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Research Article

The Role of Iron Status in Pediatric Asthma Severity

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Abstract

Higher iron status has been associated with a lower prevalence of asthma and asthma attacks. However, the associations between iron status and asthma-related outcomes have not been well investigated in pediatrics. For this reason, we evaluated the iron status in asthmatic children and determined its relation to clinical asthma severity. A total of seventy cases aged from 6-17 years were recruited in this study - including fifty asthmatic patients and twenty age and sex-matched healthy controls. Complete blood count, iron profile including (Serum iron, ferritin, Total Iron Binding Capacity (TIBC) and transferring saturation) were measured in patients and controls and according to them, asthmatic patients were divided into asthmatic children without Iron Deficiency Anemia (IDA), asthmatic children with IDA. Associations between iron status and the severity of bronchial asthma were assessed in the patient groups. The study found that IDA was presented among 34% of the studied asthmatic patients compared to 20% in the control group (P<0.001). Moreover, the asthmatic attacks were significantly more frequent and severe in asthmatics with IDA (88.3%, 64.7%) than those without IDA (51.5%, 45.5%) (P<0.001) with frequent emergency room visits and hospital admissions among asthmatics with IDA (70.6%, 41.1%) (P=0.037, 0.041). Thus IDA is prevalent among asthmatic children and lower iron status has been associated with higher rates of asthma attacks and more severe course of the disease.

Keywords: Asthma; Asthma Attacks; Iron Deficiency Anemia; Pediatric; Severity

Abbreviations

CBC: Complete Blood Count; TIBC: Total Iron Binding Capacity; IDA: Iron Deficiency Anemia; ER: Emergency Room; ICU: Intensive Care Unit; BMI: Body Mass Index; Hb: Hemoglobin; GINA: Global Initative for Asthma; K3EDTA: Tripotassium Ethylene Diamine Tetraacetic Acid; Hct: Hematocrit; MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin; RDW: Red Cell Diameter Width; ELISA: Enzyme-Linked Immunosorbent Assay; RBCs: Red Blood Cells; URTIs: Upper Respiratory Tract Infections

Introduction

Asthma is common public health problem worldwide [1] and it is a major cause of morbidity and mortality among the pediatric age group [2]. Asthma is defined as a chronic disorder of the airways that's complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation.The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment [3].

Iron Deficiency Anemia (IDA) is that the commonest nutritional disorder within the world. The prevalence of anemia was found to be especially high among children especially in the developing countries [4,5]. IDA is a common disease in Egypt, with a very high prevalence. Egypt Demographic Health Survey reported a 48.5% prevalence of iron deficiency anemia among Egyptian children and 26.6% among Egyptian adults [6].

Childhood asthma is associated with increased rates of doctor visits, hospitalizations, school absenteeism, parental work absenteeism, child activity limitations, and child disability [7,8]. Furthermore, iron deficiency is also associated with impaired immune competence, and therefore, can lead to increased morbidity [9].

Iron deficiency exerts adverse effects on immune response [10]. Disruptions in iron homeostasis with decreased concentrations of available metal can initiate pathophysiologic events culminating in asthma. Such events include (1) inflammation and (2) muscle contraction involved in bronchoconstriction and obstruction [11].

Imbalance between Oxidative Stress (OS) and antioxidant system is present in IDA patients. Oxidative damage to cells can be caused by the formation of superoxide radicals that affect the equilibrium between prooxidants and antioxidants in biological systems which play an important role in the pathophysiology of asthma [12-14].

Materials and Methods

Study Design and Setting

This cross sectional case control study was conducted on a total of seventy children aged from 6-17 years during the period from May 2017 to May 2018 -Fifty asthmatic children who attended pediatric chest clinic, Children's Hospital, Ain Shams University, Egypt, and twenty healthy children with matched age and sex as the study group who attended the out-patient clinic for non respiratory problems and without any history suggestive of asthma, allergy, or family history of atopic diseases,were taken as controls.

Study Subjects

The patients were included in the study if they have documented

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asthma diagnosis. Asthmatic children were diagnosed by clinical examination together with applying the following criteria [15-17]:

1. Episodic symptoms of airflow obstruction.

2. The demonstration of variable expiratory airflow limitation by spirometry "post-bronchodilator changes in FEV1>12 %" [18].

