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Original Research Article

Impact of Prolonged Inhaled Corticosteroid Therapy on Glycaemic Control in Paediatric Patients with Persistent Asthma

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Abstract

Background: Asthma is a prevalent chronic respiratory condition in children, often managed with inhaled corticosteroid (ICS) therapy. While ICS therapy is effective in controlling asthma, concerns have arisen about its potential impact on glucose metabolism, particularly in paediatric patients. This study aims to investigate the association between the duration and dose of ICS therapy and glycaemic control in children with persistent asthma, shedding light on the need for monitoring and management of metabolic effects.

Methods: This prospective observational study enrolled 156 children aged 2-18 with persistent asthma. Participants were categorized into groups based on ICS therapy duration and dose. Clinical and demographic data, including HbA1c levels, were collected. Statistical analyses, including correlation and subgroup analyses, were performed to assess the relationship between ICS therapy, HbA1c, and glycaemic control. Ethical approval was obtained, and informed consent was obtained from participants or guardians.

Results: We observed significant differences in HbA1c and fasting glucose levels between cases (children on ICS therapy for over six months) and controls (children on ICS therapy for 1-6 months). Cases had higher HbA1c levels (6.6% ± 0.4%) compared to controls (5.9% ± 0.3%), with a mean difference of 0.7% ($p < 0.0001$). Additionally, cases showed elevated fasting glucose levels (90.5 mg/dL ± 5.2 mg/dL) in contrast to controls (85.3 mg/dL ± 4.8 mg/dL), with a mean difference of 5.2 mg/dL ($p < 0.0001$). These findings underscore the link between prolonged ICS therapy and adverse glucose metabolism.

Conclusion: Our study highlights a significant association between prolonged inhaled corticosteroid (ICS) therapy and elevated HbA1c and fasting glucose levels in paediatric patients with persistent asthma. Regardless of age or asthma severity, longer ICS treatment was linked to higher HbA1c levels. These findings emphasize the importance of regular monitoring and management of glucose metabolism in this population to optimize asthma care and overall health.

Keywords: Asthma, Inhaled corticosteroids, HbA1c, Paediatric, Glucose metabolism.

Introduction

Asthma, a chronic inflammatory airway disease, represents a substantial global health burden, affecting millions of children worldwide. In the United States alone, approximately 5.5 million children under the age of 18 are diagnosed with asthma, making it one of the most prevalent chronic diseases in this population [1]. Although asthma is highly manageable with a variety of therapeutic interventions, the long-term effects of certain treatments on the metabolic health of paediatric patients have raised important questions and sparked ongoing research interest [2]. Inhaled corticosteroids (ICS) have revolutionized asthma management, offering effective control of airway inflammation and symptom relief. These medications have become a mainstay in the treatment of persistent asthma, playing a pivotal role in reducing asthma-related hospitalizations and improving patients' overall quality of life [2,3]. Despite their undeniable benefits, the use of ICS in children has also been associated with potential metabolic consequences, particularly alterations in glucose metabolism [3].

Haemoglobin A1c (HbA1c) is a well-established marker for evaluating long-term glycaemic control, primarily used in the management of diabetes mellitus. HbA1c reflects the average blood glucose levels over the past two to three months, providing valuable insights into an individual's metabolic health [4]. Recent studies have suggested that ICS therapy may influence HbA1c levels, raising concerns about its impact on glucose regulation in paediatric patients with persistent asthma [5].

The relationship between ICS use and HbA1c levels in children with asthma is an emerging area of interest with far-reaching clinical implications [6]. Understanding how ICS therapy may affect glycaemic control is essential, as it has the potential to influence treatment decisions, patient monitoring, and long-term health outcomes in this vulnerable population [7]. Moreover, factors that may mediate or modify the relationship between ICS and HbA1c levels, such as the duration of treatment, asthma severity, and age of the patient, warrant comprehensive investigation [8].

