Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1420858

Anatolian Curr Med J. 2024;6(2):139-143

The relationship between increased iron load and respiratory function tests in patients diagnosed with transfusion dependent thalassemia

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Cite this article as: Selim C, Çiftçiler R. The relationship between increased iron load and respiratory function tests in patients diagnosed with transfusion dependent thalassemia. *Anatolian Curr Med J.* 2024;6(2):139-143.

Received: 16.01.2024 ◆ **Accepted**: 11.02.2024 ◆ **Published**: 08.03.2024

ABSTRACT

Aims: Thalassaemia syndromes are the most common single gene disorders affecting more than 200 million people worldwide. Beta thalassaemia (BT) is the most common cause of transfusion-dependent thalassaemia (TDT). It has been reported in studies that iron accumulation occurs in the lungs, especially in the alveolo-capillary membrane, and the frequency of parenchymal disease increases in patients receiving frequent blood transfusions. In our study, we aimed to investigate whether there is a correlation between iron overload and pulmonary function in patients with TDT.

Methods: The study included 61 patients aged between 18 and 45 years with a diagnosis of TDT who were followed up in the hematology clinic of our tertiary care center between 2018 and 2023. Based on spirometry measurements, the pattern of respiratory impairment was defined and correlated with serum ferritin levels.

Results: The mean age of the 61 patients included in the study was 24.83±6.02 years and 33 were female and 28 were male. The mean ferritin value was 3150.88±2553.51 ng/ml. The annual number of transfusions was 15.39±1.90. According to the PFT results, mean FVC % value was 81.59±9.28, mean FEV1 % value was 82.11±7.6, mean FEV1/FVC % value was 102.55±7.63. Mean ferritin values were found to be significantly higher in patients diagnosed with TDT with restrictive lung pattern (p=0.004).

Conclusion: Our study showed that high ferritin levels are related to increased restrictive lung disease in the adult age group.

Keywords: Thalassemia, respiration, iron load

INTRODUCTION

Thalassaemia syndromes are haemoglobinopathies in which globin chain biosynthesis is affected and can be classified as α, β, or β thalassaemia syndromes according to the affected globin chain or according to transfusion dependency.[1] Thalassaemia syndromes are the most common single gene disorders affecting more than 200 million people worldwide. Beta thalassaemia (BT) is the most common cause of transfusion-dependent thalassaemia (TDT).[2] BT is a disease that varies from asymptomatic anemia to severe chronic anemia that may be fatal if not approached correctly.[3] Depending on the degree of impairment in globin chain biosynthesis and clinical reflection, β-thalassemia is classified as minor, intermedia, and major. Cooley anemia or β-thalassaemia major (BTM) is the most severe form characterised by ineffective erythropoiesis, haemolytic anemia, and decreased tissue oxygenation capacity.[4] Patients with BTM are in need of regular blood transfusions. This leads to short- and long-term complications in patients. Both blood transfusion and ineffective erythropoiesis leading to increased iron absorption lead to parenchymal iron overload.[5] Histologically, the amount of iron increases in almost all organs, especially in the liver, heart, and pancreas, and to a minor extent in the endocrine glands.[5,6] In addition, it has been reported in studies that iron accumulation occurs in the lungs, especially in the alveolo-capillary membrane, and the frequency of parenchymal disease increases in patients receiving frequent blood transfusions.[6,7]

It has been reported that patients with TDT may have a high rate of pulmonary dysfunction, but restrictive or obstructive pulmonary lung disorders have been found separately in different studies.[8,9] Although the pathophysiology of pulmonary dysfunction has

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not been fully defined, autopsy data demonstrating pulmonary iron accumulation in patients with TDT who received more than one transfusion have suggested that iron accumulation resulting from repeated blood transfusions is a possible cause of pulmonary dysfunction.[10,11]

Markers including transferrin saturation and serum ferritin are used to measure iron toxicity and accumulation in patients diagnosed with TDT.[12] Although pulmonary function has been examined by pulmonary function test (PFT) in patients with TDT, the number of studies demonstrating the correlation between transferrin saturation and ferritin, which are indicators of disease iron load, and pulmonary function, especially in adult patients, is limited. In our study, we aimed to investigate whether there is a correlation between iron overload and pulmonary function in patients with TDT.

