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Original Article

Association between inhaled corticosteroid use and risk of hyperglycemia in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis

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Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) patients have a higher risk of developing diabetes, and studies suggest that inhaled corticosteroids (ICSs) use may be associated with a higher risk of diabetes, particularly at higher doses. This study aims to investigate the effects of ICS use on the risk of diabetes and blood glucose levels in COPD patients. **Materials and Methods:** A systematic search was carried out on the PubMed, EBSCOhost, and ProQuest databases using the terms "Inhaled Corticosteroids," "Diabetes," and "Chronic Obstructive Pulmonary Disease" for the period between 2013 and 2023. The systematic review adhered to the PRISMA 2020 guideline. A meta-analysis was conducted using a random-effects model using the RevMan 5 software. **Results:** A total of 14 studies were included in the final analysis, with 10 randomized controlled trials (RCTs) and 4 observational studies. Two observational studies investigated the relationship between ICS dose and diabetes risk. A meta-analysis of the RCTs studies showed a nonstatistically significant tendency toward increased blood glucose (odds ratio [OR] 1.07 and 95% confidence interval [CI] 0.88–1.30) after a 52-week follow-up. Whereas the observational studies showed a tendency toward an increased risk of diabetes (OR 1.40 and 95% CI 0.96–2.03). Furthermore, a subgroup meta-analysis of high-dose ICS (>900 μg/day) showed a significant increase in the risk of diabetes (OR 1.20 and 95% CI 1.09–1.32). **Conclusion:** Short-term use of ICS does not have a significant effect on blood glucose. However, long-term use, especially at higher doses, can increase the risk of developing diabetes.

Keywords: *Chronic obstructive pulmonary disease, Diabetes, Inhaled corticosteroids*

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 defines chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition that leads to persistent airflow obstruction due to abnormalities in the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema), which results in chronic respiratory symptoms such as dyspnea, cough, expectoration, and/or exacerbations. The GOLD 2023 classification system divides COPD patients into three groups (A, B, and E) based on their symptoms and exacerbation history. Group E refers to individuals with ≥2 moderate exacerbations or ≥1 leading to hospitalization, regardless of reported symptoms. In addition to long-acting beta-agonist and long-acting muscarinic agonist, the GOLD 2023 guideline recommends considering inhaled corticosteroids (ICSs) in this group, especially if the blood eosinophil count is ≥300 cells/μL [1].

Using ICS for COPD treatment has reduced the risk of side effects associated with oral corticosteroids, but there are still potential issues [2]. ICS can increase the risk of respiratory infections such as pneumonia, oropharyngeal candidiasis, mycobacterial infections, and upper respiratory tract infections by impairing monocyte chemotaxis, bactericidal activity, interleukin-1, and T-cell activation [3].

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A systematic review has shown that ICS use for COPD can cause oral candidiasis and dysphonia, followed by infectious complications such as pneumonia and mycobacterial diseases [2]. The association was also found between the risk of osteoporosis and diabetes, although it still remains less clear [2].

Diabetes is a common comorbidity in COPD patients [4,5]. A retrospective study in Italy, which covers approximately 1.5% of the Italian population, reported that COPD patients had a higher risk of developing diabetes compared to non-COPD individuals (18.7% vs. 10.5% in the general population) [6]. Although the effect of ICS on COPD is still unclear, studies have reported that the use of ICS may be linked to the risk of diabetes, particularly in higher doses [7-9]. The impact ICS on glucose metabolism remains unclear, as some studies show conflicting results in both diabetic and nondiabetic individuals. Some studies indicate that ICS treatment can cause systemic side effects that disrupt glucose metabolism, whereas other studies do not show any clinically significant adverse effects of ICS treatment on glucose metabolism [10]. Therefore, this study aims to investigate the effect of ICS use in COPD patients on the risk of diabetes and its effects on blood glucose.

Materials and Methods

Research design

This research did not involve human subjects; therefore, it was exempt from ethical clearance. We used a systematic review to investigate the use of ICS and the risk of diabetes. This systematic review and meta-analysis study have been registered in PROSPERO (CDR42023417396).

