The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 5, 2025

COMPARATIVE EFFECT OF INHALING CORTICOSTEROIDS IN DIFFERENT DOSES AND DURATIONS WITH RISK OF DIABETES MELLITUS TYPE 2 IN CHRONIC ASTHMA PATIENTS

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DOI: https://doi.org/10.5281/zenodo.15429725

Keywords
Type 2 Diabetes Mellitus(T2DM), Inhaled Corticosteroids (ICS), Fating blood Sugar (FBS), Dry Powder Inhaler (DPIs), Complication Effect (CE)

Article History
Received on 07 April 2025
Accepted on 07 May 2025
Published on 16 May 2025

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Abstract

Asthma is a heterogeneous disease identified by chronic inflammation, airway hyperresponsiveness. The occurrence of exacerbations is a main parameter for asthma control. Recent research depicts that there is a link of ICS therapy and diabetes in asthmatic patients. In patients with type-2 diabetes who were mainly taking ICS for lung related disorders were found to show a higher (HbA1c) level than those who did not consume ICS. Recent studies suggests that disorders of glucose metabolism are associated with worsening of asthma. (ICS) are the spine of treatment for patients with asthma. In small comparative study in patients with type 2 diabetes mellitus glycosylated hemoglobin levels showed a noticeable increase in levels pointedly after 6 weeks of treatment with inhaled fluticasone, these observations suggest that ICS may exacerbate diabetes in asthma by increasing blood glucose levels in patients. The aim of the study is to assess the complication effect of inhaling corticosteroids in Diabetes mellitus type 2 patients with chronic asthma patients since different durations (1 year, 5-year, 10-year post asthma).

INTRODUCTION

Ambulance personnel face challenging Asthma is an assorted disorder categorized by wonted inflammation and augmented airway hyper-responsiveness. Traditionally viewed as a primary lung complaint, it's now known that asthma is accompanying with extrapulmonary comorbidities analogous as obstructive sleep apnea pattern (OSAS) and systemic conditions like diabetes mellitus (DM) and metabolic pattern(1) According to Fireman, asthma is a contemporary seditious airway complaint, generally managed with inhaled corticosteroids(ICS) still, achieving asthma control remains grueling in patients with severe asthma, who represent 5 to 10 of asthma cases, indeed when using high boluses of ICS and other anti-inflammatory specifics medications. Type 2 Diabetes Mellitus (DM) is marked by the failure to regulate blood glucose due to a combination of insulin resistance and ineffective

pancreatic beta cells. This pathogenesis frequently leads to diabetic dyslipidemia, characterized by increased tube triglycerides, remnant lipoproteins, and small thick low- viscosity lipoprotein, as well as dropped high- viscosity lipoprotein, adipose liver complaint, and an accustomed seditious state. (2) Recent investigation indicates a link between gobbled corticosteroid (ICS) remedy and insulin resistance, hyperglycemia, and diabetes in cases with asthma and COPD. Cases with type- 2 diabetes using ICS for respiratory conditions tend to have poorer glycemic control and advanced glycated hemoglobin (HbA1c) situations compared to those not taking ICS (3) The advance of inhaled corticosteroids for respiratory conditions, firstly for asthma and subsequently COPD, depicted a significant breakthrough by letting effective treatment with less pilules and downgraded systemic exposure to the medicine (4) Inhaled corticosteroids have significantly excelled asthma treatment due to their superior pharmacokinetic properties . The superlative inhaled corticosteroid should have better lung residence time, high natural activity, low oral bioavailability, and high systemic concurrence. presently, five corticosteroids are available for application in the management of asthma 1) triamcinolone acetonide (TAA), 2) flunisolide, 3) beclomethasone dipropionate(BDP), 4) budesonide, and 5) fluticasone propionate(5) Also recent trainings now proved that high- dose inhaled corticosteroid remedy or not taking duly the inhaled corticosteroids leads to disturbances in glucose metabolism which leads to hyperglycemia and consequently affluences the peril of onset of diabetes mellitus type 2 therefore the adverse effects of hyperglycemia have been well proved(6).

