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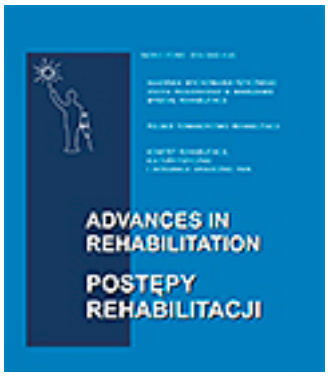

Original article

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Authors: Esraa Elsayed Abaas, Faten Hassan Abdelazeim, Manal Salah Abdel Wahab, Gehan Mosad Abd-Elmaksoud, Mona Hassan Eltagui

Esraa Elsayed Abaas - 0009-0007-8778-4846
Faten Hassan Abdelazeim - 0000-0003-0266-0320
Manal Salah Abdel Wahab - 0000-0002-9623-1588
Gehan Mosad Abd-Elmaksoud - 0000-0003-3673-5255
Mona Hassan Eltagui - 0009-0008-9777-1413

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Pulmonary Functions in Relation to Physical Fitness in Children with β-Thalassemia

Esraa Elsayed Abaas*[1,A-D], Faten Hassan Abdelazeim[2,3,A,C,F], Manal Salah Abdel Wahab[2,3,A,C], Gehan Mosad Abd-Elmaksoud[1,E-F], Mona Hassan Eltagui[4,A,F]

[1]Department of Physical Therapy for Paediatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[2]Department of Physical Therapy for Paediatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[3]Department of Physical Therapy for Paediatrics, Faculty of Physical Therapy, 6 October University, Giza, Egypt
[4]Department of Hematology, Faculty of Medicine, Cairo University, Egypt

Abstract

Introduction: Thalassemia, a genetic hemoglobinopathy, results from a defect in globin chain production. The morbidity associated with thalassemia can arise from the deleterious effects of ineffective erythropoiesis or the complications related to multiple transfusions. Accordingly, this study aims to examine the correlation between pulmonary function and physical fitness in children with β- thalassemia major.
Material and methods: This observational-correlation study was conducted between August 2022 to January 2023 at Abo EL-Reesh Al Mounira Hospital for children. The study included 34 children with β- thalassemia major of both sexes (17 boys and 17 girls) aged 6–10 years. The exclusion criteria included children with defined cardiovascular or respiratory disorders, renal failure, and recent thoraco-abdominal surgery or aneurysm. The pulmonary functions (including vital capacity (VC), maximal voluntary ventilation (MVV), forced expiratory volume in 1st s (FEV1), and peak expiratory flow (PEF) rate) were assessed using a spire spectrum neuro-soft spirometer. Health-related physical fitness as functional capacity was measured by a 6-min walk test while using the energy expenditure index (EEI) to determine energy expenditure. A paediatric balance scale was employed to measure skill-related fitness as balance.
Results: The results revealed that a statistically significant positive correlation was observed between functional capacity and pulmonary functions as well as between balance and pulmonary functions in children with β- thalassemia major ($p < 0.05$).
Conclusions: Pulmonary function was significantly correlated with physical fitness in children with β-thalassemia, indicating the importance of pulmonary rehabilitation.

Keywords: Functional capacity, Beta-thalassemia major, Balance, Respiratory function test

***Correspondence:** Esraa Elsayed Abaas; Department of Physical Therapy for Paediatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt; email: esraaelsaid299@cu.edu.eg

Introduction

Thalassemia is an inherited autosomal recessive hematological disease characterized by a genetic defect in hemoglobin chains [1], which leads to malfunction and rapid hemolysis of red blood cells, decreased oxygen delivery to tissues, iron overload, and inconsequence chronic anemia [2]. Patients with thalassemia receive periodic blood transfusions to increase their oxygen-carrying capability of the blood. However, this could lead to generalized iron overload in the body, including the lungs, heart, liver, and endocrine glands [3]. According to clinical features, the disease severity is categorized into three types: thalassemia minor, intermediate, and major [4].

The World Health Organization has considered thalassemia the most common inherited blood disorder, with an estimated 150 million carriers worldwide. Children across the Middle East, the Mediterranean, and South Asia have a high prevalence of this disorder [5,6]. The prevalence of β-thalassemia in Egypt is 85.1%, making it one of the most common forms of chronic hemolytic anemia in the country. Consanguineous marriage is common in Egypt, which contributes to the accumulation of harmful genes within families, leading to an estimated one thousand to one-and-a-half million cases of thalassemia in live births yearly [7].

β-thalassemia major, also known as "Cooley's Anemia" or "Mediterranean Anemia," is a severe form of thalassemia. Clinical symptoms usually emerge between six months and two years of age when the γ-globin genes responsible for producing hemoglobin F are physiologically deactivated. The signs indicating that a child is suffering from this condition include severe anemia (hemoglobin 7 g/dL), pallor, jaundice, irritability, feeding difficulties, inability to thrive, structural deformities, abdominal expansion due to increasing splenomegaly and hepatomegaly, or recurring episodes of infection [8]. One of the body systems most often impacted by blood problems is the respiratory system. Children with thalassemia major have been reported as having various pulmonary function problems, including restrictive large-airway obstruction, diffusing impairment, and small-airway disease. Patients with thalassemia major may have a lung abnormality due to iron accumulation from frequent transfusions. However, the underlying origin of this condition is unclear. Additionally, a less active lifestyle brought on by the systemic deficits associated with thalassemia major can contribute to an overall decrease in muscle strength and a corresponding drop in functional capacity [9]. Previous studies have suggested that the severity and duration of iron overloading may have a role in the etiology of pulmonary function problems [10].