Data sources and search strategy

Literature was retrieved from three search engines: PubMed, EBSCOhost, and ProQuest. The inclusion criteria were articles that performed empirical studies on the use of ICS and the risk of diabetes in COPD patients that reported effects on blood glucose and/or incidence of new-onset diabetes. The following terms and their derivatives were used in the search strategy: ("Inhaled Corticosteroids") AND ("Diabetes Mellitus" OR "Type 2 DM" OR "T2DM" OR "Hyperglycemia") AND ("Chronic Obstructive Pulmonary Disease" OR "COPD").

Study selection and data extraction

The inclusion criteria for this research were fulltext, written in the English language, and reported effects on blood glucose and/or incidence of new-onset diabetes. The exclusion criteria for this study were incomplete outcome, not full-text studies, case reports, literature review, and irrelevant studies.

Two independent reviewers conducted this systematic review and meta-analysis. All authors screened search results from titles and abstracts. Full papers were then retrieved to be reviewed further. Mendeley™ was used to remove duplicates and manage the bibliography of the selected literature. Data extraction tables were created to gather the required data for the review.

Risk of bias

Risk-of-bias 2 (RoB-2) tool will be used to assess the risk of bias in randomized studies, whereas the ROBINS-E tool will be used to assess risk of bias in observational studies. GRADE assessment will be provided after reviewing all available evidence.

Statistical analysis

Quantitative analyses using the random-effects model with inverse-variance method will be used to compare the outcome between baseline and after intervention. The measure of effects and the heterogeneity of selected studies will be measured using the I^2 heterogeneity index. The I^2 higher than 50% was considered having high heterogeneity. A 95% confidence interval (95% CI) and P value were presented ($P < 0.05$ was considered statistically significant). All statistical analysis was conducted with Review Manager (5.4 version, Cochrane Collaboration, Copenhagen, Denmark).

Results

Study characteristics

A total of 80 studies were identified from three databases, of which 14 were included in the final synthesis. PRISMA 2020 flow chart can be seen in Figure 1. Among these, seven were randomized controlled trials (RCTs) [11-17], and three were *post hoc* analyses of RCTs [18-20]. The RCTs reported effects on blood glucose without specifying a diabetes diagnosis, whereas hyperglycemia/new-onset diabetes mellitus (DM) was the reported outcome in the *post hoc* analyses. Fluticasone was the ICS used in nine of the studies and was compared to placebo, usual care, or a regimen that did not contain ICS. The follow-up period for these studies ranged from 14 weeks up to 1 year.

The remaining four studies were retrospective cohort studies that reported the incidence of new-onset diabetes [8,9,21,22]. In one study, any ICS use was compared to long-acting bronchodilators (LABDs), whereas the other three studies compared ICS use to not using ICS. The follow-up period for these studies was at least 2 years, with one study having an average follow-up of more than 15 years. Two studies analyzed the dose-dependent relationship between ICS use and the risk of diabetes [8,9]. A summary of the studies can be found in Table 1.

Risk of bias

RoB in all studies was low-risk overall. RoB is shown in Figures 2 and 3. Funnel plot of randomized studies and observational studies can be found in Figures 4 and 5, respectively.

Short-term effects on blood glucose

A meta-analysis was performed on 10 studies with a follow-up period of up to 1 year. They all reported whether ICS influences blood glucose. There was no statistically significant increase in risk of ICS affecting blood glucose (odds ratio [OR] 1.07 and 95% CI 0.88–1.30). Statistical heterogeneity was found to be low (I^2 = 15%). The result of the meta-analysis can be seen in Figure 6.

