Iron Deficiency as a Risk Factor for Bronchial Asthma in Late Childhood and Adolescence

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ABSTRACT
Background: Asthma is a major global public health issue worldwide. It's the most frequent chronic disease in children and one of the primary causes of morbidity. Hemoglobin, myoglobin, and a number of enzymes all include iron, which is an essential mineral.
Objective: It was to evaluate iron deficiency as a risk factor affected children with bronchial asthma in order to back up the clinical findings at Mansoura University Children Hospital.
Patients and Methods: In this study, 50 asthmatic patients and 50 control participants, ranging in age from 6 to 18, were matched. We investigated the effects of iron deficiency on children with bronchial asthma by analysing laboratory results for the following tests and parameters; **1**) Pulmonary function tests (FEV1, FVC, PEF, FEV1/FVC), **2**) Complete blood count (HB, MCV, MCH, MCHC, RBC, RDW, HCT), **3**) Serum iron, **4**) Serum ferritin level, 5) Total iron binding capacity, and **6**) Transferrin saturation.
Results: Both FEV1/FVC and FEV1/FVC percent had statistically significant relationships with RBCs. Among the cases analysed, there was no statistically significant association between ferritin and pulmonary function tests or between TIBC and pulmonary function tests. All lung function tests had no statistically significant link with transferrin saturation (Tsat).
Conclusion: Iron deficiency anaemia may have a negative impact on spirometry in asthmatic children, resulting to an increase in the severity of asthmatic attacks. Iron supplementation in infants may show to be a safe and successful technique for reducing the incidence of asthma, but further research is needed to determine the causality.
Keywords: Forced expiratory volume, Total iron binding capacity, Global Initiative for Asthma.

INTRODUCTION

Asthma is a widespread chronic respiratory illness that affects 1–18% of the population. Asthma symptoms include wheezing, shortness of breath, chest tightness, and/or cough, as well as intermittent expiratory airflow limitation. Both symptoms and airflow restriction are known to change over time and intensity. Exercise, allergy or irritant exposure, changes in weather, or viral respiratory infections are all known to trigger these changes[(1)].

Asthma is a chronic inflammatory disease of lung airways that causes recurrent airflow blockage. Asthma is caused by a variety of etiological reasons including hereditary and environmental variables. Infection, allergen exposure, absence of controller drugs, black race and the winter season are all risk factors for asthma exacerbation[(2)].

Symptoms and airflow restriction can go away on their own or in response to therapy, and they can even remain away for weeks or months at a time. But, experienced individuals can predict asthma flare-ups, which can be life-threatening and put a huge burden on patients and the community. Asthma is linked to airway hyper-responsiveness and inflammation that present even with absent symptoms or normal lung function but may disappear with therapy[(1)]. Dietary issues have been linked to the onset of asthma in both children and adults[(3)].

Iron deficiency is a condition in which there isn't enough iron in the body to keep tissues like the blood, brain, and muscles functioning normally. If the anemia has not lasted long enough or been severe enough to cause the hemoglobin concentration to fall below the threshold for the certain sex and age group, iron deficiency can persist without anemia[(4)].

Some reports made a spot on the link between iron deficiency and allergic illnesses. **Maazi *et al.***[(5)], cited that iron supplementation declines airway hyper reactivity as well as eosinophilia in a mouse model of allergic asthma, while **Hale *et al.***[(6)] study showed that diet rich with iron stepped inflammation severity down.

OBJECTIVES

They are to clearly understand the importance of the high prevalence of iron deficiency and atopic morbidities and to know the effect of iron deficiency on asthma and wheezing in childhood. So, our specific objective is to evaluate the effect of iron deficiency as a risk factor of bronchial asthma on children.

PATIENTS AND METHODS

Over the course of a year (November 2019-2020), we conducted a comparative study on 50 asthmatic children aged 6 to <18 years who visited Mansoura University Children Hospital's Pediatric Outpatient Chest Clinics.

The population putted in two groups; 50 asthmatic children represented as group A with further sub-grouped according to [Global Initiative for Asthma, 2017 (GINA[(1)])] into; well-controlled, partially-

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controlled and uncontrolled while the healthy children represented as group B include 50 healthy children. Included patients from the different genders were less than 18 years. Children with lower respiratory tract infection, anemia other than iron deficiency anemia, recent chest, heart, or abdominal surgery, chronic heart, liver or kidney disease and children younger than 6 years were excluded.