METHODS

The study included 61 patients aged between 18 and 45 years with a diagnosis of TDT who were followed up in the hematology clinic of our tertiary care center between 2018 and 2023. Patients with diagnosed lung diseases (asthma, pneumonia, COPD, tuberculosis, bronchiectasis, etc.), smokers, and patients with chronic diseases that may lead to secondary immunodeficiency were excluded from the study. Approval for the study was obtained from Harran University Clinical Researches Ethics Committee (Date: 05.06.2023, Decision No: HRÜ/23.10.02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients were instructed to avoid other drugs (except chelators) 24 hours before transfusion. Chest X-ray radiography was performed before PFT and PFT was performed in patients with normal radiographs. Immediately before transfusion, venous samples were obtained from all patients and serum ferritin levels were evaluated and pulmonary function tests were performed using standardized spirometry. Patients were advised to perform several normal breaths, followed by deep breathing, followed by momentary breath holding and forced and rapid expiration. For 6 seconds, expiration was made as hard and long as possible. The same process was repeated 3 times, and the best possible effort was made. Based on spirometry measurements, the pattern of respiratory impairment (obstructive or restrictive) was defined and correlated with serum ferritin levels. Patients with PFT results showing obstructive or restrictive patterns were referred to the pulmonology department.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as Mean±SD or Median (IQR) for continuous variables. The data were analysed by Kolmogorov Smirnov test in terms of normal distribution and since $p<0.05$, Mann Whitney U test, one of the nonparametric tests, was used for continuous variables and pair group comparisons. The correlation between continuous variables was analysed by Spearman Correlation test. $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the 61 patients included in the study was 24.8±6 years and 33 were female and 28 were male. The mean ferritin value was 3150.8±2553.5 ng/ml and transferrin saturations were 42.4±14.4. The annual number of transfusions was 15.3±1.9. According to the PFT results, mean FVC % value was 81.5±9.2, mean FEV1 % value was 82.1±7.6, mean FEV1/FVC % value was 102.5±7.6, mean PEF1 % value was 68.4±10.4, mean MEF 25-75% value was 72.2±14.3 (**Figure 1**).

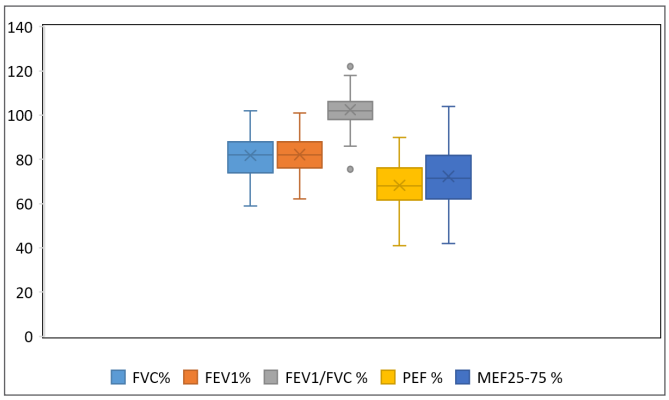

Figure 1. Pulmonary function test distribution summary

Accordingly, 35 (57.4%) of the patients evaluated by the pulmonology department were found to have normal PFTs, while 25 (41%) were found to have restrictive pattern lung disease and were followed up by the pulmonology department for further examination and treatment. Obstructive pulmonary disease was found in only 1 patient (1.6%) and this patient was also followed up in the pulmonary diseases department. Sociodemographic and Clinical Characteristics data of the patients are presented in **Table 1**.

Ferritin value was found to be significantly lower in patients diagnosed with TDT with normal PFT ($p=0.004$). However, transferrin saturation values did not show a statistically significant difference between the groups ($p=0.066$) (**Table 2**).

Table 1. Sociodemographic and clinical characteristics of the patients

Variables	n	%
Age		
Mean±SD	24.83±6.02	
Median (min-max)	23 (18-45)	
Gender		
Female	33	54.1
Male	28	45.9
Normal		
No	26	42.6
Yes	35	57.4
Obstructive		
No	60	98.4
Yes	1	1.6
Restrictive		
No	36	59.0
Yes	25	41.0
Parameters	**Mean±SD**	
Ferritin	3150.89±2553.52	
Annual number of transfusions	15.39±1.91	
Transferrin saturation	42.89±14.22	
FVC %	81.59±9.28	
FEV1 %	82.11±7.6	
FEV1/FVC %	102.55±7.63	
PEF %	68.44±10.45	
MEF25-75 %	72.26±14.33	

Table 2. Comparison of ferritin and transferrin saturation values in patients with normal Pulmonary function tests

Variables	Normal PFT		p
	No N=26 Median (IQR)	Yes N=35 Median (IQR)	
Ferritin	3384.0 (2602.5)	1750.0 (2015.0)	0.004
Transferrin saturation	44.5 (13.2)	39.0 (24.0)	0.066

Mann Whitney U test, p<0.05 is statistically significant

Mean ferritin values were found to be significantly higher in patients diagnosed with TDT with restrictive lung pattern (p=0.004). However, transferrin saturation values did not show a statistically significant difference between the groups (p=0.062) (**Table 3**).