METHODOLOGY

This observational study was conducted over a period of three months in the Pulmonology Department of Fatima Memorial Hospital (FMH) and Social Security Hospital, Lahore, Pakistan, following ethical approval and the approval of the research synopsis. A total of 107 participants were enrolled through non-probability convenience sampling. The sample size was calculated based on a 90% confidence interval with a margin of error of 8%, ensuring sufficient precision while considering the feasibility of recruitment. Eligible participants were adults between 40 to 60 years of age who had a history of chronic asthma for more than five years and had been using inhaled corticosteroids (ICS) via Dry Powder Inhalers (DPIs) for at least one year. Additionally, included individuals had coexisting allergic rhinitis and seasonal cough. Exclusion criteria included patients diagnosed with tuberculosis, bronchitis, pneumonia, diabetes mellitus, cancer, or those who had recently undergone surgery. Individuals who declined to provide informed consent were also excluded from the study.

Data collection was carried out at three defined time points: baseline (Day 1), mid-point (Day 45), and end-point (Day 90). At each time point, fasting blood sugar (FBS) levels were measured using a calibrated glucometer following an overnight fast. In addition, HbA1c levels were evaluated to assess long-term glycemic control, providing a retrospective measure of average blood glucose levels over the preceding two to three months. Participants' ICS usage was monitored throughout the study period, with both dosage and frequency of inhalation being recorded to evaluate adherence and potential changes over time. Questionnaires were administered in the outpatient department to collect demographic and clinical information. Prior to participation, each subject was informed about the study's purpose, potential risks, and benefits, and written informed consent was obtained. The longitudinal design of the study allowed for the assessment of changes in FBS, HbA1c, and ICS usage patterns over time, enabling a comprehensive evaluation of potential associations between ICS therapy and glycemic alterations.

Statistical analysis was performed using SPSS version 27. Repeated Measures ANOVA was employed to assess differences in FBS levels, ICS frequency, and dosage across the three time points. Correlation analysis was also conducted to determine the relationship between ICS usage and glycemic indices. Ethical principles were adhered to throughout the study, including the maintenance of confidentiality and voluntary participation of subjects, in compliance with established research ethics guidelines

RESULTS

There are several possible connections between asthma, using inhaled corticosteroids, and having elevated hemoglobin A1c (HbA1c) levels Asthma and Corticosteroid Use: Because inhaled corticosteroids help reduce airway inflammation and improve breathing, they are a typical asthma treatment. However long-term corticosteroid treatment, particularly systemically corticosteroids, can have negative side effects including elevated blood sugar and weight gain. This may be a factor in elevated HbA1c levels in patients receiving corticosteroid therapy for asthma. During the previous two to three months, HbA1c readings indicate the average blood sugar levels. Elevated insulin resistance or poorly managed diabetes are marked by high HbA1c values. Insulin resistance and elevated blood sugar levels can result from long-term systemic corticosteroid treatment, which can may be a factor in high HbA1c readings. The dataset reveals a total of 107 asthmatic patients categorized based on their HbA1c levels. Among these patients,57 are males and 50 are females. Out of the total asthmatic patients, 9 males (15.79%) and 12 females (24%) are classified as diabetic, accounting for approximately 43.14% of the total. The prediabetic group comprises 18 patients, making up about 16,82%. The remaining are non-diabetic. The sample's most common age is 45 varies between 30 and 90 years with Mean +-SD (54+_13.9).

Table 1: Relation between Males and ICS duration less than 2years considering Hba1c

Row Labels	Count of HBA1C	StdDev of BSR Day-1	StdDev of BSR Day-45	StdDev of BSR Day-90
40 mg	2	18.4	6.4	20.5
Pre-Diabetic	2	18.4	6.4	20.5
Grand Total	2	18.4	6.4	20.5

Table 2: Relation between Females and ICS duration is less than 2years

Row Labels	Count of HBA1C	StdDev of BSR Day-1	StdDev of BSR Day-45	StdDev of BSR Day-90
40 mg	2	5.7	26.9	4.2
Pre-Diabetic	2	5.7	26.9	4.2
Grand Total	2	5.7	26.9	4.2

