



## ARAŞTIRMA / RESEARCH

# Asymptomatic respiratory dysfunction in patients with thalassemia major

Talasemi major hastalarında asemptomatik solunum fonksiyon bozukluğu

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### Abstract

**Purpose:** Regular transfusions cause progressive iron deposition in critical organs such as heart, liver and lungs in transfusion-dependent thalassemia (TDT). We aimed to evaluate respiratory dysfunction and factors affecting respiratory dysfunction in patients with TDT.

**Materials and Methods:** Patients with TDT treated at department of Pediatric Hematology/Oncology of Sağlık Bilimleri University, Adana Education and Research Center were evaluated retrospectively.

**Results:** Respiratory function tests were performed in 40 patients (19 female; 21 male) with TDT. The mean age at diagnosis was 6.63±5.74 months, mean body mass index was 18.57±2.27 kg/m<sup>2</sup>, mean transfusion program duration was 151.67±50.48 months. Splenectomy rate was 48%. All of the patients were using iron chelation therapy. Respiratory function tests revealed normal findings in 57.5%, restrictive lung dysfunction with small airway obstruction findings in 27.5% and isolated restrictive dysfunction in 15% of patients. There was no statistically significant difference in respiratory dysfunction according to age, gender, transfusion program duration, ferritin and hemoglobin levels, presence of splenectomy, or type of chelation therapy. Patients with ferritin levels above 2500 ng/dl had significantly lower values for forced expiratory volume (FEV1) and forced vital capacity (FVC).

**Conclusion:** In our study, restrictive respiratory dysfunction was detected in nearly half of the patients with TDT who had no respiratory symptoms. Higher ferritin levels may indicate the need for close follow-up for respiratory symptoms.

**Keywords:** Thalassemia, respiratory dysfunction, pulmonary function tests

### Öz

**Amaç:** Düzenli transfüzyonlar, transfüzyona bağımlı talasemide (TDT) kalp, karaciğer ve akciğer gibi kritik organlarda ilerleyici demir birikmesine neden olur. Bu çalışmada TDT'li hastalarda solunum fonksiyon bozukluğunu ve solunum fonksiyon bozukluğunu etkileyen faktörlerin değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntem:** Sağlık bilimleri üniversitesi, Adana Eğitim Ve Araştırma Merkezi Çocuk Hematolojisi / Onkoloji Ünitesi'nde TDT nedeniyle takip ve tedavi edilmekte olan hastalar içinden solunum fonksiyon testi yapılan hastalar retrospektif olarak değerlendirildi.

**Bulgular:** Solunum fonksiyon testleri 40 TDT tanılı hastada (19 kadın; 21 erkek) yapıldı. Tanı sırasındaki ortalama yaş 6.63 ± 5.74 ay, ortalama vücut kitle indeksi 18.57 ± 2.27 kg / m<sup>2</sup>, ortalama transfüzyon programı süresi 151.67 ± 50.48 ay idi. Splenektomi oranı%48 idi. Bütün hastalar demir şelasyon tedavisi kullanıyordu. Solunum fonksiyon testlerinde hastaların%57,5'inde olan normal bulgular, %27,5'inde küçük hava yolu tıkanıklığı bulguları ile restriktif akciğer disfonksiyonu ve%15'inde izole restriktif disfonksiyon saptandı. Solunum fonksiyonlarında yaş, cinsiyet, transfüzyon programı süresi, ferritin ve hemoglobin düzeyleri, splenektomi varlığı veya şelasyon tedavisi tipi açısından istatistiksel olarak anlamlı bir fark saptanmadı. Ferritin düzeyi 2500 ng / dl'nin üzerinde olan hastalarda zorlu ekspiratuar hacim (FEV1) ve zorlu vital kapasite (FVC) için anlamlı olarak düşük değerler bulundu.

**Sonuç:** Çalışmamızda, solunum semptomu olmayan TDT tanılı hastaların yaklaşık yarısında kısıtlayıcı solunum fonksiyon bozukluğu tespit edildi. Yüksek ferritin düzeyleri solunum disfonksiyonunu işaret edebileceğinden hastaların bu açıdan yakın takip edilmesi uygun olacaktır.

