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Effect of Inhaled Corticosteroids on Blood Glucose Homeostasis in Asthmatic Children

Alshaimaa Mohammed Essam^[a]; Mohamed Ibrahim Abdel-Aal ^[b]; Hesham Samir Abd Al-samee^[c]

Department of Pediatrics, Faculty of Medicine, Mansura University, Egypt ^[a].

Department of Pediatrics, Damietta Faculty of Medicine, Al-Azhar University, Egypt^[b]

Department of Clinical Pathology, Damietta Faculty of Medicine, Al-Azhar University, Egypt^[c]

Corresponding author: **Alshaimaa Mohammed Essam**

Email: dr_shin89@yahoo.com

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ABSTRACT

Background: Asthma is a common disease especially in kids. The development of asthma symptoms appears to involve a combination of genetic predisposition and environmental factors. There are many medicines for asthma management, the most important of which is corticosteroid. High doses of inhaled corticosteroids can be associated with hyperglycemia risk increase.

Aim of the work: To detect the effect of inhaled corticosteroids on blood glucose homeostasis in asthmatic children.

Patients and Methods: This study was conducted at pediatric inpatient and outpatient clinic of New Damietta Al-Azhar University Hospital in the period from September 2018 to September 2019, included 90 asthmatic children chosen randomly, 55 of them were males and 35 of them were females, aged from 2 to 12 years, For each child, the demographic data were collected, divided into three groups according to type of treatment, group I [using ICS only for more than 3 months], group II [using SCS] and group III [using ICS & SCS].

Results: Regarding WBCs and its differentiation there was a significant increase in WBCs $[7.8 \pm 2.1]$ and eosinophil $[2.7 \pm 0.83]$ in [group III] more than [group I]; WBCs $[5.8 \pm 2.2]$ and eosinophil $[1.4 \pm 0.6]$ and [group II]; WBCs $[6.4 \pm 2.0]$ and eosinophil $[1.5 \pm 0.7]$. Regarding blood glucose, [group I] mean value was $[89.6 \pm 22.8]$; [group II] was $[91.6 \pm 17.3]$; [group III] was $[104.4 \pm 36.1]$. There was statistically significant difference between group I with III and group II with III [P2: 0.032 and P3: 0.043].

Conclusion: Blood glucose level increased in children using both inhaled and systemic corticosteroids and it was significant statistically.

Keywords: Corticosteroids; Inhaled; Glucose; Asthma; Children.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways of the lungs which is characterized by recurring symptoms of airway obstruction secondary to mucosal edema, the development of excess mucus and bronchoconstriction with episodes of wheezing, coughing, chest tightness, and shortness of breath^[1]. Globally, around 300 million people are estimated to be asthmatics. Asthma is estimated to cause approximately 180,000 deaths worldwide annually^[2]. Asthma severity is classified into four levels based on symptoms level, airflow limitations, and lung function: intermittent, mildly persistent, moderately persistent, and severely persistent^[3].

To handle patients with asthma, it is important to include pharmacological and non-pharmacological treatments, and follow-up assessment of asthma control and exacerbations. Pharmacological asthma therapies include: device medicines, e.g. Inhaled corticosteroids [ICS], antagonists of leukotriene [LTRA], drugs to relieve symptoms [i.e. short-acting β 2-adrenoceptor agonists [SABA] or β 2-agonists] and add-on controller medications e.g. long-acting β 2-adrenoceptor agonists [LABA], monoclonal antibody anti-IgE and systemic corticosteroids in chronic asthma cases^[4]. The anti-inflammatory nature of systemic corticosteroids [SCS] is the key to their efficacy in asthma. At present, at least half of all people with asthma are suspected to have primarily eosinophilic inflammation, including the majority of allergy-related early onset illness. Corticosteroids are effective in targeting many of this pathway's^[5]. Exogenous glucocorticoid administration can induce altered glucose metabolism including hyperglycemia. This can lead to either the development of new-onset diabetes or a decline of glycemic control in those with pre-existing diabetes^[6]. Glucocorticoids exert their dysglycemic actions by different mechanisms including: reduced insulin secretion [beta cell dysfunction], increased insulin resistance, reduced insulin sensitivity and increased neoglucogenesis and glycogenolysis. Steroids also cause body fat redistribution. Leptin and adiponectin from adipose tissue improve insulin signaling and induce insulin resistance, exacerbating dysglycemia^[7]. Glycosylated hemoglobin and fasting blood sugars are criteria used in this analysis to determine the glycemic state ^[8]. HbA1c is a better parameter than

fasting blood sugar [FBS] and postprandial blood sugar [PPBS] because it's a correlate of glucose levels over the life span of red blood cell [RBC] approximately, 80-120 days^[9].

With various methods to detect glycosylated hemoglobin, values are accepted only if labs are NGSP [National glycosylated hemoglobin program] certified and standardized to Check for Diabetes and Complications^[10].

AIM OF THE WORK

To detect the effect of inhaled corticosteroids on blood glucose homeostasis in asthmatic children.

