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The association between microcytic anemia and spirometric parameters

The authors declare no financial dislosure

Abstract

Introduction: Microcytic anemia is a type of anemia with smaller than normal red blood cells. Iron deficiency anemia and thalassemia are some of the major causes. The aim of the study was to compare the pulmonary function of the subjects with microcytic anemia to the respective results of the normal population.

Material and methods: This was a cross-sectional study in Bandar Abbas, Iran, conducted on the patients attending yearly occupational health checkups. Complete blood cell count and a standard spirogram were attained from each consenting participant and occupational histories of exposure to dust, fumes, solvents, and noxious gases were obtained.

Results: At last, 2,199 subjects were included in the analysis, of which 335 cases had microcytic anemia. There was a significant association between having microcytic anemia and forced vital capacity (FVC) reduction, and to a lesser degree, the reduction of forced expiratory volume in the first second (FEV_1). These parameters were also significantly increased together with the rise of mean corpuscular volume (MCV) in the sample population.

Conclusion: It can be concluded that having microcytic anemia may reduce some spirometric parameters. Even though these changes are small, adjusting for the reduced values can help prevent an overestimation of lung disorders, mostly in borderline cases.

Key words: thalassemia, anemia, iron deficiency, respiratory function tests, spirometry

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Introduction

Microcytic anemia is a type of anemia with smaller than normal red blood cells (RBCs). It is widely categorized as iron deficiency anemia (deficiency in iron delivery to the heme group), thalassemia (deficiency of globin production), anemia of chronic disease (reduced iron delivery to the heme group), and anemia because of other minor causes [1]. Hemoglobinopathies (including thalassemia) constitute one of the most common inherited diseases that are transmitted by single genes [2]. Iron deficiency anemia is the most common type of the condition [1].

Each year, 60,000 new babies with severe thalassemia are born, mostly in the tropical and subtropical regions of the world. Unfortunately, there is no definitive treatment for thalassemia and the care is mostly supportive [3]. Milder cases of thalassemia are more common and usually symptom-free. Mild anemia is the only finding in these cases [4]. Basing on the genes involved, thalassemia is divided into alpha and beta thalassemia. Beta-thalassemia is defined by abnormal synthesis of the beta chains of the hemoglobin (due to mutation or deletion of the beta-globin gene). The disorder range from asymptomatic and mild to moderate and severe anemia [5]. Alpha-thalassaemia is also an inherited condition (affecting alpha-globin genes) that causes microcytic anemia. It is a predominant illness in the Middle East [6].

Iron deficiency anemia is a disease with diverse causes. About 50% of the anemia cases worldwide are iron deficiency anemia. The causes of the disorder can be the following: reduced

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intakes of iron, decreased absorption of it, or even blood loss. The gold standard for the diagnosis of the disorder is bone marrow aspiration or biopsy, which is invasive and is replaced by less invasive methods [7]. Mean corpuscular volume (MCV) less than 80 fL has been used as the screening method for thalassemia [8]. It is also reduced in many cases of iron deficiency anemia.

Impairment of lung function has been shown to be associated with major thalassemia. Both restrictive and obstructive patterns have been observed. A higher prevalence of restrictive lung function has been found in one study. There has not been any association between lung function and serum ferritin in the study [9, 10]. Impairment of lung function can exist even in asymptomatic thalassemia patients [11]. The number of studies on the association between lung function and the minor cases of thalassemia are limited. In patients with other hemoglobinopathies (like sickle cell anemia), both obstructive and restrictive changes have been observed in previous studies [12]. The study of lung function in iron deficiency anemia is mostly limited to some predefined lung disorders like chronic obstructive lung disease [13].

The association between microcytic anemia and pulmonary function tests have not been thoroughly investigated. The previous researches have highlighted the possibility of this association. The aim of this study was to assess the pulmonary function of patients with microcytic anemia and to compare the results with the outcomes of the normal population in the city of Bandar Abbas, Iran.

Material and methods

The study was conducted from the first of June 2016 to the first of June 2017 (one year). The study population consisted of all the patients admitted to the occupational medicine center in one of the general hospitals of the city of Bandar Abbas (Shahid Mohammadi hospital). The city is situated in the southern part of Iran (27 degrees north and 56 degrees east), and it has a subtropical climate with a high prevalence of thalassemia [14].