**Anahtar kelimeler:** Talasemi, solunum fonksiyon bozukluğu, solunum fonksiyon testleri

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## INTRODUCTION

$\beta$ -thalassemia is caused by the reduced or absent synthesis of the **beta** globin chains of the hemoglobin tetramer. There are mainly three clinical and hematological conditions of thalassemias as the  $\beta$ -thalassemia carrier state, thalassemia intermedia, and thalassemia major, the last one being severe transfusion-dependent anemia<sup>1,2</sup>.  $\beta$ -thalassemias are quite heterogeneous at the molecular level, and more than 200 disease-causing mutations have been previously identified<sup>1,2</sup>.

Due to  $\alpha$ -globin chain excess in erythrocytes; membrane damage, hemolysis, ineffective erythropoiesis in the bone marrow, and eventually anemia is seen. Extramedullary hematopoiesis develops as erythropoietin production increases as a result of anemia. In patients with extramedullary hematopoiesis, skeletal-facial changes such as nasal root scarring, mongoloid facial appearance, and hepatosplenomegaly are seen<sup>3</sup>. Clinical findings in patients with transfusion-dependent thalassemia (TDT) vary widely depending on whether patients receive appropriate treatment. Complications are less common in effectively treated patients. Death is mostly because of heart failure resulting from iron accumulation in untreated patients<sup>4</sup>.

The most important complication in patients with TDT is progressive iron accumulation secondary to transfusion of the blood (secondary hemochromatosis), and iron accumulation-induced organ damage<sup>5,6</sup>. Complications are less frequently seen in patients treated with regular iron chelation therapy and standardized blood transfusions<sup>7</sup>. The lung is one of the organs of iron accumulation. Iron accumulation in the lungs leads to a decrease in lung capacity, restrictive and/or obstructive pulmonary dysfunction as a result of tissue damage caused by hydroxyl radicals. Another reason for changes in lung dynamics, is disruption of rapid alveolar growth in children with TDT<sup>8</sup>.

Although the fact that iron accumulation in the lungs is known in these patients, the issue of how this accumulation affects the lungs is still a matter of debate<sup>9</sup>. Accordingly, the objective of this study was to evaluate respiratory functions and factors influencing respiratory dysfunction in patients with the TDT under regular transfusion program.

## MATERIALS AND METHODS

Among 92 TDT patients, the hospital files of 40 cases evaluated with PFT in the department of Pediatric Hematology and Oncology of Saglik Bilimleri University, Adana Education and Research Center, between October 2015 and October 2016 were evaluated retrospectively after approval of Ethical Committee of Çukurova University (Date: 07/10/2016, Decision number: 38). Patients who had smoking history, had signs of upper and lower acute respiratory tract infections, underwent lung operation, or followed for asthma or chronic pulmonary disease, and who were not under a regular transfusion program were excluded from the study.

### Assessment

PFT was assessed by MIR 'SpirolabII' (MIR, Rome, Italy) spirometry performed by the same technician. Clinical and demographical features such as current age and age at diagnosis, gender, body weight, height, body mass index (BMI), follow-up duration, physical examination findings, history of splenectomy, the time passed after transfusion program was started (transfusion program duration), type of chelation therapy, ferritin levels were recorded.

In the respiratory function test, FEV1, FVC, FEV1 / FVC, FEF25-75, PEF results are expressed as percentages of normal. The patients were categorized into 3 groups according to the PFT results<sup>10</sup>; normal with no abnormalities in the PFT; restrictive disorder with decreased total lung capacity (<80%), (FVC<80% and FEV1/FVC $\geq$ 80%); restrictive + small airway obstruction with FEF25-75 <60% + FVC > 80% + FEV1 / FVC >70%.

### Statistical analysis

IBM SPSS Statistics Version 20.0 package program (SPSS reference: IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used for statistical analysis of the data. Demographic features of the patients were given with descriptive statistics. Chi-square test was used to compare categorical measurements between groups. The Kolmogorov-Smirnov test was used to evaluate distribution pattern of the numeric variables. Mann-Whitney U test was used to compare two groups of numerical variables without normal distribution. Independent groups Student t test was used to make comparison between two groups with

normal distribution. The statistical significance level ( $p$ ) for all tests was  $<0.05$ .

