose ICS therapy might contribute to the development of type-2 diabetes in COPD patients, this idea remains controversial and requires further investigation. Nevertheless, there is reason to consider the clinical implications associated with high-dose ICS therapy in COPD patients. In fact, in order to reduce the potential risk of ICS-induced diabetes, the efficacy and pharmacokinetics of these drugs at low or moderate doses may need to be more thoroughly evaluated. Also, ICS overuse represents a critical issue that must be addressed. In addition, as we learn more regarding the adverse effects associated with ICS therapy, adequate patient selection and monitoring will be necessary to improve the safety and efficacy of these treatments. In this regard, current evidence may suggest that care should be taken when administering high-dose ICS therapies to COPD patients with comorbid diabetes. Taken together, future research into the potential role of ICS in the development and progression of diabetes, as well as improved therapeutic regimens to reduce side effects (i.e. optimal dosing), can lead to improved management of COPD patients.

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