The study subjects were mostly symptom-free persons who were referred for an occupational fitness assessment. All of the participants went through physical examination and the Persian version of the Epworth Sleepiness Scale (to rule out obstructive sleep apnea) was filled by all of them [15]. The exclusion criteria consisted of the following: cigarette smoking (present and past), inability to perform an acceptable and reproducible spirogram based on the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [16], history of recent respiratory tract infection (e.g. common cold in the past month) and other diseases that could affect the results of the study (pulmonary disorders like asthma and chronic obstructive lung disease, chest surgery, morbid obesity, history of any type of lung fibrosis, collagen-vascular disorders, neuromuscular diseases, and systemic muscle diseases), pregnancy, other known hemoglobinopathies (except minor thalassemia), iron deficiency anemia requiring intravenous or oral treatment, having had very high occupational exposure to dust, fumes, solvents or noxious gases in the workplace, and not giving consent to the study.

The results of spirometry for all the patients were obtained by the same technician and the same device (Mir spirolab III) with BTPS (Body Temperature and Pressure Saturated) correction. The tests were performed between 8:00 a.m. and 12:00 noon. None of the subjects had hypoxemia before the maneuvers (determined by the pulse--oximetry accessory of the device). For about 42% of the subjects (939 subjects), maximum voluntary volume (MVV) was also obtained. Basing on the ATS/ERS criteria, forced expiratory volume or forced vital capacity (FVC) is defined as "maximal volume of air exhaled with maximally forced effort from a maximal inspiration, performed with a maximally forced expiratory effort". Forced expiratory volume in the first second (FEV_1) is defined as "maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration" [16]. The forced expiratory flow between 25% and 75% of the FVC is designated as FEF25-75 in this article. The ratio of FEV_1 to FVC has also been included in the analysis. The reference value equations were derived from the Global Lung Initiative (GLI-2012) [17], i.e.its excel sheet calculator [18].

For assessment of microcytic anemia, hemoglobin levels less than 13.5 g/dl for men and less than 12.0 for women were considered anemic, and MCVs less than 80 fL were considered microcytic. The Mentzer index was also used because it incorporates both MVC and red blood cell (RBC) count [19]. All the lab results were gathered from a single laboratory (belonging to the same general hospital) with the same technique throughout the study.

For every occupational health workup, physical and chemical exposures in the workplace are assessed by occupational hygienists and are

the part of occupational hazards. Because of the possible work-related reduction in the lung function, the exposures which had the possibility to deteriorate lung function (including exposure to dust, fumes, solvents, and noxious gases) were gathered as a variable called "exposures". The variable was used in the analysis to adjust for the level of possible spirometric parameter deterioration attributable to the subjects' occupation.

Basing on the anemia type, the subjects were categorized into 3 main groups. One of them were normal persons with neither anemia nor microcytosis. The second group consisted of patients with both anemia and microcytosis. The third group included subjects with either anemia or microcytosis.

The data were analyzed using SPSS version 16 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Linear regression was applied to determine the relationship between the variables, and a p-value < 0.05 was considered statistically significant. Informed consent was obtained from all individual participants included in the study, and the study was approved by the ethics committee of Hormozgan University of Medical Sciences.

Results

A total of 2,548 subjects participated in our cross-sectional study and 349 were excluded due to smoking, previous lung or other organ system disorders (mostly asthma), using treatment for iron deficiency, or inability to perform an acceptable maneuver. At last 2,199 subjects were included in the analysis. There were 1,903 men (86.5%) and 296 women (13.5%). 335 subjects (15.2%) had microcytic anemia, 1,686 subjects (76.7%) had neither anemia nor microcytosis, and 178 subjects (8.1%) had either anemia or microcytosis. Table 1 shows the demographic data and spirometric percentage values and hematologic indices in the sample population.

For comparing the spirometric parameters between the subject groups, first, the patients

Table 1. Demographic data and spirometric and lab data in four subcategories of the subjects