## RESULTS

There were 40 patients with TDT (19 females, 21 males) in whom PFT was performed. The mean age at diagnosis was  $6.63 \pm 5.74$  months and the mean current age was  $13.27 \pm 4.26$ . Clinical and demographical features are summarized in Table 1. In

37 patients deferasirox and in 3 deferiprone were used for iron chelation.

Physical examination revealed hepatomegaly and splenomegaly in 17 (42.5%) and 12 (30%) patients, respectively. Twenty-three of the patients (57.5%) had normal PFT, however 6 patients (15%) had restrictive type pulmonary disorder and 11 patients (27.5%) had combined restrictive and small airway obstruction disorder.

**Table 1. Clinical and demographical features. and pulmonary function test scores of the patients**

Variables	Mean $\pm$ SD	Range
Age (years)	13.27 $\pm$ 4.26	6-20
Height (cm)	140.82 $\pm$ 19.66	103-176
Weight (kg)	38.20 $\pm$ 14.04	18-67
BMI (kg/m <sup>2</sup> )	18.57 $\pm$ 2.27	15-23.4
Diagnosis Age (months)	6.63 $\pm$ 5.74	1-24
Transfusion Duration (months)	151.67 $\pm$ 50.48	48-234
Hb (g/dL)	8.36 $\pm$ 1.36	4.6-10.4
Ferritin (ng/dL)	3268.25 $\pm$ 2991.44	480-11671
FEV <sub>1</sub>	77.25 $\pm$ 17.10	40-113
FVC	71.87 $\pm$ 15.65	36-104
FEV <sub>1</sub> /FVC	106.42 $\pm$ 6.96	91-120
FEF <sub>25-75</sub>	84.87 $\pm$ 28.23	34-145
PEF	74.72 $\pm$ 30.51	25-210

SD: standart deviation BMI: Body mass index (kg/m<sup>2</sup>). Hb: Hemoglobin. PFT: Pulmonary function test. FEV1: Forced expiratory volume in the first second. FVC: Forced vital capacity. FEF<sub>25-75</sub>: Forced expiratory flow from 25% to 75% of vital capacity. PEF: Peak Expiratory Flow

**Table 2. Comparison of hemoglobin concentration, transfusion program duration, splenectomy rate and pulmonary function test results according to the gender**

Variables	Female (n=19)	Male (n=21)	p-value
Hb (gr/dL)	8.29 $\pm$ 1.42	8.41 $\pm$ 1.34	0.77
Transfusion program duration (month)	154.63 $\pm$ 49.83	149 $\pm$ 52.18	0.73
Splenectomy	n (%)	n (%)	
Yes	8 (42.1)	11 (52.4)	0.516
No	11 (57.9)	10 (47.6)	
PFT Results	n (%)	n (%)	
Normal	10 (%52.6)	13 (%61.9)	
Restrictive	2 (% 10.5)	4 (%19.0)	0.406
Restrictive + Small Airway Obstruction	7 (%36.8)	4 (%19.0)	
FEV <sub>1</sub>	75.68 $\pm$ 15.56	78.66 $\pm$ 18.66	0.589
FVC	70.89 $\pm$ 14.72	72.76 $\pm$ 16.76	0.712
FEV <sub>1</sub> /FVC	103.854 $\pm$ 6.37	108.76 $\pm$ 6.78	0.024*
FEF <sub>25-75</sub>	79.00 $\pm$ 26.59	90.19 $\pm$ 29.28	0.215

Hb: Hemoglobin PFT: Pulmonary function test. FEV1: Forced expiratory volume in the first second. FVC: Forced vital capacity. FEF<sub>25-75</sub>: Forced expiratory flow from 25% to 75% of vital capacity. PEF: Peak Expiratory Flow. \*: statistically significant

Comparison of the patients in terms of hemoglobin concentration, transfusion duration, frequency of splenectomy and PFT results according to the gender is shown in Table 2. FEV<sub>1</sub>/FVC was significantly

higher in the males than the females ( $p=0.023$ ). However no significant difference was observed between the males and females in terms of the Hb levels, transfusion duration, frequency of splenectomy, PFT

results, FEV1, FVC, and FEF<sub>25-75</sub> (all  $p > 0.05$ ).