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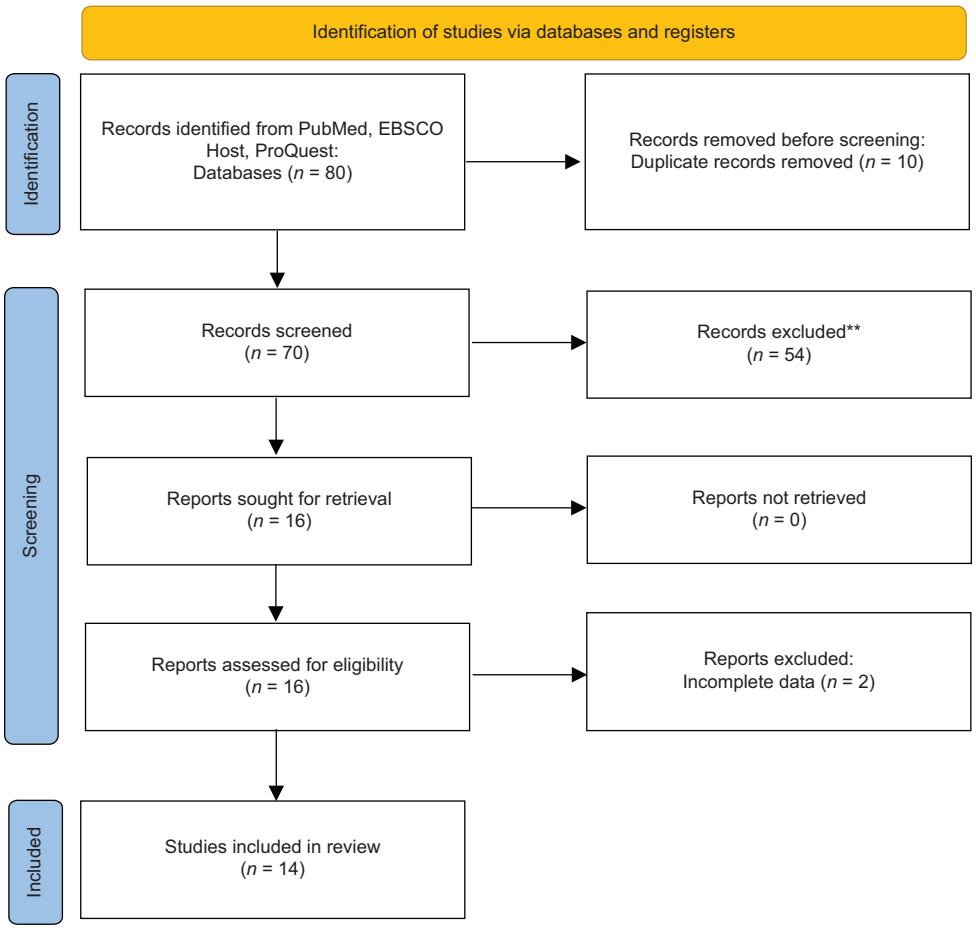

Figure 1: PRISMA 2020 flow chart

Long-term effects on risk of diabetes

Data from four studies with a minimal follow-up period of 2 years were pooled together. There was no statistically significant increase risk of new-onset diabetes (OR 1.40 and 95% CI 0.96–2.03) [Figure 7]. A subgroup analysis was performed on two studies that reported a dose-dependent relationship. High-dose ICS (>900 μg/day) was associated with a 20% increased risk of new-onset diabetes (OR 1.20 and 95% CI 1.09–1.32) [Figure 8]. There was no heterogeneity found in the subgroup analysis of high-dose ICS (I^2 = 0%).

GRADE assessment

Quality of evidence

- Study design: The systematic review included a total of 14 studies, comprising 10 RCTs and 4 observational studies. The inclusion criteria focused on empirical studies that investigated the use of ICSs and the risk of diabetes in patients with COPD
- Risk of bias: The systematic review employed the RoB-2 tool for assessing the risk of bias in RCTs and the ROBINS-E tool for observational studies. Overall, the included studies were deemed to have a low risk of bias
- Consistency: The meta-analysis showed consistent findings across the included studies regarding the effects of ICS on blood glucose levels and the risk of diabetes
- Directness: The studies directly examined the association between ICS use and hyperglycemia/diabetes in COPD patients
- Precision: The sample sizes of the included studies were substantial, and the meta-analysis provided precise estimates of the effects of ICS on blood glucose levels and the risk of diabetes
- Publication bias: The systematic review included funnel plots to assess the potential publication bias, which did not indicate substantial asymmetry.