Methodology

A medical history, which involved inquiries regarding asthma symptoms as cough, wheezes or chest tightness was taken from whole children. Also, they had clinical examination inform of general examination (include: general appearance, vital signs, pallor and anthropometric measurements, which included weight and height), and chest examination (include: inspection, palpation, percussion, and auscultation).

Laboratory investigations were done to whole children including: pulmonary function tests [forced expiratory volume in the first second (FEV1), Forced vital capacity (FVC), peak expiratory flow (PEF), and FEV1/FVC], complete blood count hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell (RBC), red blood cell distribution width (RDW), and hematocrit (HCT)], serum iron, serum ferritin level, total iron binding capacity, and transferrin saturation [(serum iron Total iron-binding capacity (TIBC) X 100].

Interpretation

Hb level was estimated in the blood samples using an automated blood cell counter. The cut-off point for low level was 11 gm dl for children below 5 years and <12 gm dl in children five years or older; meeting the definition of anemia as Hb level being two standard deviations (SD) below the mean for age and gender, as fixed by the WHO[(7)]. As for ferritin, the Enzyme Linked Immuno-Sorbent Assay (ELISA) was used with a cut-off point of ferritin <12 micrograms/L in children up to five years old, and <10 micrograms/L in individuals five years and older.

Ethical consent:

Approval from Institutional Review Board (IRB) of Faculty of Medicine, Mansoura University was obtained. In addition, each participant and the related care giver who participated in the study gave their informed consent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association Declaration of Helsinki for studies involving humans.

Statistical analysis

The data was analyzed with (Statistical Package for the Social Sciences, version 20.0, SPSS Inc, Chicago, III, USA) (SPSS 20). Quantitative data were presented as mean ± standard deviation. Quantitative variables were compared by the student t test. Qualitative data were presented as frequency and percentage and comparison between qualitative data were done by Chi-square test. Differences were considered significant if p values ≤ 0.05. Other appropriate statistical tests were used when needed.

RESULTS

In this study, 50 cases of asthma patients were compared to 50 healthy children to evaluate the effect of iron deficiency as a risk factor on children with bronchial asthma.

Of the total number of children surveyed, 58% of asthmatic and 54% of healthy children were males and 42% of asthmatic and 46% of healthy children were females. The mean age (±SD, in years) for asthmatic versus control children was 11.84±3.75 versus 11.84±3.89. **Table 1** shows the sociodemographic characteristics of the studied children (asthmatics VS controls). There were statistically insignificant differences between the 2 groups regarding to age (P = 1) and sex (gender) (P = 0.687).

Table (1): Demographic characteristics of the studied groups

	Patients group n=50	Control group n=50	test of significance
Age/years Mean±SD*	11.84±3.75	11.84±3.89	t=0.0 p=1.0
Sex n (%)**			
Male	29(58.0)	27(54.0)	χ^2=0.162
Female	21(42.0)	23(46.0)	p=0.687

*****t: Student t test ******χ^2=Chi-Square test

Table (2) showed that, as a result of studying the correlation between complete blood count (Hb, MCV, MCH, MCHC, RBC, RDW, HCT) and pulmonary function test parameters (FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF %) in the examined children with asthma, there's no correlation between complete blood picture and pulmonary function tests and there's no statistically significant difference (P>.05) between them in the studied cases.

Table (2): Correlation between complete blood picture and pulmonary function tests among studied cases:

		HCT	RBC	MCV	MCH	MCHC	RDW	HB
FEV1	r	-.069	.099	-.183	.013	.061	-.026	-.016
	p	.633	.495	.203	.929	.674	.856	.913
FEV1%	r	-.066	.095	-.106	.047	.139	-.079	-.020
	p	.650	.515	.470	.750	.341	.591	.891
FVC	r	.014	.140	-.074	.090	.187	-.076	.081
	p	.921	.331	.609	.536	.194	.598	.577
FVC%	r	-.054	.078	-.010	.082	.080	-.086	-.027
	p	.711	.589	.948	.570	.580	.552	.852
FEV1/FVC	r	.181	.374**	.176	.095	.231	-.199	.096
	p	.208	.008	.221	.511	.106	.166	.506
FEV1/FVC%	r	.217	.417**	.135	.068	.277	-.138	.123
	p	.130	.003	.349	.638	.051	.338	.396
PEF	r	.086	.267	.018	.174	.301*	-.173	.131
	p	.551	.061	.899	.227	.034	.231	.363
PEF%	r	.035	.095	-.053	.123	.037	-.228	.112
	p	.814	.522	.720	.404	.802	.119	.449
Pulmonary function	r	.152	-.031	.115	.001	-.027	.087	.081
	p	.291	.830	.427	.996	.851	.550	.576

R: Spearman correlation co-efficient

Table (3) showed the analysis of correlation between iron level and pulmonary function test parameters (FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF %) among studied cases and demonstrated statistically insignificant difference (P>.05) between the mentioned variables. In the studied cases, iron level wasn't found as an important factor affecting the result of lung function tests.