PATIENTS AND METHODS

This study was cohort that had been conducted in two days per week at New Damietta Al-Azhar University Hospital's [pediatric department and outpatient clinic] between September 2018 and September 2019. The study included 90 children with asthma chosen randomly, 55 of whom were males and 35 were females. The children were split into 3 groups: **Group 1:** 30 asthmatic children receiving ICS only for more than three months. **Group 2:** 30 asthmatic children receiving systemic corticosteroids only. **Group 3:** 30 asthmatic children receiving both ICS and systemic corticosteroids.

Inclusion criteria were; asthmatic children, of both genders aged from 2-12 years and were receiving treatment with steroids for different periods. We excluded all children with apparent congenital anomalies e.g. down syndrome, congenital heart disease etc., Children with any disease affect glucose homeostasis e.g. diabetes mellitus [DM], hyperthyroidism etc. and positive Family history of D.M.

We clarified the intent of this research to the guardians, and an informed consent to do it. Furthermore, protection of all data was guaranteed. All children in the sample are subjected to complete history, detailed medical review, laboratory investigations [Blood glucose level, Hemoglobin A1c level, CBC and differential count]. Diabetic fasting blood glucose: more than 126mg/dl, 2 hours postprandial diabetic blood glucose: more than 200mg/dl and random diabetic blood glucose: more than 200 mg/dl ^[11].

Statistical analysis: Using IBM SPSS software package version 20.0 the data was fed to the

computer. Using number and per cent, qualitative data were described. Comparison between different groups was tested by Chi-square test [χ^2] or Fisher Exact. Quantitative data were represented using mean and standard deviation [SD] for normally distributed data, while abnormally distributed results were expressed using the median. F-test [ANOVA] was used in comparison between more than two populations. If [P-value < 0.05] the p-value was considered significant.

RESULTS

This study included 90 asthmatic children, they were 55 males [61.1%] and 35 females [38.8%]. Mean age of group 1, 2, 3 was 7.07 ± 2.67 , 6.73 ± 3.27 and 6.45 ± 3.09 respectively. There was no significant difference in all demographic data and vital signs between all studied groups. In addition, it was found that there was no statistically significant difference between the studied groups regarding level of asthma symptoms control [Table 1]. The duration of asthma and duration of treatment were

nearly the same among studied groups with no significant difference [Table 2].

Regarding WBCs and its differentiation, there was a significant increase in WBCs and eosinophil in group III more than group I and Group II; but there was no statistical significant difference between the three studied groups regarding other components of complete blood count [CBC] [Table 3].

Table [4] shows comparison between the studied groups regarding random blood glucose and HA1c. In group I, the mean value of blood glucose was 89.6 ± 22.8 , and in group II, it was 91.6 ± 17.3 and in group III, it was 104.4 ± 36.1 . HA1C was 4.9 ± 0.3 , 4.9 ± 0.4 and 5.0 ± 0.5 in groups I, II and III respectively. There was no significant difference between group I and II while there was statistical significant difference between group I with III and group II with III regarding blood glucose and there was no statistically significant difference between three studied groups regarding HA1C.

Table [1]: Comparison between the three studied groups regarding level of asthma symptoms control.

Level of asthma symptom control	Group I [ICS] [n=30]	Group II [Systemic Corticosteroids] [n=30]	Group III [ICS + S. corticosteroids] [n=30]	X ²	P value
Well Controlled %	8 [26.7%]	11 [36.7%]	6 [20.0%]	1.36	0.231
Not well controlled	16 [53.3%]	13 [43.3%]	11 [36.7%]	2.07	0.107
Very poorly Controlled	6 [20.0%]	6 [20.0%]	13 [43.3%]	3.01	0.068

ICS: inhaled corticosteroids / S. corticosteroids: Systemic corticosteroids

Table [2]: Disease duration and duration of treatment among studied groups.

	Group I [ICS] [n=30]	Group II [Systemic Corticosteroid] [n=30]	Group III [ICS + S. corticosteroids] [n=30]	ANOVA	P value
Disease duration [years]	4.05 ± 2.0	3.33 ± 1.69	3.27 ± 1.87	1.75	0.123
Duration of treatment [months]	12.32 ± 3.15	10.25 ± 4.22	10.2 ± 3.54	2.01	0.621

Table [3]: Comparison between the three studied groups regarding blood picture

	Group I [ICS] [n=30]	Group II [Systemic Corticosteroids] [n=30]	Group III [ICS + S. corticosteroids] [n=30]	ANOVA	P value
RBC	$4.5 \pm [0.9]$	$4.5 \pm [0.7]$	$4.4 \pm [0.7]$	0.652	0.824
HB gm/dl	$12.3 \pm [2.7]$	$12.2 \pm [2.2]$	$12.6 \pm [2.6]$	0.265	0.589
HCT %	$34.5 \pm [6.0]$	$34.2 \pm [5.5]$	$34.5 \pm [5.6]$	0.115	0.798
MCV [fl]	$73.1 \pm [12.0]$	$68.7 \pm [18.6]$	$69.9 \pm [14.2]$	2.32	0.104
MCH [pg]	$31.1 \pm [9.6]$	$25.6 \pm [5.1]$	$27.0 \pm [3.9]$	1.25	0.214
MCHC %	$33.8 \pm [3.5]$	$33.9 \pm [3.1]$	$33.5 \pm [3.2]$	0.12	0.789
PLT	$164.3 \pm [75.2]$	$156.9 \pm [49.0]$	$152.4 \pm [43.1]$	1.98	0.121
WBC	5.8 ± 2.2	6.4 ± 2.0	7.8 ± 2.1	6.03	0.015*
Neutrophils	1.4 ± 0.7	1.7 ± 0.65	1.2 ± 0.7	0.98	0.651
Lymphocytes	2.7 ± 0.9	3.1 ± 1.0	2.9 ± 0.8	2.11	0.104
Eosinophils	1.4 ± 0.6	1.5 ± 0.7	2.7 ± 0.83	5.82	0.044*
Monocytes	1.6 ± 1.1	1.9 ± 1.0	1.6 ± 1.0	0.4123	0.714