PFT scores according to the ferritin levels are shown in Table 3. While 23 of the patients had ferritin levels lower than 2500 ng/dl, 17 of them had ferritin levels of >2500 ng/dl. When PFT findings were compared according to serum ferritin levels of patients; there was a statistically significant difference between FEV1 and FVC mean values between two groups with ferritin levels <2500 ng/dL and >2500 ng/dL ( $p=0.009$  and  $p=0.004$ , respectively) There was no statistically significant difference between FEV1 / FVC, FEF<sub>25-75</sub> and PEF mean values and ferritin levels ( $p > 0.05$ ). When the patients were classified

into two groups as normal and abnormal according to the PFT; there was no statistically significant difference between the two groups in terms of ferritin level, Hb level, age at diagnosis, and the time passed after transfusion program was started ( $p=0.167$ ,  $p=0.727$ ,  $p=0.075$ ,  $p=0.758$ , respectively).

PFT was normal in 12 (52.2%) and PFT abnormal in 7 (41.2%) of 19 patients with splenectomy. There was no significant difference between the patients with and without splenectomy in terms of PFT findings ( $p=0.491$ ). There was no statistically significant difference between PFT parameters according to splenectomy status ( $p > 0.05$ ).

**Table 3. Pulmonary function parameters according to serum ferritin levels**

PFT	<2500 ng/dL (n=23)	>2500 ng/dL (n=17)	p-value
FEV1	83.17+15.94	69.23+15.65	0.009*
FVC	77.73+15.60	63.94+12.09	0.004*
FEV1/FVC	106.73+7.18	106.00+6.85	0.745
FEF <sub>25-75</sub>	91.39+28.29	76.05+26.44	0.090
PEF	81.78+34.06	65.17+22.48	0.089

FEV1: Forced expiratory volume in the first second. FVC: Forced vital capacity. FEF<sub>25-75</sub>: Forced expiratory flow from 25% to 75% of vital capacity. PEF: Peak Expiratory Flow. \*: statistically significant

## DISCUSSION

Numerous factors are responsible for pulmonary function disorders seen in thalassemia patients. These include iron accumulation, chest wall restriction due to hepatosplenomegaly and poor muscle function, damage to alveolar growth, and desferoxamine related pulmonary toxicity. The most important of these factors is the accumulation of iron in tissues due to chronic transfusion. In most studies evaluating pulmonary functions in thalassemic patients, restrictive disorder is the most common type of respiratory dysfunction detected in patients with thalassemia <sup>8,12</sup>.

Iron storage in the lungs is theoretically linked to serum ferritin levels and iron stores in the liver. Borgna-Pignatti et al. found that when serum ferritin levels were  $\geq 3000$  ng/dL, there was a high likelihood of pulmonary injury and with levels of  $\geq 2500$  ng/dL, the risk of death was reported to increase fourfold <sup>12</sup>. In our study, FEV1 and FVC values significantly were better in patients with ferritin levels of <2500 ng/dl compared to patients with ferritin levels above

2500 ng/dl. In a study conducted by Ozyörük et al. it was reported that there was a significant relation between ferritin levels and FEV1 and FVC values <sup>13</sup>.

It was reported that iron accumulation in TDT is usually seen over the age of 10 years <sup>14</sup>. However, recently published studies highlighted that iron accumulation can be seen even under the age of 5 years <sup>14,15</sup>. In a study conducted by Evangelia et al, 52 TDT patients between 9-34 years treated with transfusion were evaluated and an increase in incidence of restrictive respiratory dysfunction with age was reported <sup>16</sup>.