Table (3): Correlation between iron level and pulmonary function tests among studied cases:

		IRON
FEV1	r	.156
	p	.278
FEV1%	r	.202
	p	.165
FVC	r	.276
	p	.052
FVC%	r	.193
	p	.180
FEV1/FVC	r	.107
	p	.461
FEV1/FVC%	r	.098
	p	.498
PEF	r	.327*
	p	.020
PEF%	r	.230
	p	.116
pulmonary function	r	-.094
	p	.516

R: Spearman correlation co-efficient

Table (4) did not show any relationships between ferritin and pulmonary function test parameters among the patient's group and control group in terms of FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF%. Where the p value >.05 which indicated statistically insignificant difference between the asthmatic group and control group.

Table (4): Correlation between ferritin level and pulmonary function tests among studied cases:

		Ferritin
FEV1	r	.007
	p	.960
FEV1%	r	.067
	p	.646
FVC	r	.189
	p	.188
FVC%	r	.113
	p	.435
FEV1/FVC	r	.024
	p	.867
FEV1/FVC%	r	-.003
	p	.986
PEF	r	.248
	p	.083
PEF%	r	.166
	p	.260
Level of control	r	.170
	p	.238
Pulmonary function	r	-.033
	p	.822

R: Spearman correlation co-efficient

Table (5) demonstrated that, when studying the Correlation between total iron binding capacity (TIBC) and pulmonary function tests in terms of FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF% among studied cases, we found a negative Correlation between them. There was statistically insignificant relationship (P>.05) between TIBC and pulmonary function tests among studied cases.

Table (5): Correlation between TIBC and pulmonary function tests among studied cases:

		TIBC
FEV1	r	-.023
	p	.874
FEV1%	r	-.100
	p	.493
FVC	r	-.105
	p	.467
FVC%	r	-.135
	p	.352
FEV1/FVC	r	-.134
	p	.353
FEV1/FVC%	r	-.106
	p	.466
PEF	r	-.218
	p	.129
PEF%	r	-.165
	p	.262
Pulmonary function	r	.086
	p	.552

R: Spearman correlation co-efficient

Table (6) showed Analysis of the Correlation between Transferrin saturation and pulmonary function tests in terms of FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF% among studied cases. The result reported that statistically significant correlation between transferrin saturation and pulmonary function tests were not evident (P>.05).

Table (6): Correlation between Tsat and pulmonary function tests among studied cases:

		Tsat
FEV1	R	.090
	P	.532
FEV1%	R	.160
	P	.272
FVC	R	.209
	P	.146
FVC%	r	.179
	p	.213
FEV1/FVC	r	.069
	p	.635
FEV1/FVC%	r	.037
	p	.800
PEF	r	.241
	p	.092
PEF%	r	.202
	p	.169
pulmonary function	r	-.108
	p	.455

r: Spearman correlation co-efficient

Table (7) showed that there was no associations and also no statistically significant difference at p >.05 between the laboratory findings which are Complete blood count (Hb, MCV, MCH, MCHC, RBC, RDW and HCT) and iron indices findings (Serum iron, Serum ferritin level, Total iron binding capacity (TIBC), Transferrin saturation) on level of asthma control.

Table (7): Correlation between laboratory findings and level of asthma control among studied cases:

		level of control
HCT	r	.084
	p	.561
RBC	r	.215
	p	.133
MCV	r	.039
	p	.786
MCH	r	.162
	p	.260
MCHC	r	.198
	p	.169
RDW	r	-.167
	p	.246
HB	r	.172
	p	.232
Iron	r	.269
	p	.058
Ferritin	R	.170
	P	.238
TIBC	R	-.125
	P	.387
Tsat	R	.214
	P	.136

