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Lung Function Disorders among Sickle Cell Disease Patients in Basrah City, Iraq

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Abstract

In sickle cell disease (SCD), lung function impairments might be obstructive, restrictive, or both. Due to the lack of extensive investigations, the exact prevalence of sickle cell chronic lung illnesses and the way to identify them have yet to be determined. The aim of this study is to determine the impact of SCD on pulmonary function tests (PFTs) in adult patients in Basrah, Iraq, as well as to describe the patients' respiratory disorder. This is a cross-sectional study conducted in Basrah City, Iraq, in which two groups of individuals were enrolled: 110 healthy subjects (group1) and 102 sickle cell disease patients (group 2). Measurements of PFTs and several hematological tests were done for each individual of the two groups**.** Significant decline ($p < 0.05$) in different tests of pulmonary function (FEV1; FVC; FEV1%PEF and MVV) were found in SCD patients with a significant elevation in estimated lung age. Several hematological tests (WBC; RBC; HGB; Neutrophils and lymphocytes were also showed significant changes ($p< 0.05$) in the patients. Lung functions differ significantly in patients with SCD compared with matched healthy control individuals of a similar age, gender and standing weight. This study has also shown that PFT abnormality in SCD patients was restrictive disease pattern.

Keywords: Pulmonary function tests, Sickle cell disease, Respiratory diseases patterns

اعتلال وظائف الرئه لمرضى فقر الدم المنجلي في مدينه البصره,العراق

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الخلاصه

مرض فقر الدم المنجلي (SCD)، قد يكون مصحوب بخلل في وظائف الرئة معوقة أو مقيدة أو كليهما. بسبب الافتقار إلى التحقيقات المكثفة لم يتم تحديد الانتشار الدقيق لأمراض الرئة في مرض فقر الدم المنجلي وطريقة التعرف عليها. الهدف من هذه الدراسة هو تحديد تأثير فقر الدم المنجلي على اختبارات وظائف الرئة (PFTs)في المرضى البالغين في البصرة ، العراق ، وكذلك لوصف نوع اضطراب الجهاز التنفسي لدى المرضى. المواد والطرق: هذه دراسة رصديه مستعرضه أجريت في مدينة البصرة ، العراق ، حيث تم تسجيل مجموعتين من الأفراد: ١١٠ أفراد أصحاء (المجموعة ١) و ١٠٢ مريض بمرض الخلايا المنجلية (المجموعة ٢). تم إجراء قياسات PFTs والعديد من الاختبارات الدموية لكل فرد من المجموعتين. النتائج: تم كشف انخفاض واضح ($p< 0.05$) في اختبارات مختلفة لوظيفة الرئة (FEV1 ؛ FVC ؛ FEV1٪ PEF و (MVVفي مرضى SCD مع ارتفاع كبير في العمر التقديري للرئة. كما أظهرت العديد من الاختبارات الدموية (WBC، RBC، HGB ، العدلات والخلايا الليمفاوية تغيرات كبيرة ($p> ٠,٠٥$) في المرضى.الاستنتاج : تختلف وظائف الرئة بشكل كبير في المرضى الذين يعانون من داء فقر الدم المنجلي مقارنةً بأفراد السيطرة الأصحاء المتطابقين من نفس العمر والجنس والاوزان. أظهرت هذه الدراسة أيضًا أن اعتلال وظائف الرئه في المرضى كان نمط مقيد.

الكلمات المفتاحية :وظائف الرئه ، فقرالدم المنجلي

Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder results from a single point mutation in the gene that encodes for beta-globin chain of hemoglobin[(1,2)]. It is a common monogenetic disorder that affects people all over the world. Patients who are homozygous for the this hemoglobin (HbS) gene mutation (Hb-b; glu6val) have the most severe hemolytic anemia.[(3)]. The sickling phenomenon is the fundamental pathophysiology of SCA, which is characterized by abnormal red blood cells shape, obstructing microvasculature. This condition affects all of the body's organs and tissues, involving lung[(4)]. Recurrence of sickling events may result in an impairment of lung function. This impairment is caused by certain potential problems such as pulmonary fibrosis, chronic hypoxia or pulmonary hypertension[(5)]. Acute chest syndrome, pulmonary thromboembolism, pulmonary fat embolism and lung fibrosis are all pulmonary consequences of sickle cell anemia[(3)]. Repeated acute chest syndrome in early childhood is generally a precursor to these abnormalities, which commonly known as sickle cell chronic lung disorders (SCCLD). It is a chronic condition that progresses into adulthood, resulting in pulmonary hypertension, heart disease and mortality[(6,7)].

