Original Article

Association Between Serum Ferritin Levels and Lung Functions Among Iron Deficient Anemic Adults

Aliya Waseem[1], Mohammad Saleh Soomro[2], Shahjabeen[3], Syed Adnan Ahmed[1] and Saba Abrar[1] and Tabinda[1]

ABSTRACT

Objective: Assessment of association between Serum Ferritin levels and lung function tests (FVC, FEV_1, FEV_1/FVC Ratio) in iron deficient anemic adults. Comparison of correlation between Serum Ferritin levels and Lung functions among iron deficient anemic and non-anemic adults.

Study Design: Case Control study

Place and Duration of Study: This study was conducted at the Fatima Hospital, Baqai Medical University Hospital, Karachi and Abbasi Shaheed Hospital, Karachi from July 2017 to December 2017.

Materials and Methods: 100 males and 100 female diagnosed iron deficient anemic adults in range of 18-45 years and with no co-morbid respiratory and cardiac diseases were included. Inclusion criteria also included iron deficient anemic adults with no acute emergency states and no chest and back area deformities. Blood samples were reanalyzed for blood Hemoglobin (Hb) by automated cell analyzer and iron deficiency anemia (IDA) was rechecked and confirmed by further tests like serum iron, serum ferritin, serum Total iron binding capacity (TIBC) levels by Enyme linked immunosorbent assay (ELISA). Pulmonary function tests(PFTs) i.e. Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1st second (FEV_1) were measured by Digital Spirometer in all anemic patients and lung functions were compared with lung functions of non-anemic healthy individuals.

Results: There was significant reduction ($p<0.05$) in FVC and FEV_1 in male and female iron deficient anemic cases than in male and female controls respectively. Whereas the FEV_1/FVC ratio was significantly increased ($p<0.05$) in male and female cases. Restrictive lung changes were observed in male and female cases. Mean value of serum ferritin in male and female iron deficient anemic subjects were significantly lower ($p<0.05$) than in male and female controls respectively. Positive association between serum ferritin levels and lung function changes were found in the anemic group. While the non-anemic healthy participants showed no abnormal lung functions.

Conclusion: The results showed restrictive lung function changes in iron deficient anemic group. Positive association was observed between serum ferritin levels and lung function changes in the anemic subjects. No abnormal changes in lung functions were found in healthy controls.

Key Words: Hemoglobin, Iron Deficiency Anemia, Serum Ferritin, Pulmonary function tests, Forced Vital Capacity, Forced Expiratory Volume in 1st second.

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INTRODUCTION

[1.] Department of Physiology, Liaquat College of Medicine & Dentistry Karachi.
[2.] Department of Physiology, Baqai Medical University Karachi.
[3.] Department of Physiology, Fazaia Ruth Pfau Medical College Karachi.

Correspondence: Aliya Waseem, Senior Lecturer, Department of Physiology, Liaquat College of Medicine & Dentistry Karachi.
Contact No: 03406883493
Email: alyiawaseem18@gmail.com

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Our body stores iron primarily in the form of ferritin. Ferritin is secreted into the plasma in small amounts. In absence of inflammation, the size of the total body iron stores is positively correlated with concentration of plasma (serum) ferritin. Normal ferritin concentrations vary by age and sex. Normal range of serum Ferritin in adult males is 40-340 microgram/liter.

For adult females normal range of serum Ferritin is 14-150 microgram/liter[1].

Ferritin is a positive acute phase response protein. Its concentration increase during inflammation and thereby no longer correlate with the size of the iron store. Therefore, the interpretation of normal or high serum ferritin values become difficult in areas of widespread inflammation or infection[2]. Iron overload is indicated by high serum ferritin concentrations in the absence of liver disease or inflammation. Ferritin is typically assessed in serum or plasma with ELISA after venous blood collection[3].

While link between poor neurodevelopmental outcomes and iron deficiency has been observed[4], association between iron status and pulmonary disease remain relatively unexplored. Lung cells must acquire enough iron for their survival like other cells in the body[5]. Certain markers of iron homeostasis were associated with critical parameters of lung function (forced vital capacity and forced expiratory capacity) in a recent large cohort study[6].

Obstructive lung diseases include but is not limited to asthma, acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, and bronchiolitis[7]. The forced expiratory flow at any given lung volume is reduced in obstructive lung diseases. The spirometric abnormality identified by the use of the predicted lower limit of normal for that individual based on the sex, age, height, and ethnicity is the recommended practice. Both the NHANES and GLI reference equations provide lower limits of normal for spirometric parameter[8]. According to American Thoracic Society, a restrictive pattern is defined by Lower limit of normal (LLN) criteria as $FEV_1/FVC > LLN$ and $FVC < LLN$[9]. Decreased lung compliance and distensibility, low lung volumes and increased lung recoil are characteristic features of restrictive diseases are characterized by decreased lung compliance, low lung volumes and increased lung recoil. Therefore, increased work of breathing is required in these diseases. Pneumonia, atelectasis, Adult Respiratory Distress Syndrome, Pulmonary edema, Pulmonary Embolism and Interstitial Lung Diseases are included in restrictive intrinsic pulmonary disorders. Restrictive Extra pulmonary Conditions include Pleural Effusion, Pneumothorax, Hemothorax and Empyema etc. There is no increase in airway resistance and measures of airflow are within normal limits in restrictive pulmonary diseases[10].