Based on the above evaluation, we can assess the quality of evidence as follows:

- Quality of evidence for effects on blood glucose: Moderate
- Quality of evidence for risk of diabetes: Low.

Strength of recommendations

Based on the GRADE assessment, we can determine the strength of recommendations as follows:

- Short-term effects on blood glucose: The evidence indicates that short-term use of ICS does not have a statistically significant effect on blood glucose levels. Recommendation strength: Weak/conditional
- Long-term effects on risk of diabetes: The evidence suggests a tendency toward an increased risk of diabetes

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Table 1: Summary of studies

Author	Study design	Follow-up duration	Total participants	ICS	Comparison	Outcome of interest	Results
Ajmera *et al,* 2017[21]	Retrospective cohort	>2 years	6554	Any ICS use	Not using ICS	New-onset diabetes	ICS use alone or combined with statins and/or antidepressants were more likely to have new-onset diabetes
Flynn *et al,* 2014[22]	Retrospective cohort	>2 years	4305	Any ICS use	Not using ICS	New-onset diabetes, diabetes progression	ICS use was not associated with new-onset diabetes or worsening of existing diabetes
Price *et al,* 2019[8]	Retrospective cohort	15.6–17.5 years	37,922	Any ICS use	LABD	New-onset diabetes, diabetes progression	ICS increases the risk of diabetes onset with no overall increase in diabetes progression
Saeed *et al,* 2020[9]	Retrospective cohort	7 years, until death, or T2DM events	50,148	Any ICS use	Not using ICS	New-onset diabetes	ICS use was associated with a moderate dose-dependent increase in the incident of T2DM
Bakerly *et al,* 2019[11]	RCT	1 year	2799	FF/VI	Usual care	Effects on glucose	There was no increased incidence of effects on glucose
Bhatt *et al,* 2017[12]	RCT	24 weeks	430	FF/VI	VI and placebo	Effects on glucose	The incidence of adverse events was similar in both groups
Dransfield *et al,* 2013[13]	RCT	1 year	3255	FF/VI	VI	Effects on glucose	The incidence of adverse events was similar in both groups
Kerwin *et al,* 2013[14]	RCT	24 weeks	1030	FF, FF/VI	VI, placebo	Effects on glucose	The incidence of adverse events was similar in both groups
Martinez *et al,* 2013[15]	RCT	24 weeks	1224	FF, FF/VI	VI, placebo	Effects on glucose	The incidence of adverse events was similar in both groups
Siler *et al,* 2016[16]	RCT	14 weeks	1620	FF/VI	VI	Effects on glucose	The incidence of adverse events was similar in both groups
Vestbo *et al,* 2016[17]	RCT	1 year	2802	FF/VI	Usual care	Effects on glucose	The incidence of adverse events was similar in both groups
Han *et al,* 2020[18]	*Post hoc* analysis of RCT	1 year	10,335	Prior ICS use	No prior ICS use	Hyperglycemia/ new-onset diabetes	The incidence of adverse events (hyperglycemia/new-onset DM) was similar in both groups
Thompson *et al,* 2022[19]	*Post hoc* analysis of RCT	1 year	10,250	FF/VI, FF/ UMEC VI	UMEC/VI	Hyperglycemia/ new-onset diabetes	The incidence of adverse events (hyperglycemia/new-onset DM) was similar in both groups
Zheng *et al,* 2020[20]	*Post hoc* analysis of RCT	1 year	535	FF/VI, FF/ UMEC/VI	UMEC/VI	Hyperglycemia/ new-onset diabetes	The incidence of adverse events (hyperglycemia/new-onset DM) was similar in both groups

ICS: Inhaled corticosteroids, FF: Fluticasone furoate, VI: Vilanterol, UMEC: Umeclidinium, LABD: Long-acting bronchodilator, DM: Diabetes mellitus, T2DM: Type 2 DM, RCT: Randomized controlled trial

with long-term use of ICS, particularly at higher doses. However, the analysis did not find a statistically significant association. Recommendation strength: Weak/ conditional

- Subgroup analysis of high-dose ICS: The evidence from the subgroup analysis indicates a significant increase in the risk of diabetes with high-dose ICS (>900 μg/day). Recommendation strength: Weak/conditional.