This study was conducted with an aim to find the correlation between ICS therapy and HbA1c levels in children with persistent asthma. By exploring the potential impact of ICS treatment on glycaemic control and identifying key determinants of HbA1c alterations, we seek to provide critical insights that can inform clinical practice and enhance the care of paediatric asthma patients. In doing so, we hope to contribute to the ongoing dialogue surrounding the safety and efficacy of ICS therapy in this population, ultimately improving the management and long-term outcomes of children living with persistent asthma.

Materials and Methods

Study Design

We conducted a descriptive cohort study among children with persistent asthma receiving inhaled corticosteroids (ICS) in the department of Paediatrics in a tertiary care hospital of North India for a period of 1 year between January 2020 to January 2021. Ethical approval for the study was obtained from the Institutional Review Board (IRB) ensuring compliance with ethical guidelines and informed consent procedures. The study adhered to the principles outlined in the Declaration of Helsinki and local regulatory requirements. We obtained informed consent from the parents or legal guardians of all participants, and for individuals aged 14 years and older, we also sought their assent.

Study Population

The study included paediatric patients aged 2 to 18 years with confirmed diagnoses of persistent asthma based on the National Asthma Education and Prevention Program (NAEPP) guidelines (5).

Inclusion criteria required that patients had been on continuous ICS therapy for a minimum of one month and had undergone HbA1c measurements during the study period. Children with coexisting pulmonary, renal, or cardiac disease and those with diabetes were excluded from the study to maintain a specific focus on paediatric patients with persistent asthma without complicating factors, ensuring a more homogeneous study population for the investigation of the relationship between inhaled corticosteroid therapy and HbA1c levels.

Sample size

To calculate the sample size for our study with a mean difference of 0.3, we used the formula $n = (Z\alpha/2+Z\beta/\text{Mean Difference})2\times SD^2$ where n represents the required sample size, $Z\alpha/2$ corresponds to the chosen significance level (e.g., 1.96 for 95% confidence), $Z\beta$ represents the desired power (e.g., 0.84 for 80% power), the Mean Difference was the expected difference (0.3 in a study by Daniel et al.,), and SD stands for the standard deviation [2]. For instance, with a 95% confidence level and 80% power, assuming a standard deviation of 0.5, the calculation yielded a minimum sample size of approximately 141 participants required to detect a mean difference of 0.3. So, a total of 156 participants were included in the study taking drop out into consideration.

Sample collection

A 3 mL whole blood sample was aseptically collected from each participant using a vacuum collection tube containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. The choice of EDTA was made to prevent coagulation and maintain blood sample integrity. Subsequently, HbA1c levels were quantified using the D-10 Haemoglobin Program, a well-established and standardized method for HbA1c measurement. This program is recognized for its accuracy and reliability in assessing long-term glycaemic control, particularly in individuals with diabetes. The entire process, from sample collection to analysis, was conducted following established laboratory protocols and quality control measures to ensure the precision and validity of the results.

Data Collection

Data for this study was collected using preformed questionnaire and encompassed demographic characteristics (age, gender, ethnicity, height, weight), clinical variables (asthma severity, duration of ICS therapy, blood pressure, steroid dose), and laboratory measurements (HbA1c levels, a recommended HbA1c measurement cut-off value of ≥ 6.0% for the diagnosis of diabetes, and fasting blood glucose levels). In accordance with the Global Initiative for Asthma (GINA) guidelines, the selection of inhaled corticosteroid (ICS) dosages was based on the age and severity of asthma among study participants. For adolescents aged >11 years, the recommended dosages for budesonide were categorized into low (200-400 micrograms/day), medium (>400-800 micrograms/day), and high (>800 micrograms/day) levels. Similarly, dosages of fluticasone propionate for adolescents included low (100-250 micrograms/day), medium (>250-500 micrograms/day), and high (>500 micrograms/day) levels. For children aged 6-11 years, budesonide dosages consisted of low (100-200 micrograms/day), medium (>200-400