	Subjects with either anemia or microcytosis	Microcytic anemia subjects	Normal subjects
Demographic data			
Total number	178 (8.1%)	335 (15.2%)	1686 (76.7%)
Age	34.23 ± 0.66	34.04 ± 0.46	33.75 ± 0.19
Sex (percentage of males)	56.7%	74.3%	92.1%
Weight (kg)	66.31 ± 0.96	68.58 ± 0.75	75.64 ± 0.35
Height (cm)	169.4	169.5 ± 0.44	172.8
Subjects with exposure (Percent)	38.2%	51.3%	55.8%
Spirometric data			
FEV_1 percentage*	85.96 ± 0.88	84.53 ± 0.59	85.83 ± 0.268
FEV_1 Z score*	–1.13 ± 0.07	–1.24 ± 0.04	–1.14 ± 0.02
FVC percentage*	85.86 ± 0.84	84.64 ± 0.59	86.23 ± 0.27
FVC Z score*	–1.15 ± 0.06	–1.15 ± 0.06	–1.13 ± 0.02
FEV_1/FVC Z score*	0.01 ± 0.06	0.01 ± 0.05	–0.03 ± 0.02
FEF 25–75 Z score*	–0.55 ± 0.06	–0.58 ± 0.04	–0.54 ± 0.02
MVV percentage**	81.95 ± 1.82	84.2 ± 1.41	84.75 ± 0.58
Laboratory data			
WBC (103/μL)	6.22 ± 0.14	6.34 ± 0.19	6.52 ± 0.04
RBC (106/μL)	4.69 ± 0.04	5.54 ± 0.05	5.41 ± 0.01
Hemoglobin (g/dL)	12.47 ± 0.06	12.23 ± 0.09	14.98 ± 0.02
MCV (fL)	82.27 ± 0.45	70.40 ± 0.48	82.32 ± 0.16
Platelet count (106/μL)	249.7 ± 4.7	242.5 ± 5.6	233.6 ± 1.3

*Based on GLI-2012 equations; ** MVV was performed on only 939 subjects; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEF 25–75: forced expiratory flow between 25% and 75% of expiration; MVV: maximum voluntary volume; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume

Table 2. ANOVA test for comparing the spirometric variables between those with microcytic anemia and normal population (those with either microcytosis or anemia are not included)

	Microcytic anemia (n = 335)		Normal patients (n = 1681)		p-value
	Mean	Standard deviation	Mean	Standard deviation	
FEV_1 percent	84.53	10.82	85.83	11.01	0.049
FEV_1 Z score	–1.24	0.85	–1.14	0.88	0.053
FVC percent	84.64	10.93	86.23	11.33	0.019
FVC Z score	–1.25	0.89	–1.13	0.93	0.030
FEV_1/FVC Z score	0.01	0.96	–0.03	0.92	0.370
FEF25–75 Z score	–0.58	0.89	–0.54	0.85	0.370
MVV percent	84.24	15.56	84.75	15.94	0.746

FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEF 25–75: forced expiratory flow between 25% and 75% of expiration; MVV: maximum voluntary volume

Table 3. Correlation between spirometric indices and Hematologic indices

	WBC	RBC	Hemoglobin	MCV	Mentzer Index	Platelet count
FEV_1 percent	–0.028	–0.064**	0.014	0.057**	0.065**	–0.029
FEV_1 Z score	–0.023	–0.065**	0.015	0.060**	0.067**	–0.029
FVC percent	–0.013	–0.070**	0.030	0.074**	0.077**	–0.047*
FVC Z score	–0.008	–0.076**	0.024	0.076**	0.082**	–0.044*
FEV_1/FVC Z score	–0.034	0.012	–0.035	–0.034	–0.025	0.034
$FEF_{25–75}$ Z score	–0.014	0.002	0.014	–0.003	–0.006	0.002
MVV percent	0.011	0.050	0.082*	0.008	–0.028	0.004

* Significant at 0.05 level
** Significant at 0.01 level

with microcytic anemia were compared to the normal subjects. For spirometric parameters, we used the GLI-2012 reference values for both percentages and Z scores. These values are adjusted for stature (height), age, sex, and ethnicity. Table 2 shows that there are statistically significant differences between FVC percentages and Z scores between the groups, and there are lower values in the subjects with microcytic anemia. There is also a reduction in FEV_1 in the individuals with microcytic anemia, which has borderline significance (the percentage is statistically significant but the Z score is not).

In Table 3, the correlations between various hematological indices and spirometric parameters in the whole sample population are shown. The connections are not strong, but the correlation of some hematologic indices (RBC, MCV, and the Mentzer index) with FEV_1 and FVC is statistically significant. The relationship of FEV_1 and FVC with RBC is negative, but the correlation with MCV and the Mentzer index is positive.

Because the GLI-2012 reference equations automatically adjust for height, sex, age, and ethnicity, there is no need for adjustment of these parameters. Since the subjects of the study were derived from an occupational clinic and because occupational exposures can influence the spirometric values, the exposures between the two groups were adjusted using linear regression. Table 4 shows the regression model with previously significant variables. As an example it can be adduced that a 20 units increase in MCV (e.g. from 65 to 85) predicts almost a 1.5 percent increase in FVC in the sample population.