3. A history of more than three episodes.

4. An alternative diagnosis was excluded.

The patients were excluded from the study if 1) they had anemia other than IDA, 2) they were taking any iron supplementation at the time of the study or in the previous three months prior to the study, 3) they had chronic lung diseases other than asthma as bronchiectasis or cystic fibrosis or if 4) They have any systemic illness as congenital heart disease, protein energy malnutrition or immunodeficiency.

Study Methods

A detailed history was taken from the study participants including personal data as age, gender, consanguinity, presenting symptoms as cough, dyspnea, wheezes, respiratory distress, pallor with a special stress on frequency of asthma attacks Emergency Room (ER) visits, hospital and Intensive Care Unit (ICU) admissions. A thorough clinical examination was conducted including full general examination, anthropometric measurements including (the weight, length or height and Body Mass Index (BMI) were measured using standardized methods, the calculation of BMI was done by dividing the weight in kilograms on height meters squared). Full chest examination and laboratory investigations including CBC and iron profile (Serum iron, serum iron binding capacity, serum ferritin and transferrin saturation) were done for the studied patients and controls.

A child was considered anemic if the Hemoglobin (Hb) level was below 11 g/dL [19]. The diagnosis of iron deficiency anemia was supported by criteria provided by World Health Organization guidelines [20,21].

Asthma exacerbation was identified by the following clinical signs (the use of accessory muscles of respiration, chest wall retractions, tachypnea, the presence of inspiratory and expiratory wheezing and cyanosis) [22].

Asthma exacerbations were classified as mild, moderate, severe, or life threatening according to GINA guidelines 2017 and National Asthma Education and Prevention Program guidelines [15,23]. Criteria for severity were based on symptoms and physical examination parameters, as well as lung function and oxygen saturation [24].

Study Procedure

Blood sampling was performed by withdrawal of 5 ml of venous blood by veni-puncture under complete aseptic conditions using K3EDTA tube, non additive chemical tube for the CBC and the iron profile, respectively.

Complete Blood Count (CBC) with peripheral smear was done using Beckman Coulter-Gen system and it included the levels of (Hemoglobin (Hb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) & Red Cell Diameter Width (RDW), Platelets count, Reticulocyte count) and was compared to age related reference range [25].

Iron studies including (Serum ferritin level by ELIZA, Total Iron Binding Capacity values (TIBC) and Serum iron by spectrophotometer, Transferrin saturation was calculated by using the following formula: iron level/TIBC×100) were compared to age related reference range [26].

The study was approved by the Ethics Research Committee of the faculty of medicine, Ain Shams University. All patients were invited to participate and informed consents were obtained from the parents and children older than 8 years prior to inclusion in the study.

Statistical Analysis

The results were statistically analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA) [27]. Quantitative data were expressed as mean± Standard Deviation (SD). Qualitative data were expressed as frequency and percentage. Correlation between various variables was done using Pearson correlation equation for measuring linear relation in normally distributed variables and P value less than 0.05 was considered to be statistically significant.

Results

The study included seventy children -Fifty cases diagnosed as bronchial asthma, twenty healthy children taken as controls aged from 6 to 17 years. The studied subjects were divided according to CBC and iron profile into group A (asthmatic children without IDA) (n=33), group B (asthmatic children with IDA) (n=17), and group C as controls, (n=20). The IDA was presented in 34% of all asthmatics versus 20% in the controls (P=<0.001).

There was no statistically significant difference between groups A, B and C regarding demographic data and anthropometric measurements, P value>0.05.

Table 1 summarizes the CBC parameters among the three studied groups where in asthmatics with IDA, mean HCT%, HB, MCV, MCH (33.38±1.23, 11.18±0.47, 69.22±3.44, 23.07±1.87) were significantly lower than asthmatics without IDA (37.9%1±1.39, 12.78±0.43.75.71±2.66, 25.44±1.29,) and controls (37.19±2.95,12.66±0.85,76.25±4.13, 26.22±1.93), (p< 0.001, p < 0.001, p < 0.001, p < 0.004). While, mean platelets count and RDW were significantly higher in asthmatics with IDA (360.12±85.08, 15.34±1.19) than asthmatics without IDA (344.79±50.57, 13.99±0.74) and controls (338.15±85.67, 11.95±0.74) respectively (P=0.018, 0.004).