Table 3. Comparison of ferritin and transferrin saturation values in patients with restrictive lung pattern

Variables	Restrictive		p
	No N=36 Median (IQR)	Yes N=25 Median (IQR)	
Ferritin	1807.0 (1928.2)	3614.0 (3068.0)	0.004
Transferrin saturation	39.5 (23.5)	45.0 (14.5)	0.062

Mann Whitney U test, p<0.05 is statistically significant

As seen in **Table 4**, a statistically significant negative correlation was found between ferritin values and FVC % (r=-0.469, p<0.001), FEV1% (r=-0.447 p<0.001), and MEF 25-75% (r=-0.281 p=0.028). No statistically significant correlation was found between transferrin saturation values and FVC %, FEV1 %, PEF % and MEF 25-75% (p>0.05).

Table 4. Correlation between various clinical parameters

		Ferritin	Transferrin saturation
FVC %	r	-.469**	-0.241
	p	<0.001	0.062
FEV1 %	r	-.447**	-0.238
	p	<0.001	0.065
FEV1/FVC %	r	0.152	0.141
	p	0.241	0.278
PEF %	r	-0.119	-0.191
	p	0.361	0.140
MEF25-75 %	r	-.281*	-0.218
	p	0.028	0.091

Correlation is significant at 0.05 level (Spearman correlation test), ** Correlation is significant at 0.01 level (Spearman correlation test)

DISCUSSION

In our study, PFT results were compatible with restrictive lung disease in 41% of patients with TDT and ferritin levels of these patients were found to be significantly higher than patients with TDT who were evaluated as normal lung findings according to PFT results. According to the results of our study, high ferritin levels may be an indicator of increased pulmonary damage and restrictive lung disease.

Pulmonary diseases in patients diagnosed with TDT have been investigated previously and different results were observed in the studies. In some studies, the risk of obstructive lung disease increased in patients diagnosed with TDT, whereas the frequency of lung disease in a restrictive pattern was found to be increased in patients with TDT.[13,14] The reason for this has been shown to be the accepted hypercoagulable state resulting in microembolisation of the pulmonary arteries and the chronic hypoxemic state that may cause an abnormal alveolar enlargement limiting the volume of the air cavities in patients diagnosed with TDT, as shown in studies involving autopsies.[15,16] In addition, it has been reported that thoracic developmental disorders may lead to restrictive lung disease in patients with a diagnosis of TDT due to growth retardation.[17]

As described by these results, the number of studies showing the relationship between ferritin level, which is an indicator of increased iron load due to increased ineffective erythropoiesis and transfusion therapy, and pulmonary function is limited and the results are contradictory.

In a study by Bourli et al.[14] pulmonary function, PFT, and carbon monoxide diffusion capacity tests were measured in 52 patients with TDT, and a restrictive lung pattern was found in 38% of the patients. Although this rate is similar to our study, no correlation was found between restrictive lung disease and ferritin levels. This difference in the results may be due to the fact that patients under

18 years of age were included in this study and ferritin levels were found to be much lower (1680 ng/ml) in the patients included in this study compared to our patients.

In the study by Li et al.[18] 29 patients with TDT were evaluated in terms of pulmonary diseases. The mean age of the patients included in this study was 14 years. The patients included in this study were evaluated by PFT and MRI, and restrictive lung disease was found in 34% of the patients. This rate is similar to the rate in our study. Although ferritin level was increased in patients with restrictive lung disease, this increase was not statistically significant. In contrast to our study, the small number of patients in this study and the fact that the patients were in the pediatric age group may have caused the results to be different.

In the study by Kanj et al.[19] 36 patients from pediatric and adult age groups were analyzed in terms of the correlation between pulmonary function and ferritin levels. Patients were also evaluated with cardiac T2 MR. In this study, patients from the pediatric age group were included in the study, which is different from our study. Restrictive lung pattern was observed in 47% of the patients in this study, which was slightly higher than in our study. Although the mean ferritin values of patients with normal lung function and patients with restrictive lung pattern were not given, similar to our study, ferritin levels were found to be significantly higher in patients with restrictive lung pattern.

In a study by Chan et al.[20] the relationship between pulmonary function, cardiac and liver MRIs, and iron load in 101 patients diagnosed with TDT with follow-up was evaluated. Both pediatric and adult patients were included in this study. Ferritin levels were found to be significantly higher in patients with iron accumulation in the liver and heart by MRI. The mean ferritin value of 38 patients with restrictive lung pattern on PFT was 4474 ng/ml and the mean ferritin value of 52 patients with normal lung pattern on PFT was 3625 ng/ml. Similar to our study, although ferritin values were found to be higher in patients with restrictive lung pattern on PFT, they were not statistically significant in this study.

CONCLUSION

Our study showed that high ferritin levels are related to increased restrictive lung disease in the adult age group. Regular monitoring of ferritin levels and regular use of iron chelation therapy in patients on TDT is essential. In patients with high ferritin levels, patient-drug compatibility should be evaluated, drug changes should be considered if necessary, and pulmonary complications related to this should be kept in mind.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 05.06.2023, Decision No: HRÜ/23.10.02).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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