Table 3: One Way Anova test is applied in between HBA1c with BSR day 1

Test of Homogeneity of Variances					
		Levene Statistic	df1	df2	Sig.
Hba1c	Based on Mean	1.571	21	56	.012
	Based on Median	.658	21	56	.541
	Based on Median and with adjusted df	.658	21	40.911	.025
	Based on trimmed mean	1.485	21	56	.012

Hba1c					
	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	19.750	51	.387	.806	.028
Within Groups	26.917	56	.481		
Total	46.667	107			

This is the comparison of Hba1c level with blood sugar random at day 1 of asthmatic patients. it indicates a significant difference based on,($p = 0.012$)which is($p<0.05$). However, when considering the median and adjusted degrees of freedom, the difference in variances is also significant ($F(21, 40.911) = 0.658$, $p = 0.025$).

Table 4: One way Anova test applied between Hba1c and BSR level at 45th day

Test of Homogeneity of Variances					
		Levene Statistic	**df1**	**df2**	**Sig.**
Hba1c	Based on Mean	3.998	22	51	.000
	Based on Median	1.139	22	51	.0341
	Based on Median and with adjusted df	1.139	22	17.437	.0395
	Based on trimmed mean	3.852	22	51	.030

ANOVA					
Hba1c					
	Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
Between Groups	22.542	56	.403	.851	.0323
Within Groups	24.125	51	.473		
Total	46.667	107			

The differences in HbA1c values between the various groups are statistically significant. The significant p-value (0.0323) in the ANOVA test suggests that there may be evidence of a statistically significant difference in HbA1c levels between the groups at the 45th day.

Table 5: One-way ANOVA test applied between Hba1c and BSR level at 90th day:

Test of Homogeneity of Variances					
		Levene Statistic	**df1**	**df2**	**Sig.**
Hba1c	Based on Mean	3.352	24	51	.000
	Based on Median	1.894	24	51	.028
	Based on Median and with adjusted df	1.894	24	29.580	.050
	Based on trimmed mean	3.201	24	51	.000

ANOVA					
Hba1c					
	Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
Between Groups	5.990	2	2.995	7.731	.001
Within Groups	40.677	105	.387		
Total	46.667	107			

The ANOVA test confirms that there are significant differences in the mean Hba1c levels at the 90th day of BSR level among the groups being compared, as the p-value is less than 0.05

Table 5: Relationship between Hba1c and ICS duration

Hba1c								
	N	**Mean**	**Std. Deviation**	**Std. Error**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
					Lower Bound	**Upper Bound**		
less than 2 years	4	1.0000	.00000	.00000	1.0000	1.0000	1.00	1.00

2-5 years	21	.7619	.03896	.11761	.5166	1.0072	.00	2.00
more than 5 years	83	1.3494	.05208	.07158	1.2070	1.4918	.00	2.00
Total	108	1.2222	.06041	.06355	1.0962	1.3482	.00	2.00

Test of Homogeneity of Variances					
		Levene Statistic	df1	df2	Sig.
Hba1c	Based on Mean	9.097	2	105	.000
	Based on Median	3.519	2	105	.033
	Based on Median and with adjusted df	3.519	2	101.916	.033
	Based on trimmed mean	9.565	2	105	.000

ANOVA					
Hba1c					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.990	2	2.995	7.731	.001
Within Groups	40.677	105	.387		
Total	46.667	107			

The results presented here offer an analysis of the Hba1c levels in asthmatic patients based on various ICS durations. The mean Hba1c level and SD (1.0±0.00) are displayed. The administration of ICS lasts for fewer than two years. The following results demonstrated that there was a significant difference in the mean and standard deviation (0.7619±0.038) between the asthmatic patients' ICS administration during 2–5 years. At more than 5 years of the administration of ICS, dosages showed Mean± SD (1.3494±0.05208), thus showing significant results.