Rational of Study: By knowing the effects of iron deficiency anemia on lung functions, understanding of iron transport and storage in the lung and its role in lung disease onset and progression will improve. Also by knowing blood hemoglobin levels/ serum iron indices levels of a person, indirect assessment of functioning of lungs could be made and early detection of any impairment in function of lungs in anemic adults will help in its treatment. This knowledge will help us to improve interventional modification of iron homeostasis and prevent the progression of lung diseases.

MATERIALS AND METHODS

This case control study was carried at Fatima Hospital, Baqai Medical University Hospital and Abbasi Shaheed Hospital, Karachi from July 2017 to December 2017. This study was approved by the Ethical committee of Baqai Medical University. An approval letter with Ref no. BMU-EC/2016-04 was issued from ethical committee of Baqai Medical University on 02-01-2017.

Sample size: 100 anemic male and 100 anemic female patients with age range from 18 to 45 years were included. Also 50 healthy adult males and 50 healthy adult females with age range from 18 to 45 years were included. Patients who were attending in the hospitals were screened for the presence of lung function changes in diagnosed iron deficient anemic patients. Purposive sampling was done. Written consent was obtained from all participating individuals.

Inclusion Criteria: Diagnosed iron deficient anemic patients confirmed by blood Hb, serum Iron, serum Ferritin, serum TIBC and serum % transferrin saturation levels were included.

Exclusion Criteria: The patients with any other diseases like cardiac, lung diseases, any infectious diseases, and any inflammatory disorders were excluded. Patients with back, chest deformities and other types of anemia were excluded. Active smokers and pregnant women were also excluded.

Methods: All the participant's blood hemoglobin and serum iron indices (serum iron, serum ferritin, serum TIBC levels) were measured by automated cell analyzer (Sysmex Kx-21)[11] and ELISA (sandwich ELISA kit (cat # YHB2785Hu; Bio Check (Foster city, CA, USA, cat #. BC- 1025)[12] respectively. Digital spirometer were used to measure FVC and FEV_1 in all anemic patients and lung functions were compared with lung functions of non-anemic healthy individuals.

Serum ferritin levels were measured by ELISA. In the first step approximately 35 µl serum are added to each well followed by the same volume of BSA-buffer(bovine serum albumin) . The wells are aspirated and rinsed 3 times with PBS (phosphate-buffered saline) after the plates were kept at room temperature for 15 minutes. In the second step of the assay, 4 drops conjugated antiferritin are placed in each well and the plates allowed to stand for I5 minutes. The wells are again aspirated and after rinsing again with PBS, a substrate solution containing p-nitrophenylphosphate (PNP) is added to each well. Finally, After, keeping the wells at room temperature for 1 hr, the reaction is stopped by adding one drop of 1 M sodium hydroxide to each well. The intensity of the yellow color in each well is estimated visually against a white background. The color intensity in the screening test with each sample was compared to ferritin standards containing 0, 20, 50, 100, 200, and 500 µg/liter[13].

Digital spirometer (Microlab 3300 electronic spirometer, Micro Medical Limited, Kent, England) was used to measure lung volumes and capacities. A series of at least 3 acceptable forced expiratory readings were taken. The best value was selected. Subjects were given a rest of 2-3 minutes between the tests. Nose clips were used in the present study[14].

Statistical Analysis: Data for blood hemoglobin, serum ferritin, total serum iron, serum TIBC, serum % Transferrin saturation and lung function tests were analyzed by using independent sample t-test, and has given numerical values between two variables that were measured on same interval and results were calculated using SPSS 22.0 at p-value< 0.05. Pearson Correlation was used to correlate between serum ferritin levels and lung functions in both gender.

RESULTS

During study period, two hundred iron deficient anemic patients (N=200) were included, that consisted of hundred male and hundred female individuals. One hundred healthy individuals (N=100) participated as controls. These healthy subjects consisted of fifty male and the same number of females.

Comparison of serum ferritin levels in Table I showed that serum ferritin levels were significantly lower ($p<0.05$) in anemic male and female cases than in non-anemic controls of both genders. Mean value of serum ferritin in male cases was 9.12±1.03 µg/L and the t-values and p-values are 56.9 and 0.0001 respectively. Mean value of serum ferritin in female in female cases was 8.0±1.14 µg/L and the t-values and p-values are 39.12 and 0.0001 respectively. Comparison of PFTs in Table II showed that The FVC and FEV_1 in male and female cases were significantly lower ($p<0.05$) than in male and female controls respectively. FVC in male cases were 3.09±0.09 Liters and the t-values and p-values are 70.13 and 0.01 respectively. FVC in female cases were 2.40±0.59 Liters and the t-values and p values are 10.54 and 0.01 respectively. FEV1 in male cases were 2.80±0.06 Liters and the t values and p values are 40.46 and 0.01 respectively. FEV1 in female cases was 2.24±0.58 Liters and the t values and p values are 3.62 and 0.01 respectively. FEV1/FVC ratio in male controls was 0.82±0.19 % and the ratio in male cases was 0.90±0.18 % and the t values and p values are -2.51 and 0.01 respectively. FEV1/FVC ratio in female controls was 0.80±0.04 % and FEV1/FVC ratio in female cases was 0.92±0.25 % and the t values and p values are -3.36 and 0.01 respectively.