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The exact prevalence of SCCLD and the procedures for diagnosing SCCLD have not been determined yet[8]. SCA patients' life expectancy has grown significantly over time as a result of better care. As a result, a rise in the prevalence of disease-related consequences linked to chronic morbidity is projected. Pulmonary impairment results in significant complication and death in sickle cell disease patients because they result in lung function deterioration, which has a negative influence on patients' quality of life and can lead to death in case of delayed managements[7]. Pulmonary function tests (PFT) are practical detective tests that were used to estimate the volumes and capabilities of the lungs to disclose how they are working[9].

The objective of the current study is to reveal the potential effect of SCD on pulmonary function tests of adult patients in Basrah city, Iraq, as well as to describe the pattern of respiratory disorders in the patients. Measurement of pulmonary function tests may enhance more understanding of the morbidities progress that occur with the sickle cell disease.

Materials and Method

This is a cross-sectional study conducted for the period between November 2021 and March 2022, at College of Pharmacy, University of Basrah. The study was approved by local ethics committee of University of Basrah and Basrah health directory, in addition to signed informed consents were obtained from all participants. The priority was for the health of the participants and the study has been carried out according to Helsinki statement by The World Medical Association (WMA).

Participants

The study included 212 individuals divided into two groups: 110 healthy individuals as a control group (group 1) (52 males and 58 females) in age range (21-45) years. The other group is 102 sickle cell disease patients as a test group (group 2):(45 males and 57 females) with age range 23-46 years. The patients were from the out-patient unit of the Thalassemia Center of Clinical Genetics disorders in Basrah city. Based on the results of the electrophoresis technique, the individuals were previously diagnosed with sickle disease. A thorough questionnaire was used to acquire demographics and characteristics of all participants, including age, sex, height, weight, BMI (body mass index), co-morbidities, drug use, and smoking status.

Exclusion: Patients with chronic obstructive pulmonary diseases or chronic restrictive pulmonary diseases; patients with cardiovascular disease or major diseases and patients on steroids, as well as obese patients and smoker were all excluded from the study.

Laboratory measurements

A complete blood picture was estimated by flow- cytometry using SYSMEX XT-2000i (Hoffman la Roche, Japan). Hb variations were detected using Hemoglobin Electrophoresis test [10]. For both group 1 and group 2, five ml of venous blood was collected in an ethylenediamine tetra acetic acid (EDTA), serum separating tube, and sodium citrate tube.

Pulmonary Function Tests Measurement

Spirometry was performed for all participants using a spirolab III ,SN A23-053.07832 according to the American Thoracic Society (ATS) procedure[11].Measurement of the tests was carried out in a standing position, with the patient inhaling fully and then exhaling as quickly and forcefully as possible through the mouthpiece of the MIR spirolab. The best reading of three maneuvers was adopted and recorded. Estimated parameters included forced vital capacity (FVC) in liters, forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio ,estimated lung age (ELA), maximal voluntary ventilation (MVV) and peak expiratory flow rate (PEF).According to the standard guidelines[12],absolute values were adopted to compare pulmonary function tests between healthy individuals (group 1) and sickle cell disease patients (group2). A forceful blow for more than three seconds was accepted for interpretation and statistical analysis[13]. Spirometry data can illustrate normal, obstructive, restrictive, or mixed lung function disorders. Pulmonary functions were divided into four categories using the American Thoracic Society's standards[14].