Figure (1) and Table (8) showed that, the parameter with the largest area Under the ROC curve was total iron binding capacity (TIBC) (0.595), followed by ferritin (0.569) and serum iron (0.557). The sensitivity and specificity of different cut points of serum iron, ferritin and TIBC are shown in the above Table. Cut point for which sensitivity and specificity overlapped was 64.22 for iron, where the iron has high sensitivity 70% and low specificity of 38% in differentiating cases with asthma from control group. Cut point for Ferritin was 18.33, where ferritin has low sensitivity 54% and low specificity52%. Moreover, cut off point for TIBC was 349, where the TIBC shows low sensitivity 56% and low specificity 58% as well in differentiating cases with asthma from control group. Additionally, we found no statistically significant of the three variables (serum iron TIBC and ferritin (p >.05) in order to determine and differentiate the cases with asthma from control group. Conversely, iron was the only variable high sensitivity of 70% in differentiating cases with asthma from control group. Overall, the results of the study cited inconsequential and low validity of using these tests (iron, ferritin and TIBC) in differentiating cases with asthma from control group.

Table (8): Validity of iron, ferritin and TIBC in differentiating cases with asthma from control group

	AUC (95%CI)	P value	cut off point	Sensitivity%	Specificity%
Iron	0.557 (0.442-0.672)	0.324	64.22	70.0	38.0
Ferritin	0.569 (0.455-0.683)	0.234	18.33	54.0	52.0
TIBC	0.595 (0.483-0.708)	0.101	349	56.0	58.0

AUC: Area Under Roc Curve, CI: Confidence interval

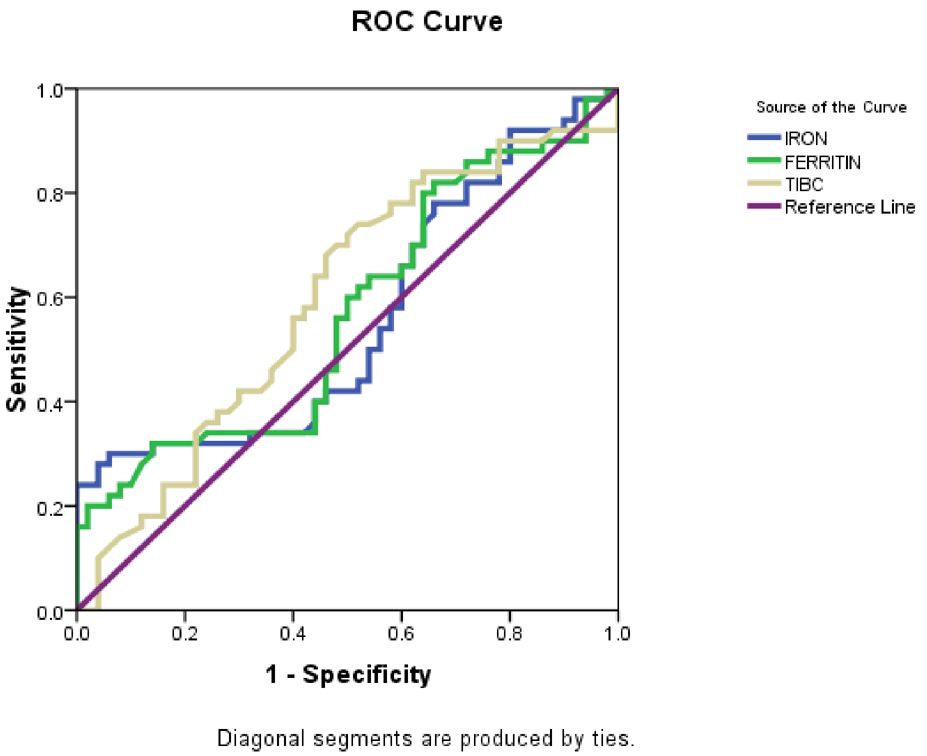

Figure (1): Roc curve for IRON, ferritin and TIBC in differentiating cases with asthma from control group.

Figure (2) and Table (9) showed that, Cut-point for which sensitivity and specificity overlapped was11.505 for HB (gm/dl), where the HB has sensitivity of 68% and low specificity of 46% in differentiating cases with asthma from control group. HB was not found as a significant factor (p >.05) in order to determine and differentiate the cases with asthma from control group. Hence regarding the sensitivity, the study demonstrated acceptable validity but with regard to low specificity, it has considered to be inconsequential and low validity of using HB test in differentiating cases with asthma from control group.