Discussion

Exogenous glucocorticoids can induce dysregulation of glucose metabolism, resulting in hyperglycemia. This metabolic disturbance can precipitate new-onset diabetes or worsening of glycemic control in individuals with preexisting diabetes [10]. While the systemic side effects of prolonged exposure to oral steroids are well established, the potential systemic effects of inhaled preparations are often overlooked. Similar to oral corticosteroids, ICS has been linked to an elevated risk of developing diabetes as well as deterioration of glycemic control in patients who already have diabetes [23].

In this study, we perform two separate meta-analyses to identify the short-term and long-term effects of ICS use on the risk of hyperglycemia. Short-term effects are identified by observing the effects on blood glucose, which are primarily shown as an adverse effect in RCTs. Follow-up period is relatively shorter, with most studies reporting only up to 1 year. On the other hand, long-term effects of new-onset DM are identified in observational studies with longer follow-up periods of more than 1 year.

Short-term data (<1 year) from 10 RCTs showed that ICS has no significant effect on blood glucose. A study conducted by O'Byrne *et al*. produced similar findings in patients with asthma and COPD who were taking ICS. The study found that

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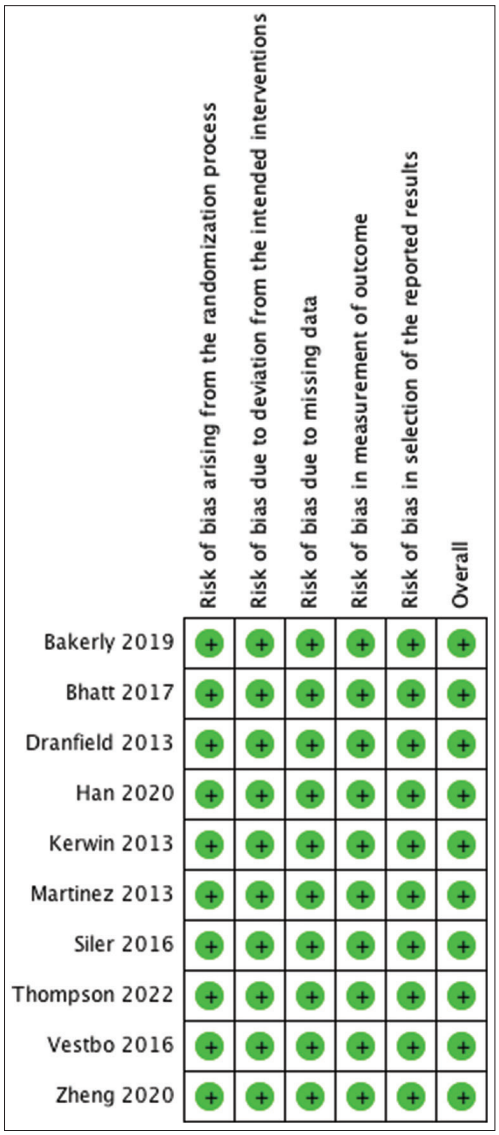

Figure 2: Risk of bias 2 in randomized studies

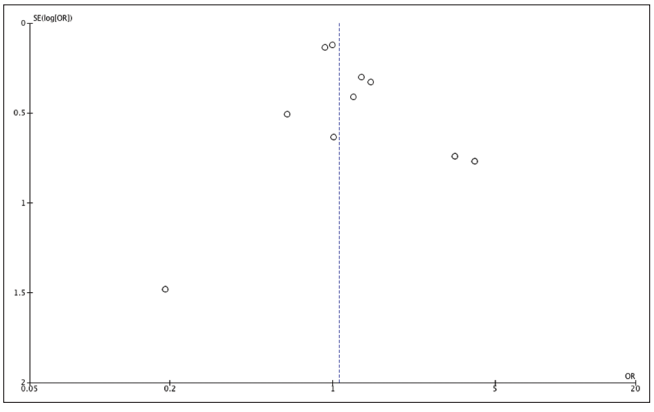

Figure 4: Funnel plot of randomized studies

ICS treatment was not linked to an increased risk of new-onset diabetes or hyperglycemia. However, the follow-up period in the study was less than a year, similar to the studies included in our review [24].