micrograms/day), and high (>400 micrograms/day) levels, while fluticasone propionate dosages included low (100-200 micrograms/day), medium (>200-400 micrograms/day), and high (>400 micrograms/day) levels. These dosages served as a guideline for tailoring the asthma treatment regimen for participants based on their age and asthma severity. Individual adjustments were made as necessary to ensure optimal asthma management throughout the study period. In this study, we classified the study participants into two distinct groups. The first group, referred to as "cases," consisted of children diagnosed with asthma who had a history of receiving inhaled corticosteroid (ICS) therapy continuously for more than six months. These cases represented individuals with a more prolonged exposure to ICS treatment. The second group, termed "controls," comprised children with asthma who had been on ICS therapy for a period ranging from 1 to 6 months. These controls were selected to represent individuals with a relatively shorter duration of ICS therapy. By distinguishing between cases and controls based on the duration of ICS treatment, we aimed to assess the potential impact of the length of exposure to ICS on various study outcomes or variables.

Statistical Analysis

Descriptive statistics, including means, and standard deviations (SD) were employed to summarize the demographic and clinical characteristics of the study population. Independent t-tests and chi-squared tests were utilized to compare continuous and categorical variables between cases and controls, respectively. A comparative analysis was performed using t-tests to examine whether there were significant differences in HbA1c levels between the "cases" (children with prolonged ICS therapy) and "controls" (children with shorter ICS therapy duration). Correlation coefficients (Pearson correlation) were calculated to explore the strength and direction of the relationship between the duration of ICS therapy (in months) and HbA1c levels. Stratified analyses were conducted within these subgroups to explore variations in the relationship between ICS therapy duration and HbA1c levels. Statistical significance was defined as $p < 0.05$. All statistical analyses were carried out using SPSS version 20.0.

Result

In the present study, we compared the characteristics of paediatric patients with persistent asthma who were receiving inhaled corticosteroid (ICS) therapy for varying durations. The study included a total of 156 participants, with 74 cases (children on ICS therapy for more than six months) and 82 controls (children on ICS therapy for 1-6 months). In this study comparing 74 cases (children on ICS therapy for over six months) and 82 controls (children on ICS therapy for 1-6 months), demographic characteristics such as age, gender, and residence were similar between the two groups ($p > 0.05$). Likewise, there were no significant differences in mean height, weight, or asthma severity. However, cases had a substantially longer mean duration of ICS therapy (8.5 ± 3.1 months) compared to controls (3.8 ± 1.9 months), and a higher mean steroid dose (343.2 ± 46.9 µg/day) compared to controls (241.3 ± 50.2 µg/day), both of which were statistically significant ($p < 0.0001$). Mean blood pressure did not significantly differ between cases and controls ($p = 0.463$). These findings lay the groundwork for investigating the relationship between HbA1c levels and ICS therapy duration (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Participants.

Characteristic	Cases (N=74)	Controls (N=82)	p-value
	n (%)	n (%)	
Mean Age (years)	9.7 ± 2.3	10.2 ± 2.1	0.157
Gender			
Male	40 (54.1%)	43 (52.4%)	0.840
Female	34 (45.9%)	39 (47.6%)	
Residence			
Urban	56 (75.7%)	58 (70.7%)	0.486
Rural	18 (24.3%)	24 (29.3%)	
Mean Height (cm)	132.5 ± 7.8	134.1 ± 8.3	0.218
Mean Weight (kg)	31.4 ± 4.5	32.8 ± 5.1	0.072
Asthma Severity			
Mild	15 (20.3%)	18 (22.0%)	0.797
Moderate	45 (60.8%)	48 (58.5%)	0.772
Severe	14 (18.9%)	16 (19.5%)	0.925
Mean Duration of ICS Therapy (months)	8.5 ± 3.1	3.8 ± 1.9	<0.0001
Mean Blood Pressure (mmHg)	116 ± 9	117 ± 8	0.463
Mean Steroid Dose (µg/day)	343.2 ± 46.9	241.3 ± 50.2	<0.0001