Table (9): Validity if hemoglobin in differentiating cases with asthma from control group:

	AUC (95%CI)	P value	cut off point	Sensitivity%	Specificity%
HB(gm/dl)	0.541 (0.427-0.655)	0.480	11.505	68.0	46.0

AUC: Area Under Roc Curve, CI: Confidence interval

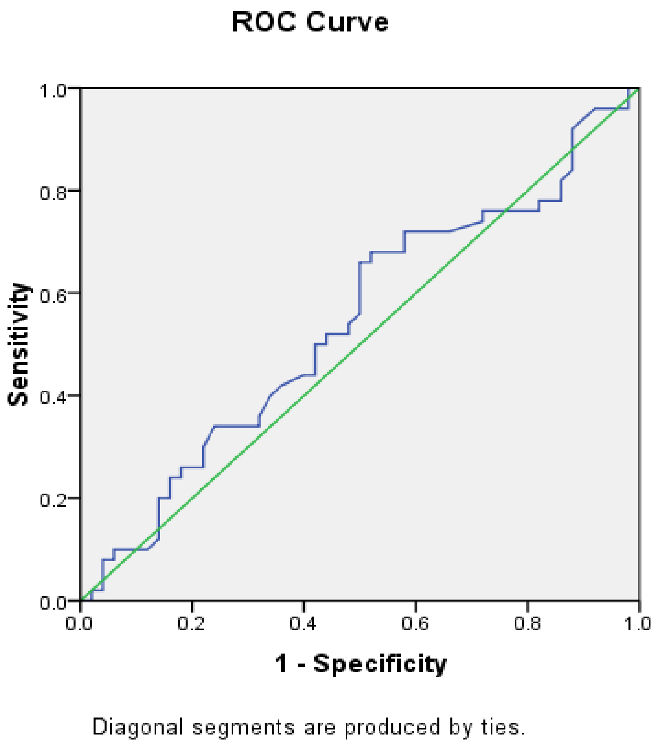

Figure (2): Roc curve for HB in differentiating cases with asthma from control group.

DISCUSSION

Asthma and other atopic illnesses are major public health issues around the world (nearly 300 million people suffer from asthma alone in the world). It is the most frequent chronic disease in children and one of the primary causes of morbidity in them, with about 90% of children diagnosed by the age of six. It has a severe negative influence by more exacerbations, need for frequent admissions, school absenteeism, parental work absenteeism, child activity restriction, child handicap and more economic burdens [(8)].

Asthma is caused by a variety of etiological reasons including hereditary and environmental variables. Infection, allergen exposure and absence of controller drugs are all risk factors for asthma exacerbation[(9)]. A study held which has cited that the dietary issues during childhood represent a significant variable in detecting the expression of wheezy disease like residence, sex, family history and atopy[(10)].

Hemoglobin, myoglobin and a number of enzymes (like cytochromes, catalase, and peroxidase) all include iron which is an important mineral. Iron deficiency has been related to behavioral challenges or learning difficulties in children as well as affecting heat production and metabolism of muscle and catecholamine. In addition to that, iron deficiency is related to impaired immune response which in turn leads to high incidence of diseases. The children from low socioeconomic groups were shown to have a higher prevalence of anemia; these children live in crowded environments and are more susceptible to recurring illnesses[(11)].

Despite that the effect of iron in asthma is unclear; the animal models suggest a physiologic relationship to asthma and inflammatory diseases like asthma. A diet poor in iron lead to significant asthma in a mouse model of allergic asthma and this can be explained by the high reactivity of mast cell in low iron setting. Due to these findings, lower iron was suggested to be linked with higher asthma incidence, higher airway inflammation and impaired lung function [(6)].

In Egypt, another major nutritional shortfall is iron insufficiency and it's thought to be more common in people who are at increased asthma risk suggesting that both conditions are linked. So, we held this study to show clearly the effect of iron deficiency as a risk factor on children with bronchial asthma in supporting the clinical findings at Mansoura University Children Hospital, Egypt as there're no enough reports pointed to this subject.

This study included 50 asthmatic cases and 50 control subjects matched with age from 6-<18 years. We studied the effect of iron deficiency on children with bronchial asthma by performing laboratory findings analysis with respect to the following tests and parameters; 1) pulmonary function tests (FEV1, FVC, PEF, FEV1/FVC). 2) Complete blood count (HB, MCV, MCH, MCHC, RBC, RDW, HCT). 3) Serum iron. 4) Serum ferritin level. 5) Total iron binding capacity. 6) Transferrin saturation.