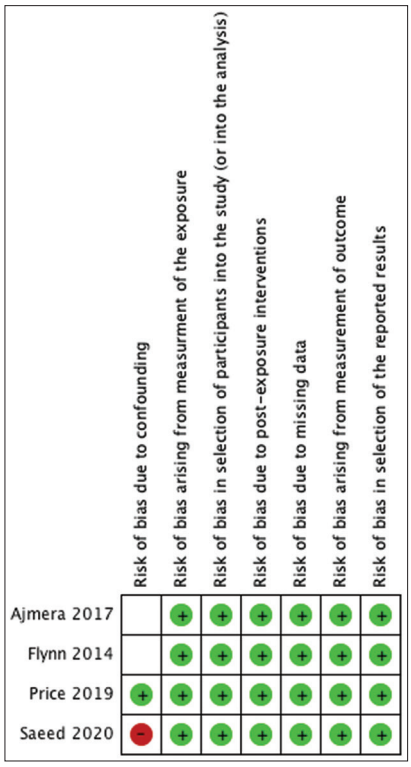

Figure 3: Risk of bias in observational studies (ROBINS-E)

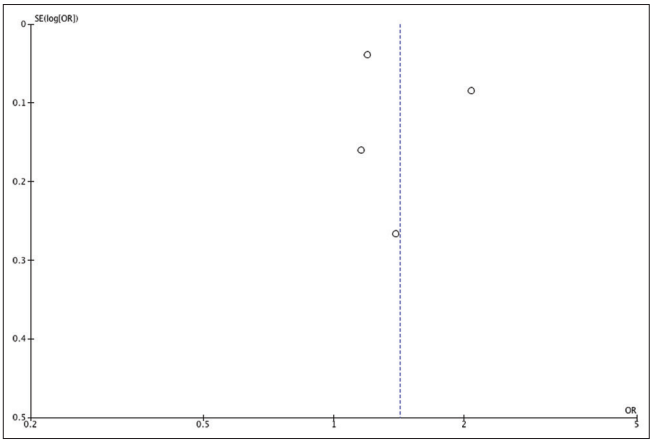

Figure 5: Funnel plot of observational studies

Long-term data in our studies were analyzed from four retrospective cohort studies. Our studies showed that there is no significant increase risk of new-onset diabetes. Two of the studies divided the population of their samples based on the dose of ICS inhaled daily [8,9]. Saeed *et al*. divided into three groups based on budesonide equivalent daily dose (low; 0.01–369.99 μg, medium; 370–969.99 μg, and high; ≥970 μg) [9]. Similarly, Price *et al*. divided their population into three groups based on ICS daily dose (<500 μg/day, 500–999 μg/day, and >1000 μg/day) [8]. After performing a subgroup analysis based on these three groups of doses, a higher dose of ICS per day (>900 μg/day) was associated with a 20% increased risk of new-onset diabetes. A dose-dependent increased risk of diabetes was demonstrated in a study by Voorham *et al*. They reported that

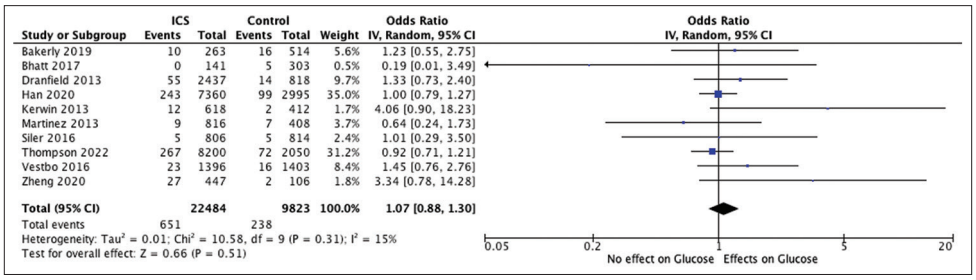

Figure 6: Short-term (1 year) effect of ICS on blood glucose. ICS: Inhaled corticosteroid, CI; Confidence interval, OR: Odds ratio