This study revealed significant differences in HbA1c and fasting glucose levels between cases (children on ICS therapy for over six months) and controls (children on ICS therapy for 1-6 months). Cases had higher HbA1c levels (5.6% ± 0.4%) compared to controls (4.9% ± 0.3%), with a mean difference of 0.7% (95% CI: 0.1% to 1.2%, p < 0.0001). Additionally, cases showed elevated fasting glucose levels (90.5 mg/dL ± 5.2 mg/dL) in contrast to controls (85.3 mg/dL ± 4.8 mg/dL), with a mean difference of 5.2 mg/dL (95% CI: 1.8 mg/dL to 12.2 mg/dL, p < 0.0001). These findings underscore the link between prolonged ICS therapy and adverse glucose metabolism, as reflected in higher HbA1c and fasting glucose levels in cases compared to controls (Table 2).

Table 2: Comparison of HbA1c and Fasting Glucose Levels Between Cases and Controls.

Parameter	Cases (N=74)	Controls (N=82)	Mean difference (95% CI)	p-value
HbA1c Levels (%)	5.6 ± 0.4	4.9 ± 0.3	0.7 (0.1, 1.2)	<0.0001
Fasting Glucose Levels (mg/dL)	90.5 ± 5.2	85.3 ± 4.8	5.2 (1.8, 12.2)	<0.0001

The analysis of HbA1c cut-off levels in cases (children on ICS therapy for over six months) and controls (children on ICS therapy for 1-6 months) revealed noteworthy differences in HbA1c distribution. Specifically, in the < 5.0% category, cases accounted for 3 (4.1%) individuals, while controls had 46 (56.1%) individuals, showing a trend toward significance (p = 0.072). For the 5.0 - 5.5% category, cases constituted 21 (28.3%) participants, while controls had 24 (29.2%) participants, demonstrating a significant difference (p = 0.017). Similarly, in the 5.6 – 5.9% category, cases included 39 (52.7%) individuals, while controls comprised 8 (9.8%) individuals, also exhibiting a significant difference (p = 0.022). Most notably, in the ≥ 6.0% category, cases comprised 11 (14.9%) participants, whereas controls had only 4 (4.9%) participants, indicating a highly significant difference (p < 0.0001). These results highlight a substantial disparity in the distribution of HbA1c levels, particularly in the higher HbA1c categories, between cases and controls, underscoring the potential impact of prolonged ICS therapy on elevated HbA1c levels (Table 3).

Table 3: Distribution of HbA1c Cut-off Levels in Cases and Controls

HbA1c Cut-off Level (%)	Cases (N=74)	Controls (N=82)	p-value
	n (%)	n (%)	
< 5.0	3 (4.1%)	46 (56.1%)	0.072
5.0 - 5.5	21 (28.3%)	24 (29.2%)	0.017
5.6 – 5.9	39 (52.7%)	8 (9.8%)	0.022
≥ 6.0	11 (14.9%)	4 (4.9%)	<0.0001

In the subgroup analysis based on asthma severity, significant differences in HbA1c levels were observed among mild, moderate, and severe cases. For individuals classified as having mild asthma (N=33), the mean HbA1c level was 4.7% ± 0.4%, which was significantly lower than both moderate and severe cases, with a mean difference of 0.9% (95% CI: 0.1% to 1.2%, p < 0.0001). Among those with moderate asthma (N=93), the mean HbA1c level was 5.2% ± 0.4%. Finally, for individuals with severe asthma (N=30), the mean HbA1c level was the highest at 5.6% ± 0.5% (Table 4).

Table 4: Subgroup Analysis of HbA1c Levels by Asthma Severity.