The iron profile among the studied groups was presented in Table 2, The mean serum iron, ferritin and transferrin saturation were significantly lower in Group B (74.20±42.13, 11.65±8.87, 27.63±10.92) than Group A (140.21±34.02, 31.24±14.76, 59.01±28.90) and C (106.18±31.55, 17.30±20.41, 31.04±24.12), while mean TIBC was significantly higher in group B (430.06±109.37) than Group A (326.00±107.61) and C (288.70±77.98), P value = .0.029, 0.014, 0.008, 0.037 respectively.

Also, there was a statistically significant difference between group A and group B according to asthma grading as shown in (Table 3) in which moderate to severe persistent asthma was more prevalent in

Table 1: Comparison between asthmatics with IDA, asthmatics without IDA and controls groups regarding the complete blood count parameters.

CBC parameters	Asthmatics without IDA Group **A** *(n=33)*	Asthmatics with IDA Group **B** *(n=17)*	Control Group **C** *(n=20)*	F/x2#	p-value
HB (gm/dl)	12.78±0.43	11.18±0.47	12.66±0.85	48.281	<0.001**
HCT%	37.91±1.39	33.38±1.23	37.19±2.95	41.685	<0.001**
RBCs	5.08±0.26	4.92±0.30	4.89±0.39	1.591	0.223
MCV (fl)	75.71±2.66	69.22±3.44	76.25±4.13	23.117	<0.001**
MCH (pg)	25.44±1.29	23.07±1.87	26.22±1.93	11.693	0.004*
MCHC (g/dl)	32.97±0.88	34.58±1.38	32.98±1.67	2.823	0.043*
RDW	13.99±0.74	15.34±1.19	11.95±0.74	9.334	0.004*
Normal RDW	25 (75.8%)	7 (41.2%)	18 (90%)	5.824#	0.016*
High RDW	8 (24.2%)	10 (58.8%)	2 (10%)		
PLT (10x3)	344.79±50.57	360.12±85.08	338.15±85.67	3.571	0.018*
Normal	33 (100%)	10 (58.8%)	20 (100%)		
Thrombocytosis	0 (0%)	7 (41%)	0 (0 %)		
IDA	0 (0.0%)	17(100%)	4(20%)	23.770	<0.001**

*p-value <0.05: Significant, **p-value <0.001: highly Significant, F: ANOVA t-test, #x²: Chi-square*

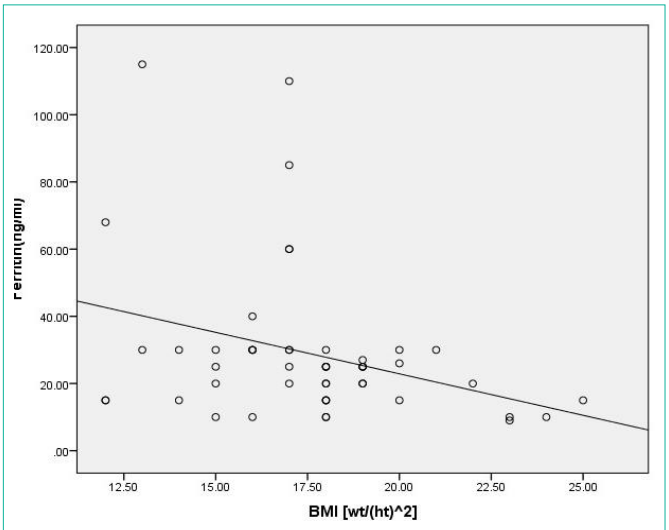

Figure 1: Shows a negative correlation between duration of asthma and serum ferritin.

group B (35.2%) than Group A (9.1%), denoting a more severe airway disease in asthmatics with IDA P=0.032.

As shown in Table 4, Table 5; frequent and severe asthmatic attacks were more pronounced among the anaemic group where the asthmatic attacks were significantly more frequent in group B (88.3%) than in group A (51.5%), with higher moderate to severe exacerbations in group B (64.7%) than group A (45.5%) (P value =0.0548, 0.0437). Also, as regard seeking medical care, frequent ER visits and hospital admissions (in the last year) were significantly higher in group B (70.6%), (41.1%) than group A (60.6%), (3.0%) respectively. (P value=0.037, 0.041). Also the number of ICU admissions (in the last year) was higher in group B (47%), than group A (42.5%), although it was statistically non-significant, which indicates a more severe disease in asthmatics with IDA than asthmatics without IDA (P value= 0.446).