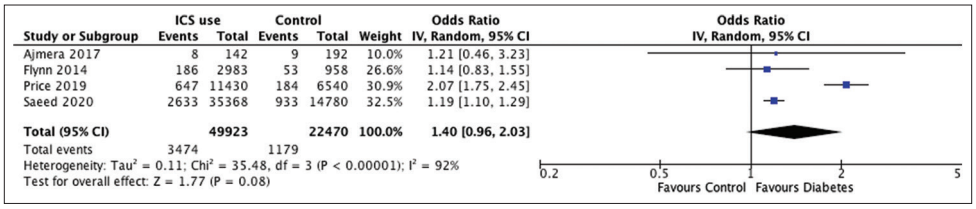

Figure 7: Long-term effect of ICS and risk of diabetes. ICS: Inhaled corticosteroid, CI: Confidence interval, OR: Odds ratio

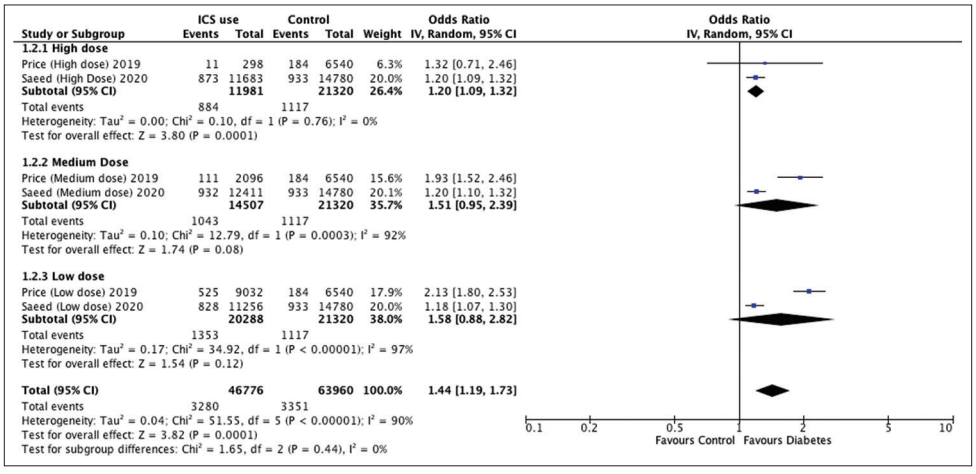

Figure 8: ICS dose and risk of diabetes. ICS: Inhaled corticosteroid, CI: Confidence interval, OR: Odds ratio

the risk of diabetes onset and progression was significantly increased in doses ≥ 500 μg/day [25].

The presence of diabetes can have negative effects on the development and outlook of COPD through the direct impact of hyperglycemia on lung physiology, inflammation, and/or vulnerability to bacterial infections. On the other hand, COPD may elevate the risk of developing type 2 DM due to the inflammatory processes involved and/or the potential adverse effects associated with the use of corticosteroids as a therapeutic approach [26].

Clinicians are recommended to analyze risk-to-benefit ratios and increase patient selectivity in prescribing ICS treatments. Our study supports avoiding high-dose corticosteroids in high-risk individuals. Careful consideration should be given to the clinical implications of high-dose ICS therapy in COPD patients to reduce the potential risk of ICS-induced diabetes. It may be necessary to evaluate the efficacy and pharmacokinetics of low or moderate doses of ICS to minimize the risk of diabetes [27].

Conclusions

Short-term use of ICS does not have a statistically significant effect on blood glucose levels. Although there is a tendency toward increased risk of diabetes in long-term use of ICS, our analysis showed that it is statistically insignificant. However, higher doses of ICS increase the risk of new-onset diabetes. Further studies with longer follow-up and dose-relationship studies are required to verify our results.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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