Subgroup	HbA1c Levels (%)	Mean Difference (95% CI)	p-value
Mild (N=33)	4.7 ± 0.4	0.9 (0.1, 1.2)	<0.0001
Moderate (N=93)	5.2 ± 0.4		
Severe (N=30)	5.6 ± 0.5		

In our investigation of the relationship between steroid dose and HbA1c levels, significant differences emerged among participants categorized by low, medium, and high steroid doses. Among those receiving a low steroid dose (200-400 µg/day, N=56), the mean HbA1c level was 4.7% ± 0.3%, which was significantly lower than both the medium and high dose groups (p < 0.0001). In the medium steroid dose category (>400-800 µg/day, N=74), the mean HbA1c level was 5.0% ± 0.4%, and in the high steroid dose group (>800 µg/day, N=26), the mean HbA1c level was the highest at 5.3% ± 0.5% (Table 5).

Table 5: Steroid Doses and HbA1c Levels

Steroid Dose	Frequency	HbA1c Levels (%)	p-value
Low (200-400 µg/day)	56	4.7 ± 0.3	<0.0001
Medium (>400-800 µg/day)	74	5.0 ± 0.4	
High (>800 µg/day)	26	5.3 ± 0.5	

The Table 6 presents the results of correlation analyses between the duration of inhaled corticosteroid (ICS) therapy and HbA1c levels in our study population, stratified by age groups. For adolescents (>11 years), we observed a moderate positive correlation (r = 0.23) between the duration of ICS therapy and HbA1c levels. This suggests that as the duration of ICS therapy increased among adolescents, their HbA1c levels tended to rise as well. The correlation was statistically significant with a p-value of 0.002. In the case of children aged 6-11 years, a weaker but still positive correlation (r = 0.11) was found between ICS therapy duration and HbA1c levels. This indicates that for this age group, as the duration of ICS therapy extended, there was a tendency for HbA1c levels to increase. The correlation was statistically significant with a p-value of 0.012. When considering the entire study population (Overall), which includes both adolescents and children, a moderate positive correlation (r = 0.27) between ICS therapy duration and HbA1c levels was evident. This suggests that as the duration of ICS therapy increased across all age groups (6-18 years), HbA1c levels showed a corresponding upward trend. The correlation in the overall population was statistically significant with a p-value of 0.003. In summary, these findings indicate that a longer duration of ICS therapy is associated with higher HbA1c levels, irrespective of age. This underscores the potential impact of prolonged ICS treatment on glycaemic control in paediatric patients with persistent asthma, highlighting the need for monitoring and management of glucose metabolism in this population.

Table 6: Pearson's Correlation Between Duration of ICS Therapy and HbA1c Levels by Age Group

Age Group	Frequency	Correlation Coefficient (r)	p-value
Adolescents (>11 years)	65	0.23 (0.06, 0.40)	0.002
Children (2-11 years)	91	0.11 (0.09 to 0.30)	0.012
Overall	156	0.27 (0.09, 0.45)	0.003

Discussion

Our study investigated the impact of prolonged inhaled corticosteroid (ICS) therapy on glycaemic parameters in paediatric patients with persistent asthma. The findings shed light on the intricate relationship between ICS therapy, glycaemic control, and potential clinical implications.

In our study the mean age of cases was 9.7 ± 2.3 years, which was in congruence with the study by Lodha et al., [9]. Also, study the male preponderance was observed which was consistent with the study by Sears et al., and Bjornson et al., [10,11]. In our study around three fourth of children in cases and controls groups were from the urban area, which was also observed in the studies by Litonjua et al. Kant et al., and Hafron et al., [12,13,14].

In our study the severe asthma was observed in about two fifth of the children [cases: 18.9%, and controls: 19.5%], which was in congruence with the study by Lodha et al., [9].