Our research examined the relation between ferritin level and pulmonary function test in children less than 18 years. It has been found statistically insignificant correlation between ferritin level and pulmonary function test parameters, overall pulmonary function tests and level of asthma control. We did not observe any relationships between ferritin and pulmonary function test parameters among the patients' group and control group in terms of FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF% Where the p value >.05 which indicated statistically insignificant difference between the asthmatics and controls.

A case-control study held by **Bener and his colleagues**[12] cited that the effect of hemoglobin (HB) on asthma and the association between iron deficiency and asthma among children. Anemia was more prevalent in asthmatics than controls. The study revealed that Hb level, iron and ferritin deficiencies were considerably more in asthmatic children versus healthy children. There was an important difference found in the mean values of HB levels between asthmatic and control children ($P = 0.006$). Moreover, the analysis revealed that the predictors for development of asthma in children were serum iron deficiency ($P < 0.001$), and ferritin ($P < 0.001$).

Ramakrishnan's study[13] findings, were in the line with **Bener *et al.***[12] study results, concluded that anemic children were 5.75 times more susceptible to asthmatic attacks than non-anemic. This can be attributed to: 1) Hb facilitates O2 and CO2 transport. 2) It carries and inactivates nitric oxide (NO) and also plays the role of a buffer. 3) It's mainly responsible for stabilizing the oxygen pressure in the tissues. 4) Qualitative and/or quantitative reduction in Hb may adversely affect the normal functions [14].

The current study showed the correlation between Transferrin saturation and pulmonary function tests in terms of FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF% among studied cases found that the statistically significant correlation between them were not evident (P>.05).

The chances of having persistent moderate and severe asthma were assessed depending on presence of latent iron deficiency in asthmatics by **Dudnyk *et al.***[15] study that found a positive association between the serum iron level and asthma control level. Also, a negative, medium-strength relation between the transferrin saturation factor of iron and asthma severity was found. Moreover, a very strong positive relation was found between ferritin content and asthma control level in children with asthma having a latent iron deficiency presented with a decline in ferritin <15 µg/l and a decline in transferrin saturation factor (CST) <20%, the risk of developing persistent moderate and severe disease is elevated by 1.5 fold**.**

Brigham *et al.*[16] doesn't support our results regarding to the correlation between iron status and pulmonary function tests as it cited that the higher the iron stores the lower the prevalence of asthma. Notably, the high iron tissue need and its low level in body, (represented by lower sTfR and lower sTfR-F Index, respectively) were found to decrease FEV1 supposing that they can affect lung function. All of these results imply that iron state has a considerable impact on lung physiology and asthma risk.

On our analysis of the correlation between iron level and pulmonary function test parameters (FEV1, FEV1%, FVC, FEV1/FVC, FEV1/FVC% and PEF %) among studied cases, we didn't find a statistically significant difference (P>.05) between them. So, iron level was not found to be an important factor showing its influence on lung function tests.

The possible role of iron deficiency anemia and iron deficiency in initiation of bronchial asthma was studied by **Elsayed and Essa**[17] whom said that asthmatics had more significantly incidence of iron deficiency anemia than healthy controls. Also, non-anemic asthmatics had great reduction in hemoglobin and serum ferritin if compared with non-anemic controls. Apart from reduced hemoglobin and serum ferritin, there was no significant variation in these measures with severe cases. As a result, even if they are not anemic, asthmatic children are at risk of iron deficit, and the intensity of asthmatic attacks raises the risk of iron deficiency.

Our results come in contact to **Elsayed and Essa study**[17] which demonstrated the effects as well as the relation of the laboratory findings that points to iron deficiency on asthma control level. No relations were found as well as no statistically significant difference at p >.05 between the laboratory findings including }complete blood count (Hb, MCV, MCH, RBC, HCT){ and }iron indices (Serum iron, Serum ferritin level, Total iron binding capacity(TIBC), Transferrin saturation){ on asthma control level.

In addition, the cut point for which sensitivity and specificity overlapped was 64.22 for iron, which has a high sensitivity (70%) but a low specificity (38%) in distinguishing asthma patients from the control group. Surprisingly, serum iron was the only variable with a 70 percent sensitivity in distinguishing asthma victims from the control group.

CONCLUSION

Children's iron deficiency could be indirect or direct risk factor for bronchial asthma development. Iron deficiency anemia may have a negative impact on spirometry in asthmatic children, resulting in an increase in the asthmatic attacks severity. More investigations into therapy timing are required. Iron supplementation for babies may show to be a safe and successful technique for lowering asthma risk, but more researches are needed to clarify the causation.

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Author contribution: Authors contributed equally in the study.

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