Statistical analysis

Data were analyzed using the SPSS software version 24.0 .The variables were expressed by means and standard deviations (mean± SD). The comparison was done using an independent t-test for normally distributed data and the Mann–Whitney U-test for non-normally distributed data. The correlation between the variables was tested by Pearson's and Spearman's rank correlation coefficient. P value less than 0.05 was used to determine statistical significance.

Results

Characteristics of the two groups of the study: healthy (group1) and sickle disease patients (group 2) are illustrated in Table1. Group 1 was within age range (21-45) years and group 2 was within age range (23-46) years. No significant differences in age range were observed between the two groups ($P>0.05$). As well as no significant differences in gender ratio and length were found. On the other hand, the two groups revealed significant variations in the mean values of weight and BMI ($P <0.05$), as shown in Table1. This Tablealso shows the percentage of respiratory disorders in group1 and 2, referring that respiratory

diagnosis patterns were higher in group 2, with a considerable increase in restrictive pattern (38 (37.25%)). On the other hand, the normal spirometry diagnosis was the higher percentage in group 1(94 (85.45%)). (Table1)

Regarding hematological profiles of the study groups, data analysis revealed several significant variations between group 1 and 2. Group 2 has significantly higher WBC (7.0725± 1.58030 VS 10.2799± 4.60317), lymphocytes (2.5670± 0.78250 vs. 3.5282± 2.24517) and neutrophils (4.8655± 1.39052 vs 5.6042± 3.09815) $p< 0.05$. On the other hand, other parameters related to RBC indices, revealed significant declines ($p <0.05$). Mean values of RBC of the two groups (4.9249± 0.61352 vs. 3.3688± 0.9473); HGB (13.4624±1.54295 vs. 9.9781±2.21839) and (MCH: 31.8950± 2.95105 vs.30.6050± 4.80292) (Table2). Interestingly, pulmonary function tests data analysis revealed significant changes in all parameters studied between group 1 and group 2, ($p<0.05$). Each of FEV1 (3.74± 0.84 vs.2.34 ±0.913); FVC (4.12± 0.74 vs.3.42± 0.76); FEV% (94.85± 5.96 vs. 78.76± 7.41) and PEF (6.53± 2.15 vs.3.67± 1.34) were statistically decreased in group 2 in comparison to group 1. While ELA (32.36± 9.07 vs.61.89±12.08) was statistically elevated in group 2 compared to group 1, as illustrated in Table3. The individuals of both groups were statistically different in weights and BMI . The patients of group 2 were sick with sickle disease, which adversely could affect their weights, therefore the showed significant reduced weight as seen in Table1. For the purpose of excluding weights as an influencing factor and causing the difference in lung function between the two groups. The current research have studied the effect of weights on the function of the lung by dividing group 2 into 3 weight categories, and the lung functions of these groups were statistically analyzed as clarified in Table4. The patients within group 2 were categorizes into 3 subgroups according weight characteristic: (patients with 40-59 Kg; 60-79 kg and 80≤). No significant changes in most of pulmonary function tests except in FEV1% between patients with 60-79 kg weight and patients who were with 80 ≥ (87.87±10.43 vs.82.98±15.09), $p< 0.05$ and in PEF between patients with 40-59 kg weight (2.89± 1.196) and patients who were 80≤ kg (3.59±1.249) $p < 0.05$, as seen in Table4, while every other comparison among the weight groups showed no significant differences $p>0.05$. However, the weight group that revealed significant change in FEV1 and PEF is the smallest weight group (N=7), while the number of the other weight groups are 54 and 41 (Table4).

The correlation between PFT and HGB in sickle diseases patients revealed that the only significant correlation was in FEV1% ($r =0.213$, p value=0.0134). On the other hand no correlation was found between HGB and each of FEV1,FVC,MVV and ELA(Table5).