Finally, there was a statistically significant negative correlation between duration of asthma with serum ferritin level (P= 0.007) in which a longer duration of asthma was associated with a lower ferritin levels and vise versa as shown in Figure 1.

Discussion

Bronchial asthma is a worldwide public health problem affecting pediatric population and iron deficiency is the commonest cause of anemia worldwide especially seen in pediatric practice [28].

Iron deficiency exerts adverse effects on immune response and alters the metabolism and growth of pathogens. It has already been reported that low hemoglobin impairs tissue oxygenation [2].

We were interested to evaluate iron status in children with bronchial asthma and define its possible role in increasing asthma morbidity in order to help to modify the disease severity.

In order to achieve our goal, CBC and iron profile were obtained from fifty asthmatic patients and twenty healthy controls, then the asthmatic patients were classified according to their iron status into two groups, group A : asthmatics with IDA and group B: asthmatics with IDA. Both groups were compared with the controls.

In the current study, the ages of the studied subjects ranged from 6 to 17 years with a mean (9.44±2.82), (8.91±1.45), (9.30±1.87) in groups A, B and C respectively.

The studied cases included (33.3%, 58.8%) males and (66.6%, 41.2%) females in group A and B respectively, while the control group included (60%) males and (40%) females.

The study showed no statistically significant difference between the groups A, B and C regarding age and sex (P > 0.05).

In the current study, IDA was prevalent among the asthmatic cases group (34%) rather than in the control group (20%) which was statistically significant (P = <0.001). Lower Hb, Hct, MCV, MCH and higher RDW and platelet count were found in asthmatic patients compared to controls (P<0.05) (Table 1). Also, the mean serum

Table 2: Comparison between asthmatic patients without IDA and asthmatic patients with IDA and control groups according to iron profile.

Iron profile	Asthmatics without IDA Group **A** ***(n=33)***	Asthmatic with IDA Group **B** ***(n=17)***	Control Group **C** ***(n=20)***	F/x2#	p-value
Total iron(ug/dl)	140.21±34.02	74.20±42.13	106.18±31.55	5.434	0.029*
Ferritin(ng/ml)	31.24±14.76	11.65±8.87	17.30±20.41	2.944	0.014*
Transferrin saturation	59.01±28.90	27.63±10.92	31.04±24.12	8.542	0.008*
TIBC(ug/dl)	326.00±107.61	430.06±109.37	288.70±77.98	4.787	0.037*

**p-value <0.05 Significant, F: ANOVA test, #x²: Chi-square*

Table 3: Comparison between asthmatics without IDA and asthmatics with IDA according to the asthma grading assessment.

Asthma grading assessment	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma
Asthmatics without IDA Group **A** ***(n=33)***	30 (90.9%)	1 (3.0%)	2 (6.1%)
Asthmatics with IDA Group **B** ***(n=17)***	11 (64.7%)	3 (17.6%)	3 (17.6%)
x²		10.543	
p-value		0.032*	

**p-value <0.05: Significant, x²: Chi-square*

Table 4: Comparison between asthmatic patients with and without IDA according to frequency and severity of asthmatic attacks.

Frequency of asthmatic attacks	Asthmatics without IDA Group **A** ***(n=33)***	Asthmatics with IDA Group **B** ***(n=17)***	x²	p-value
Less than1 attack / month	16 (48.5%)	2 (11.8%)	9.097	0.0548*
More than 1 attack/ month	9 (27.3%)	7 (41.2%)		
More than1 attack/ week	8 (24.2%)	8 (47.1%)		
Severity of asthmatic attacks			17.208	0.0437*
Mild	24 (72.7%)	6 (35.3%)		
Moderate	15 (45.5%)	9 (52.9%)		
Severe	0 (0%)	2 (11.8%)		

**p-value <0.05 Significant*

iron, ferritin and transferrin saturation were significantly lower in Group B (74.20±42.13, 11.65±8.87, 27.63±10.92) than Group A (140.21±34.02, 31.24±14.76, 59.01±28.90) and C (106.18±31.55, 17.30±20.41, 31.04±24.12), while mean TIBC was significantly higher in group B (430.06±109.37) than Group A (326.00±107.61) and C (288.70±77.98), (P value = .0.029, 0.014, 0.008, 0.037) respectively (Table 2).