In our study, there was significant difference in HbA1c levels between cases (children on ICS therapy for over six months) and controls (children on ICS therapy for 1-6 months). Cases displayed higher HbA1c levels, with a mean difference of 0.7%. This finding is consistent with study by Kiviranta et al., and Sathiyapriya et al., suggesting that prolonged ICS therapy may lead to impaired glycaemic control [15,16]. A study by Dawson et al., showed that high dose nebulized salbutamol significantly increased mean blood glucose levels [17]. But Turpeinen et al., who found no association between use of inhaled budesonide and carbohydrate metabolism [18]. Elevated HbA1c levels in our cases indicate suboptimal long-term glucose management, which could have important clinical implications. These findings underscore the need for regular monitoring of glycaemic parameters in paediatric patients with persistent asthma receiving long-term ICS therapy.

Moreover, our study delved into the distribution of HbA1c levels among cases and controls across various cut-off categories. Of particular note was the substantial difference in the ≥ 6.0% category, where cases significantly outnumbered controls. These findings were in accordance with the study by Sankaravadivelu et al., who showed 9.3% of children on long term ICS having elevated Hba1c [19]. Daniel S et al., reported high risk HbA1c in only 3.5% subjects [2]. This striking disparity in the distribution of higher HbA1c levels suggests that prolonged ICS therapy may predispose paediatric patients to elevated HbA1c levels, potentially increasing their risk of developing impaired glucose tolerance or type 2 diabetes. It is imperative for healthcare providers to be vigilant and consider glycaemic monitoring as an integral part of managing asthma in this population.

The relationship between asthma severity and glycaemic control also merits attention. Our study revealed that individuals with more severe asthma tended to have higher HbA1c levels. This finding aligns with the concept that the systemic effects of ICS therapy, including altered glucose metabolism, may be more pronounced in patients with severe asthma. Our results were in agreement with the study by Yucel et al., [20]. where they found out a

mean HbA1c value of 5.44±0.75% among the children with asthma and 5.14±0.41% in the control group [20]. A similar pattern was noted in the study by Singh et al., [21]. However, further research is needed to elucidate the mechanisms underlying this relationship and explore whether optimizing asthma control could mitigate the impact on glycaemic parameters.

Steroid dose, another key factor, exhibited a clear association with HbA1c levels. Higher steroid doses were linked to elevated HbA1c levels, signifying a dose-response relationship. This finding underscores the importance of carefully tailoring steroid doses in paediatric patients, aiming to strike a balance between effective asthma control and minimizing potential metabolic side effects. However, Bindusha et al., found no statistically significant difference was found between the mean HbA1c levels of the children using a low dose (6.013±1.185) and high dose inhaled steroids (6.206±1.365) for at least six months [22].

Our correlation analysis, stratified by age groups, provided valuable insights. Adolescents exhibited a moderate positive correlation between the duration of ICS therapy and HbA1c levels, suggesting that glycaemic control may be more susceptible to the effects of prolonged ICS therapy in this age group. Paediatric healthcare providers should pay special attention to glycaemic monitoring and management when treating adolescents with persistent asthma.

Limitations

The strengths of our study lie in its robust design, including a relatively large sample size and detailed glycaemic parameter assessments. However, several limitations should be acknowledged. Firstly, the cross-sectional nature of the study design limits our ability to establish causation. Longitudinal studies are needed to elucidate the temporal relationship between ICS therapy and glycaemic outcomes. Secondly, our study did not explore potential confounding variables such as dietary habits and physical activity, which could influence glycaemic parameters. Future research should consider these factors for a more comprehensive understanding. Lastly, our study focused on paediatric patients with persistent asthma, and the findings may not be directly generalizable to other populations or age groups.

Conclusion

In conclusion, our study highlights the association between prolonged ICS therapy and adverse glycaemic outcomes in paediatric patients with persistent asthma. The higher HbA1c levels observed in cases underscore the importance of glycaemic monitoring and individualized management strategies for this population. Asthma severity, steroid dose, and age further modulate this relationship, emphasizing the need for personalized care. These findings should prompt healthcare providers to consider the potential impact of ICS therapy on glucose metabolism and take proactive measures to mitigate the associated risks. Further research is warranted to elucidate the underlying mechanisms and long-term clinical implications of these findings in paediatric patients with asthma.

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