Table1. Characteristics of participants

parameter	**Group 1 (Mean ±SD)**	**Group 2 (Mean ±SD)**	***P value**
Number	110	102	
Age(years) Mean ±SD	(21-45) 31.85 ± 6.1	(23-46) 32.43 ± 6.4	0.085
Gender: (male/female)	52:58	45:57	
Weight (kg)	72.7822± 13.51776	61.5545± 11.27783	0.000
Length (cm)	167.9010± 13.13659	163.0594± 9.93360	0.056
BMI (kg/cm^2)	26.1680± 25.03	21.9574± 3.36	0.000
Obstructive(N(%)) Mild Moderate –severe	 7(6.36%) 0	 9(8.82)	
Restrictive(N(%)) Mild Moderate-severe	 9(8.1%) 0	 38 (37.25%) 21 (20.5%)	
Combined(N(%))	0	15 (14.7%)	
Normal respiratory (N(%))	94(85.45%)	19(18.6%)	

*P is considered significant when the value is <0.05; N: number

Table2. Hematological parameter for sickle cell disease and control

parameter	Group 1 (Mean/SD)	Group 2 (Mean/SD)	*P value
WBC(10^9/L)	7.0725± 1.58030	10.2799± 4.60317	0.000
LY(10^9/L)	2.5670± 0.78250	3.5282± 2.24517	0.002
NE(10^9/L)	4.8655± 1.39052	5.6042± 3.09815	0.001
RBC(10^12/L)	4.9249± 0.61352	3.3688± 0.94737	0.000
HGB (g/dl)	13.4624± 1.54295	9.9781±2.21839	0.000
MCV(fl)	88.5169± 6.70169	91.6554± 14.56725	0.0750
MCH(pg)	31.8950± 2.95105	30.6050± 4.80292	0.001
MCHC(g/L)	33.9238± 1.40457	32.6451± 3.38770	0.0620

*P is significant at value <0.05

WBC;LY; NE; RBC; HGB;MCV ; MCH; MCHC: for (white blood cells; Lymphocytes; neutrophils; red blood cells; hemoglobin; mean corpuscular volume; mean corpuscular hemoglobin; and mean corpuscular hemoglobin concentration respectively).

Table3. Pulmonary function tests in control and sickle cell disease patients

parameter	Control Mean/SD	Patient Mean/SD	*P value
FEV1(L)	3.74± 0.84	2.34 ±0.913	0.000
FVC(L)	4.12± 0.74	3.42± 0.76	0.000
FEV%(L)	94.85± 5.96	78.7693± 7.41	0.002
PEF(L/S)	6.53± 2.15	3.67± 1.34	0.000
ELA(years)	32.36± 9.07	61.89± 12.08	0.000
MVV(L/S)	101.45± 12.45	82.7215± 13.73	0.000

*P is considered significant when the value is < 0.05.

FEV1;FVC;FEV1%,PEF; ELA and MVV for (Forced Expiratory Volume at the first second of expiration; Forced Vital Capacity; ratio of FEV1/FVC;Peak Expiratory Flow; Estimated Lung Age and Maximum Voluntary Ventilation respectively).

Table4. Pulmonary function tests of different weight groups of sickle cell disease

Groups PFTs	(40-59) Kg N= 54	(60-79)Kg N= 40	(80≤)Kg N= 7	*P value
FEV1(L)	2.25± 1.036	2.64± 0.73	2.74± 0.422	1- 0.061 2-0.399 3-0.720
FVC(L)	1.98± 0.748	2.45±0.69	2.56±0.81	1-0.072 2-0.065 3-0.698
FEV 1%(L)	86.18±15.38	87.87±10.43	82.98±15.09	1-0.083 2-0.062 3-0.031*
PEF(L/S)	2.89± 1.196	3.28±1.47	3.59±1.249	1-0.082 2-0.048* 3-0.370
ELA(years)	71.16± 26.56	73.65±21.63	74.85±16.47	1-0.646 2-0.174 3-0.215
MVV(L/S)	76.73± 27.35	83.16±24.20	80.35±23.29	1-0.005 2-0.193 3-0.765

*P is significant when the value is < 0.05 ,N: number, the variables are expressed by mean ±SD,1: is the p between classification 1 and 2; 2: between 1 and 3; 3: between 2 and 3

Table5. Correlation between PFTs and HGB in sickle diseases patients (group 2)

	FEV1	FVC1	FEV1%	PEF	ELA	MVV
HGB (g/dl) r value	0.115	0.243	0.212	0.282	-0.231	0.237
P value	0.250	0.14	0.0134*	0.000	0.20	0.17

*p value is significant at level < 0.05; HGB: hemoglobin.