Table 6: Repeated measures apply on the Bsr level on 1st,45th and 90th day showing comparison with Hba1c

Between-Subjects Factors			
		Value Label	N
Hba1c	.00	normal	14
	1.00	prediabetic	56
	2.00	diabetic	38

Descriptive Statistics				
	Hba1c	Mean	Std. Deviation	N
bsrday1	normal	130.3571	19.50782	14
	prediabetic	126.5773	28.32138	56
	diabetic	136.4211	27.01514	38
	Total	130.5308	27.04447	108
bsrday2	normal	123.0000	22.06285	14
	prediabetic	131.1607	33.02384	56
	diabetic	140.0000	29.32668	38
	Total	133.2130	30.81117	108
bsrday3	normal	129.5714	23.11415	14
	prediabetic	132.2500	27.28653	56

	diabetic	140.5263	35.35590	38
	Total	134.8148	29.97511	108

Tests of Within-Subjects Effects							
Source		**Type III Sum of Squares**	**Df**	**Mean Square**	**F**	**Sig.**	**Partial Eta Squared**
Bsrlevel	Sphericity Assumed	428.299	2	214.149	.715	.049	.007
	Greenhouse-Geisser	428.299	1.931	221.750	.715	.049	.007
	Huynh-Feldt	428.299	2.000	214.149	.715	.049	.007
	Lower-bound	428.299	1.000	428.299	.715	.040	.007
bsrlevel * Hba1c	Sphericity Assumed	839.156	4	209.789	.700	.059	.013
	Greenhouse-Geisser	839.156	3.863	217.235	.700	.059	.013
	Huynh-Feldt	839.156	4.000	209.789	.700	.059	.vggv013
	Lower-bound	839.156	2.000	419.578	.700	.050	.013
Error(bsrlevel)	Sphericity Assumed	62911.743	210	299.580			
	Greenhouse-Geisser	62911.743	202.802	310.213			
	Huynh-Feldt	62911.743	210.000	299.580			
	Lower-bound	62911.743	105.000	599.159			

The mean difference in Hba1c levels between asthmatic patients taking inhaled corticosteroids with "less than 2 years" and "2-5 years" was not statistically significant (mean difference = 0.23810, p = 0.763). The mean difference in Hba1c levels, however, was also not statistically significant for asthmatic patients taking ICS with "less than 2 years" versus "more than 5 years" (mean difference = -0.34940, p = 0.518). Notably, the mean difference in Hba1c levels between asthmatic patients with "2-5 years" and "more than 5 years" of taking ICS was statistically significant (mean difference = -0.58749, p = 0.001.

Hba1c * bsrlevel					
: MEASURE_1					
Hba1c	**Bsrlevel**	**Mean**	**Std. Error**	**95% Confidence Interval**	
				Lower Bound	**Upper Bound**
normal	1	130.357	7.193	116.094	144.620
	2	123.000	8.170	106.800	139.200
	3	129.571	8.003	113.703	145.440
prediabetic	1	126.577	3.597	119.446	133.709
	2	131.161	4.085	123.060	139.261
	3	132.250	4.001	124.316	140.184
diabetic	1	136.421	4.366	127.764	145.079
	2	140.000	4.959	130.167	149.833
	3	140.526	4.858	130.895	150.158

DISCUSSION

Several studies suggest that ICS may contribute to increased blood glucose levels and a higher risk of diabetes onset and progression, especially when used at high doses. For instance, a population-based cohort study found a 34% increased risk of diabetes onset among asthmatic patients using ICS, with a more pronounced effect at higher doses (64% increased risk for those on high doses) This increased risk extends to the progression of diabetes, as ICS use was linked to a 34% higher likelihood of progressing to insulin use research also indicates that ICS can influence glucose metabolism, leading to potential hyperglycemia, although the results are not uniformly conclusive across all studies. Some studies report no significant difference in the risk of hyperglycemia between ICS users and non-users while others highlight a dose-dependent risk associated with high doses of ICS.

CONCLUSION

In conclusion, the results of the ANOVA analysis provide evidence for the significant relation in asthmatic patients especially males developing diabetes while taking ICS therapy. Although recent studies have suggested that high-dose ICS therapy and longer duration might contribute to the development of type-2 diabetes in asthma patients, this idea requires further investigation. Nevertheless, there is reason to consider the clinical implications associated with high-dose ICS therapy in asthma 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 asthma patients with comorbid diabetes.

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