Our results go parallel with Mohammad et al. [29] "who conducted a case-control study which involved 200 children ranged from 0.5 years to 14 years. One hundred children were presented with atopic disease and another one hundred healthy children as controls. It was found that the frequency of anemia was high among children with atopic disorders than in healthy children (P=0.001). Additionally, the results revealed that asthma is associated with higher frequency of anemia (P-value=0.007) among other atopic disorders as defined by laboratory results and hypochromic microcytic anemia was the predominant type of anemia in the patient's group (69%)".

A similar observation was noted by Fida and Kamfar 2013 [30] who conducted a cross sectional study on 117 asthmatic children aged (0.7-15-years-old) and found that the prevalence of iron deficiency anemia in asthmatic patients was 19.70% summarizing that iron deficiency anemia needs to be considered as a risk factor in asthmatic patients.

Similarly, several studies [2,31,32] reported that IDA was prevalent in (66%, 62.5%, 39.29%) of asthmatic children.

While Eissa et al 2016 [18] in a "study conducted on 100 children, 6-16 year olds who attended the outpatient pediatric clinic, with upper or lower respiratory tract infection, and they were classified into: group I: 50 children with iron deficiency anemia, subdivided into group Ia: asthmatic children and group Ib: non asthmatic children. Group II: 50 children without iron deficiency anemia, subdivided into group IIa: asthmatic children and group IIb: non-asthmatic children. It was found that children with IDA have more risk of asthma (66%) in group I compared to non-asthmatics (24%) in group II with a high statistically significant difference and suggested that asthma is associated with intermittent or chronic inflammation and can cause anemia".

Higher than our findings, Ramakrishnan K. et al 2010 [33] in a recent study conducted on "two hundred children in the age group of 2-18 years with upper respiratory / lower respiratory tract infections-100 children with asthma were taken as the study group and another 100, age and sex-matched children without asthma were taken as the control, They found that the incidence of asthma

Table 5: Comparison between group **A** and **B** according to ER visits, number of hospital and ICU admissions in the last year.

	Asthmatics without IDA Group **A** ***(n=33)***	**Asthmatics with IDA** Group **B** ***(n=17)***	**X^2**	**p-value**
Number of ER visits *(in the last year).*			4.367	0.037*
Less than 3 times	13 (39.4%)	5 (29.4%)		
More than 3 times	20 (60.6%)	12 (70.6%)		
Number of hospital admission *(in the last year).*			11.66	0.041*
No hospital admission	23 (69.7%)	8 (47%)		
Less than 3 times / year	9 (27.3%)	2 (11.8%)		
More than 3 times/ year	1 (3.0%)	7 (41.1%)		
Number of ICU admission *(in the last year).*			1.617	0.446*
No ICU admission	19 (57.6%)	9 (52.9%)		
One time	9 (27.3%)	3 (17.6%)		
More than one time	5 (15.2%)	5 (29.4%)		

**p-value <0.05: Significant*

in Indian anemic children was 74% compared to 33% of non-anemic controls with predominance of IDA (85% of anemic asthmatics) and suggested that anemia is a possible risk factor of asthma".

On the other hand, Hassan A etal [34], in a study conducted on "56 asthmatic children and 56 controls aged 4 -12 years investigating Iron Deficiency Anemia as a Prognostic Factor for Childhood Asthma, reported that there was no statistically significant difference between patient groups regarding iron deficiency anemia (P > 0.05). However the iron deficiency was little bit higher in studied asthmatic group (39.29%) than in the controls (35.71%)".

Our findings confirm the results of previous studies [34,35] that found an association between anemia and asthmatic children. This association may be explained by the hypothesis that "iron determines the balance between the intensity of Th1 and Th2 arms of the immune response and its deficiency leads to a deviation toward Th2 response and it is known that Th2 twist of immune response favors the development of allergic diseases" [36].

This explanation is also supported by the association of maternal anemia with increased wheeze, asthma and atopy in children [37]. In addition, the chronic inflammation present in an atopic disease, use of systemic immunosuppressant drugs as steroids, increased use of alternative medications [38], and increased incidence of malnutrition [39] increase the risk for anemia in asthma.