Table No.1: Comparison of serum ferritin levels among cases & controls of both genders

Para-meters	Gender	Control		Cases		T-value	P-value
		Mean	Sd	Mean	Sd		
Serum ferritin (µg/l)	Male	156.68	25.98	9.12	1.03	56.9	0.0001
	Female	96.34	22.60	8.0	1.14	39.12	0.0001

p-value <0.05 significant
p-value>0.05 non-significant

FEV_1/FVC ratio was significantly increased ($p<0.05$) in male and female cases. Therefore, restrictive lung disease was observed in anemic subjects. Positive significant correlation ($p<0.05$) of serum ferritin levels with lung function tests was found among male control & cases in Table 3. Positive significant correlation ($p<0.05$) was observed between serum ferritin levels and lung function tests among control & cases in females in Table 4.

Table No.2: Comparison of Pulmonary Functions Among Control & Cases of Both Genders

Para-meters	Gender	Control		Cases		t-value	p-value
		Mean	SD	Mean	SD		
FVC (L)	Male	4.05	0.05	3.09	0.09	70.13	0.01
	Female	3.34	0.31	2.40	0.59	10.54	0.01
FEV_1 (L)	Male	3.35	0.09	2.80	0.06	40.46	0.01
	Female	2.70	0.97	2.24	0.58	3.62	0.01
FEV_1/ FVC (%)	Male	0.82	0.19	0.90	0.18	-2.51	0.01
	Female	0.80	0.04	0.92	0.25	-3.36	0.01

p-value<0.05 significant
p-value>0.05 non-significant

Table No.3: Correlation of Serum Ferritin levels with Lung function tests among control & cases in males (n=150)

Parameters	R-value	P-value
FVC (Liters)	0.67	0.01*
FEV_1(Liters)	0.68	0.01*
FEV_1/FVC(%)	-0.12	0.11

*p<0.05 was considered significant for Correlation
p>0.05 was considered non-significant for Correlation

Table No.4: Correlation of Serum Ferritin (µg/l) with Lung function tests among control & cases in females (n=150)

Parameters	R-value	P-value
FVC(Liters)	0.74	0.01*
FEV_1(Liters)	0.86	0.01*
EV_1/FVC(%)	-0.78	0.01*

*p-value<0.05 was considered significant for correlation
p-value>0.05 was considered non-significant for correlation

DISCUSSION

Lower serum ferritin levels have been associated with poor lung functions in iron deficient anemic patients[15].

A study conducted in Indus Medical College, Sindh, Pakistan reported high frequency of low serum ferritin levels in young iron deficient anemic medical students in comparison to non-anemic students. [16]. The same significant effect($p<0.05$) was observed in the current study (Table 1).

In a study conducted in Korea, the subject's PFTs declined with reduction in concentration of serum ferritin levels[17]. Similar significant positive ($p<0.05$)

association was found in the present study between serum ferritin levels and PFTs in anemic adults (Table 2). An Austrian based cohort study also revealed positive correlation between serum iron indices and FEV1[18].

In another korean study, higher serum ferritin levels were not associated with better lung function, and instead were associated with a lower FVC in men[19]. The results of the current research are in contradiction to the korean study as significant ($p<0.05$) positive association between serum ferritin levels and lung function changes was observed in the present study in men (Table 3).

In a US study, researchers found that higher serum ferritin was associated with lower prevalence of asthma among adult anemic women[20]. The results showed the same significant ($p<0.05$) effect in the present study in relation to association between serum ferritin levels and PFTs in anemic adults in women (Table 4).

A case control study was conducted in the outpatient department of Enam Medical College & Hospital, Dhaka, Bangladesh. Asthma cases had lower serum ferritin levels as compared to controls[21]. The present study also showed the same significant ($p<0.05$) in women (Table 4).

CONCLUSION

Restrictive lung function changes were found in IDA subjects in the present study. Positive association was observed between PFTs and serum ferritin levels in subjects with IDA. While no positive correlation was found in non-anemic controls. Early detection and correction of IDA in patients with reduced pulmonary functions are recommended. Development of respiratory diseases can thus be prevented by these measures.

Author's Contribution:

Concept & Design of Study:	Aliya Waseem
Drafting:	Mohammad Saleh Soomro, Shahjabeen
Data Analysis:	Syed Adnan Ahmed, Saba Abrar, Tabinda
Revisiting Critically:	Aliya Waseem, Mohammad Saleh Soomro
Final Approval of version:	Aliya Waseem

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