Each standardized coefficient is from a different model (e.g. combined effects of exposure and MCV on prediction of FVC percent)

Discussion and conclusion

This study shows that there is an association between the spirometric parameters (FEV_1 and FVC) and microcytic anemia. This correlation is positive for MCV and negative for RBC.

Table 4. Linear regression model for assessment of the increase in hematologic indices and spirometric values in all the subjects (normal, microcytosis or anemia and microcytic anemia) adjusted for exposure to dust, fumes, solvents, and noxious gases

	Mentzer index		MCV		RBC	
	Standardized coefficient (Beta)	p-value	Standardized coefficient (Beta)	p-value	Standardized coefficient (Beta)	p-value
FEV_1 percent	0.065	0.002	0.057	0.008	–0.064	0.003
FEV_1 Z score	0.067	0.002	0.060	0.005	–0.066	0.002
FVC percent	0.076	0.001	0.074	0.001	–0.070	0.001
FVC Z score	0.082	0.001	0.076	0.001	–0.076	0.001

There has been evidence that restrictive spirometric pattern is prevalent in patients with major thalassemia [9, 11, 20], and this study shows that there is a significant reduction in FVC in the patients with microcytic anemia. There are other researches that demonstrate a possible decrease in FEV_1 in beta-thalassemia [10], and this study found that there is a reduction in this parameter in microcytic anemia with borderline statistical significance. Iron deficiency anemia has been shown to be associated with chronic obstructive lung disease [13, 21], but the studies on its effect on spirometric parameter values (not diseases) are scarce. The possible cause of these observations can be the reduced function of muscles due to iron deficiency anemia which has been shown to have an effect on the muscular function [22]. In most of the previously mentioned studies, the numbers of patients are low, which is logical because of the lower prevalence of major thalassemia and the fact that the study subjects are usually children. These studies also used the cut-points in the spirometric values to diagnose possible restrictive or obstructive patterns. In our study, the quantitative values of spirometric parameters were used.

In this study, the mechanism of the reduction in spirometric values due to microcytic anemia has not been evaluated. There are some possible causes. Mild hypoxia that can reduce the function of respiratory muscles can explain the reduction in FVC and to some extent the reduction in FEV_1. Even though the results of pulse oximetry of the subjects were normal, it should be remembered that pulse oximetry alone cannot determine the amount of hypoxia (considering the Hemoglobin Bonn as an example) [23]. We did not include the subjects with clinical hypoxia, but there is a possibility that subclinical hypoxia can be associated with this reduction. For assessment of hypoxia, arterial blood gas is suggested. Another possible cause is pulmonary arterial hypertension which can reduce FEV_1 and FVC in the patients [24]. There is also the possibility that there is a causal factor that causes both reduction in spirometric parameters and also microcytosis and anemia, and it needs to be determined.

There are limitations to our study. Because the sample was selected from yearly occupational checkups, there were fewer female subjects than male subjects. In this study, the differentiation between the causes of the types of microcytic anemia was not determined. To establish the etiology of this reduction in spirometric values, further studies are recommended. There are other factors that influence lung function. The major concern in our study was the exposure to work hazards. These hazards were not quantitatively analyzed, and the binary definition of having the exposure and not having the exposure was used to exclude the possible confounder effect. This can be improved in future studies. When the amount of exposures is above a particular limit, the employer is needed to perform certain actions. Those subjects who had this amount of exposure were not included in the study. Only occupational exposures were available for the study and recreational exposures to hazards were not assessed. Yet, there are no obvious reasons that these recreational hazards are significantly different among the groups. Because it was a cross-sectional study, only the association between the variables could be assessed, and the causality could not be determined.

The subjects that attended our clinic were mostly healthy adults that demanded a yearly checkup required by the occupational law in Iran. The rate of the disease (especially lung disease) was minimal. Therefore, it was possible to determine the effects of microcytic anemia with the spirometric parameters without the confounding effects of other disorders. In this study, only the

association between microcytic anemia and the reduced spirometric values was assessed. Further studies are suggested to assess the possible mechanisms of this reduction.

It can be concluded that microcytic anemia may reduce some spirometric parameters (mostly FVC and to a lesser degree FEV_1). Even though these changes are small, adjusting for these reduced values can help prevent the overestimation of lung disorders, mostly in the borderline cases.

Conflict of interests

The authors declare no conflict of interest.

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