*: significant; RBC: red blood cells / HCT: hematocrit / PLT: platelets / WBC: white blood cells

Table [4]: Comparison between the three studied groups regarding blood glucose and HA1c.

	Group I [ICS] [n=30]	Group II Systemic Corticosteroids [n=30]	Group III ICS + S. corticosteroids [n=30]	ANOVA P value	P1 P2 P3
Blood glucose	89.6±22.8	91.6±17.3	104.4±36.1	14.2 0.032*	0.352 0.032* 0.043*
HA1C	4.9± 0.3	4.9 ±0.4	5.0± 0.5	1.25 0.211	0.459 0.119 0.162

P1 comparison between group I and II; P2 comparison between group I and III; P3 comparison between group II and III; *: significant

DISCUSSION

Over the past two decades the occurrence of asthma among children has steadily increased worldwide. Significant evidence shows that, there is a major regional variation in asthma prevalence and the relative weight of risk factors^[12].

Treatment of rapidly worsening symptoms of asthma is usually with an inhaled short-acting beta-2 agonist such as salbutamol and/or oral corticosteroids. In very severe cases, hospitalization and intravenous cortico-steroids may be required. The use of inhaled corticosteroids [ICS] will reduce asthma by preventing stimuli such as allergens and irritants. Long-acting beta2 agonists [LABA], inhaled cortico-steroids, antileukotriene agents may be used if the asthma symptoms stay uncontrolled^[13].

Inhaled corticosteroids [ICS] are the preferred treatment of chronic asthma in children of any age. Chronic use of ICS increases long-term results for children of all ages with chronic mild to severe asthma. Nevertheless, chronic use of ICS can cause systemic adverse effects^[14].

Hemoglobin A1c [HbA1c] levels indicate the normal blood glucose concentration during the preceding 2-3 months. Another research has shown that blood glucose levels in children with asthma have increased with high doses of inhaled or oral corticosteroids^[15].

In our study the blood picture in the three groups show non-significant difference regarding RBC, HB, HCT, MCV, MCH, MCHC and PLT. WBCs of the other hand showed statistical variance between groups [it was 5.8±2.2, 6.4±2.0 and 7.8±2.1 in groups I, II and III successively]. Eosinophil showed similar distribution.

These results agree with the study of **Pasternak et al.**^[16]. They found that conventional dose

administration of currently used inhaled CSs significantly increased the WBC. This effect was mainly attributed to an increase in absolute neutrophil count [ANC]; thus, the percentage of neutrophils in the total leukocyte count increased significantly, while the lymphocyte count decreased significantly. Such results were found in all inhaled CS classes, although the amount of change and the extent of statistical significance varied based on the individual CS and the inhalation process^[16].

We observed that blood glucose and HA1c showed significantly different findings.

In a prospective cohort study involving 1698 subjects, it was found that the use of ICS was linked to a dose-dependent increase in serum glucose levels in patients known to have diabetes. This study showed that there was a 1.82 mg/dL rise in plasma glucose concentration in patients with COPD and pre-existing diabetes for every additional 100µg of inhaled triamcinolone used [or equivalent]. However, such glycemic control effects have not been observed among patients without a history of diabetes^[17].

In partial agreement with our results, a study by **Bindusha et al.**^[17] reported that, there was no significant difference in fasting blood sugar [p=0.447] and glycosylated hemoglobin levels [p=0.305] in low-dose and high-dose asthmatic children with Budesonide/Fluticasone for at least 6 months.

Earlier report by **Yucel et al.**^[18] concluded that, asthmatic children with low-dose corticosteroids [budesonide and fluticasone] had higher glycolysated hemoglobin values, 5.44 per cent higher than healthy subjects [p=0.006]. In both groups, the mean HbA1c levels were less than 6.5 per cent within the normal range.

A comparative study by **Daniel et al.**^[19] showed similar results, a higher glycosylated hemoglobin

level seen in asthmatic children on ICS for 6 months compared to baseline values [$p < 0.001$]. The study also found that glycosylated hemoglobin levels were higher in children on medium-dose ICS compared with lower doses [$p < 0.001$].

In conclusion, results of the current work revealed that, glucose level increased in children using both inhaled and systemic corticosteroids.

Financial and Non-Financial Relationships and Activities of Interest

None

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