The current study also showed that moderate to severe persistent asthma was significantly higher in asthmatics with IDA (35.2%) than asthmatics without IDA (9.1%) (P=0.032) (Table 2). In addition, there was a significant negative correlation between serum ferritin and duration of asthma (p=0.007).

Our findings were consistent with a study conducted by Hassan A, et al [34] which revealed that among the asthmatic cases, (64.3%) were mild cases, (26.8%) were moderate, and (8.9%) severe asthmatics. Also, reported that there was a significant negative correlation between the mean values of serum ferritin concentration and serum hemoglobin level and severity of asthma (P = < 0.001); low values were in concordance with severe asthma while normal values were relatively related to mild asthma.

Our results might be attributed to the fact that "low hemoglobin impairs tissue oxygenation which may add more to the severity of the disease" [2].

According to National asthma education and prevention program; asthmatic attacks were classified according to their severity into mild, moderate and severe. Our study showed that frequent and severe asthmatic attacks were more pronounced among asthmatics with IDA (88.3%, 64.7%)) than in asthmatics without IDA (51.5%, 45.5%).) respectively. (P value =0.0548, 0.0437). Also, as regard seeking medical care, frequent ER visits and hospital admissions (in the last year) were significantly higher in anemic group (70.6%), (41,1%) than in non anemic group (60.6%), (3.0%) respectively. (P value =0.037, 0.04).

These results were consistent with that of a study conducted by Ramakrishnan et al [33] which reported that "the incidence of asthmatic attacks were more in the study group compared to the controls and among the anemic group 50 (50%) had moderate asthma 10 (10%) had mild persistent asthma and the remaining 14 (14%) had mild intermittent asthma. In the control group 33 (33 %) had asthmatic attacks and. It also stated that anemic children were 5.75 times more susceptible to asthmatic attacks when compared with non-anemic children".

Our results were also in agreement with Eissa et al. [18] who found children with IDA have more risk of asthma attacks (66%) compared to non-asthmatics (24%).

Similarly, a case control study conducted by Elsayed et al [32] to assess iron deficiency and iron deficiency anemia in children with bronchial asthma who reported that among 40 cases of asthma, 8 cases (20%) presented with mild acute attack, 22 cases (55%) moderate acute attack and 10 (25 %) cases presented in severe acute attack. In addition, moderate cases of asthma showed lower Hb, RBCs count, serum ferritin relative to mild cases (P was 0.000, 022, and 0.002, respectively). With no difference in serum iron (P =0.341) which was explained by that serum iron was suggested to not to be a reflector of

body iron state. Also, he concluded that iron deficiency increases with severity of asthmatic attacks and asthmatic children have risk of iron deficiency even when they are not anemic.

In contrast to these findings, a recent study examined the effects of iron deficiency with and without anemia on asthma, lung function, and pulmonary inflammation conducted by Brigham et al. [40] on 1046 adolescent females in the age group from 12-19 years, from the 2007 to 2010, "found no associations between iron deficiency anemia and asthma outcomes. They did not observe any relationships between ferritin and asthma outcomes among adolescent females. However, it was noted that the distribution of ferritin was lower in this younger age group than in the adult female population".

Thus our study supports the hypothesis that iron deficiency is associated with impaired immune competence [41] and "it significantly increases the morbidity of upper respiratory tract infections (URTIs)" [42] which is responsible for the bulk of asthma exacerbations, particularly in children [43]. The current study therefore raises the opinion that iron supplementation may decrease the morbidity of URTI and decrease the frequency and severity of asthmatic attacks and thus reduces the disease severity.

Limitations of Study

This study has some limitations. Only fifty asthmatic children were studied. So the results cannot be generalized on all asthmatics and a larger number of patients are needed to confirm our findings.

Conclusion

We found that the asthmatic children have a higher risk of IDA compared to healthy children. Besides, IDA was associated with more frequent and severe asthmatic attacks and a higher incidence of seeking medical advice.

Based on our results, Screening of asthmatic children for IDA and iron deficiency may be helpful in asthma management. Moreover, future clinical trials are needed to justify the use of iron therapy for reduction of frequency and severity of asthma attacks. Thus ameliorating the disease severity.

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