Discussion

Sickle cell disease is one of highly distributed hereditary diseases[2]. The sickle phenomenon is characterized by microvascular obstruction impact all organs and tissues of body involving the lungs that may result in deterioration of lung functions[15]. The goal was to evaluate the impact of sickle cell disease (SCD) on lung functions in Basrah City, Iraq, which may be considered as a first study that associate between pulmonary function tests and the disease in that region. In our study, pulmonary function test (PFT) parameters as measured by spirometry showed significantly decline in group 2 (Hb-SS patients) in steady states compared to group 1 (healthy control people) and this is consistent with finding of prior studies[8,16].There are no significant differences regarding to the age, gender, standing height and HGB were found. Regarding to the weight factor, no significant findings were found in most of PFT except in FEV% between patients with (60-79) Kg and those who were with weight ≥ 80kg and in PEF between patients with (40-59) Kg and those with ≥80kg. The present study revealed abnormal lung functions, showing a restrictive disease pattern. This result confirms the finding of previous studies that displayed a range of PFT abnormalities in patients with SCD such as increased restrictive physiology and decreased obstructive pattern[17].Furthermore, we found a positive significant correlation between HGB and FEV1% as seen in Table5,which confirms the association between the pathological process and the decline in FEV1%. Reduced lung compliance, which may be attribuTableto sickle cell vasoculopathy, a problem in SCD, has been associated to the initiation of pulmonary hypertension and chronic lung complications, as well as recurring episodes of cut chest syndrome[18]. Moreover, the restrictive pattern might be caused by subclinical obstruction of capillaries and post capillary venules affected by leukocytes over abundance[13]. One of the important results of the study is the identification of an increase of white blood cells (WBC), that might act as a factor for the decline in lung volumes. The mechanism of which WBC may impact the lung volumes are unclear[19]. However, sticking of WBC to the blood vessel walls and obstructing the lumen may stimulate the vascular endothelium , which in turn stimulates the expression of ligands for adherence the molecules on blood cell surfaces[20]. This could set off a chain events that results in tissue damage and an inflammatory response, favoring vascular blockage even more[21]. Repeating subclinical microvascular trapping of blood cells most likely plays a part in microcirculation blockage, resulting in a reduction in lung volume and restrictive pattern.[22]. Long-term inflammation can cause lower airway blockage in the early stages, which might lead to fibrosis later on. This could explain why the restrictive pattern is becoming more common in adults[23]. Patients with SCD, on the other hand, have disproportionate chest wall growth, i.e., a tiny chest wall in comparison to their body size, which could explain the observed decrease in lung volumes[24]. The cause of that condition was thought to be repeated infarctions in the ribs, sternum, and vertebrae, which resulted in impaired bone growth and development.[25].

Conclusion

Lung functions differ significantly in patients with SCD compared with matched healthy control individuals of a similar age, gender and standing height. The decline in PFTs might be due to several pathological events that occur in the lungs and all over the body as denoted by several hematological changes. This study has also shown that PFT abnormality in adult SCD patients was restrictive disease pattern.

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Conflicts of Interest

The authors declare that there is no conflict of interest

Ethics Statements

This study was conducted in accordance with the guidelines of the local ethical committee in University of Basrah , College of Pharmacy, and Basrah Health Directory

Author Contribution

Azza Sajid Jabbr: Supervision, Conceptualization, Methodology,Writing - Review & Editing; Abeer Jafar Mohammed: Writing – Original Draft Software, Formal analysis; Nawal Khalil Ibrahim: Investigation,Data Curation and Visualization.

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