The study by Landing et al. suggested that haemosiderosis due to iron accumulation in the alveolar septum which in turn causes interstitial fibrosis in thalassemic patients <sup>17</sup>. In the study performed by Carnelli et al, a total of 62 TDT patients aged between 8-33 years were subjected to pre-transfusion PFT. Although the mean FEV1 and FVC values of the patients were reduced compared to controls, the mean FEV1/FVC value was found within the normal limits. The authors also reported the reduced diffusion capacity of the lungs for carbon

monoxide (DLCO) and the dominant PFT disorder was restrictive in patients with TDT. Besides, they showed that the spirometric values did not correlate with serum ferritin levels <sup>18</sup>.

In a study by Canatan et al, the effect of recurrent transfusions and iron burden on respiratory function in 25 TDT patients were investigated. 11.6% of the patients had obstructive type, 30.2% had restrictive type, 32.5% had combined type disorder and 11% had normal respiratory functions. In this study, no relation was found between age, cumulative transfusion associated iron load, chelation therapy and pulmonary function test abnormalities <sup>19</sup>. In our study, no statistically significant difference was found in PFT according to gender and the time passed after transfusion program was started.

In a study done by Azarkeivan et al, 139 patients (35 Thalassemia intermedia and 104 TDT) with an average age of 21.1 years and transfusion duration of 18 years were evaluated and pre-transfusion PFT was performed. Restrictive pattern was found in 72.7% of patients, normal PFT findings in 25.1%, and combined (restrictive + obstructive) change in 2.2%. There was a significant relationship between PFT and duration of transfusion program ( $p = 0.05$ ). In the same study, restrictive type of respiratory dysfunction was detected in 72.7% of patients, while 95.7% of patients with TDT had no respiratory system complaints and 89.3% had normal lung radiographic findings <sup>20</sup>. Sağlam et al. reported the results of 27 patients who had no respiratory complaints subjected to PFT. Restrictive dysfunction has been reported to be the most common type of respiratory dysfunction <sup>21</sup>. In our study, none of the patients had any complaints about respiratory system. Our results showed that PFT abnormalities can be detected in patients with TDT without any symptom or finding involving respiratory system.

A study conducted by Li et al. included 13 female and 16 male TDT patients with a median age of 14.2 years. 55% of patients were found to have normal PFT and the remaining 34% had diffuse impairment<sup>22</sup>. Several studies have suggested that basic respiratory impairment in patients with TDT is an obstructive or non-restrictive diffuse impairment <sup>19, 23-25</sup>. They reported that alveolar-capillary dysfunction with low hemoglobin concentration resulted in a decrease in diffusion capacity.

In the study of Priftis et al, PFT and fiberoptic bronchoscopy were performed in 1 patient with

sickle cell anemia without any transfusion story, 1 patient with hereditary spherocytosis with 4 times transfusion history, 6 patients with TDT under regular transfusion program, aged between 7-20 years. In this study, iron accumulation in bronchial epithelial cells and mucous glands leading to bronchiolar obstruction and inflammation development was shown as the cause for the small airway obstruction <sup>26</sup>.

In conclusion, despite the major limitation of this study including low number of patients, like many studies in the literature, we found that the dominant PFT disorder was restrictive respiratory dysfunction in patients under regular transfusion program. Combined restrictive and small airway obstruction can also be observed in these patients. Respiratory dysfunction can be detected even in asymptomatic patients. Therefore, regular monitoring of pulmonary functions should be done in patients with TDT. Respiratory infections may cause additive damage to lungs in thalassemic patients. Routine vaccination with influenza and pneumococcal vaccines may prevent further respiratory impairment in patients under risk for lung dysfunction.

**Yazar Katkıları:** Çalışma konsepti/Tasarımı: BYK; Veri toplama: TK; Veri analizi ve yorumlama: BYK, TK, AKÖ; Yazı taslağı: BYK, TK, AKÖ İçeriğin eleştirel incelenmesi: BYK, TK, AKÖ; Son onay ve sorumluluk: BYK, TK, AKÖ; Teknik ve malzeme desteği: AKÖ; Süpervizyon: BYK; Fon sağlama (mevcut ise): yok.

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