The World Health Organization defines fitness as "a dynamic physical state involving cardiovascular/pulmonary endurance; muscle strengthening, power, endurance, and flexibility;

relaxation; along with body composition which enables optimal and effective performance of daily in addition to leisure activities." Physical activity focused on health fitness is the groundwork for children to find pleasure in various physical activities [11]. Health and competence are both components of physical fitness. Cardiovascular fitness, body mass index (BMI), muscular strength, endurance, and flexibility are all important for good health. Skill-focused fitness enhances agility, balance, coordination, strength, speed, and reaction time [12]. The health potential of an individual is reflected in their physical fitness level, including their cardiorespiratory fitness. The heart rate after exercise is one sign of cardiorespiratory fitness [13], among other measures of physical fitness. The ability to recover from exercise and the heart rate during exercise have an aerobic base in a factorial analysis of energy capacities [14]. Thalassemic adults exhibited a marked decline in exercise capacity, most likely attributable to anemia, deconditioning, and an absence of exercise-induced hemoconcentration [15].

Thalassemia's physical health impacts can include delayed puberty, growth retardation, and physical deformities. Its effects on physical characteristics, such as low stature and bone abnormalities, also lead to a negative self-image. In general, children with thalassemia have reduced muscle strength and flexibility and are less active than their counterparts in good health [16]. Children with thalassemia may have reduced joint pain, a reduced ability to exercise, and impaired physical function, all of which may contribute to their diminished strength. Pain is a thalassemia emerging consequence that is becoming more prevalent. Although the precise etiology of thalassemia discomfort is still unknown, low hemoglobin levels, low bone mass, and iron overload have all been proposed [17].

Children with thalassemia may have decreased strength as a result of the substantial long-term effects of continuous transfusion on growth, development, and nutrition. Since lower hemoglobin levels are linked to a number of symptoms, including weariness, overall weakness, and decreased mental alertness, which may result in a worsened quality of life, the lowered hemoglobin levels in these children may cause a loss in muscle strength [18]. Previous research examining physical fitness and pulmonary functioning in adult populations. There is an increasing need to fill in the information gap about the relationship between physical fitness and pulmonary functioning in Egyptian children with β-thalassemia, as there is currently no data on this subject. Along with a strong focus on medical care, physical rehabilitation is neglected. In order to enable early detection and rehabilitation of pulmonary and fitness issues, the purpose of this study was to examine the relationship between pulmonary functions and physical fitness in children with β-thalassemia.

Materials and methods

Participants

This study included 34 children with blood transfusion dependent β- thalassemia major with (hemoglobin < 8 g/dL) from both sexes recruited from Abo El-Reesh Al Mounira Hospital for Children. Their age ranged from 6–10 years old, and their body mass index ranged from 13.4-20.6 kg/m^2. The exclusion criteria included the following: children with recent splenectomy or thoracic-pulmonary surgery, defined cardiorespiratory disorders, and renal failure.

Ethics

The procedures of the study were reviewed and approved by The Research Ethics Committee at the Faculty of Physical Therapy at Cairo University with (approval number P.T.REC/012/003478), approval date December 5, 2021, and was registered on clinical trials gov (Registration number: NCT05494333). Parents were given information about the study and signed informed consent before performing any assessments.

Sample size calculation

The sample size was calculated based on a pilot study of 13 children with a thalassemia major. Utilizing a two-tail exact correlation bivariate normal model, a sample size of 28 would be adequate to determine whether or not there is a correlation among pulmonary functions and physical fitness in children with thalassemia major, with a significance level (α) of 0.05, a power of 95%, a correlation coefficient (r) of 0.616, and a coefficient of determination (r^2) of 0.38. Herein, we used G Power and sample size calculations, version 3.0.11, for Microsoft Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

Outcome measures

a. Assessment of pulmonary functions

Computerized spirometry Spiro-spectrum version (2000–2013), a quick and easy process, was used to assess pulmonary function. Weight and height scales were utilized to measure the weight and height of the participating ildren. Three pulmonary tests were performed, including slow vital capacity (VC), forced expiratory, and maximal voluntary ventilation (MVV) tests. The chair was put at an appropriate height and had a back support so the child could comfortably sit.

Each child was told to take a few deep breaths as they blew a piece of paper. After inserting a clean mouthpiece to which the flow sensor was attached, we secured their nose so that no air could escape. In the slow VC test, the child was asked to inhale and exhale two to three tidal breaths, then exhale slowly as much as they could empty the chest, and then inhale slowly as they could to fill the lungs. In the "Forced expiration" test, children took a deep breath and held their breath for as long as necessary to completely seal their lips around their mouthpiece. Lastly, they expired as strongly and forcefully as possible until they could no longer expel any air. Candle was appeared on screen to encourage the child to blow it. In the MVV test, the child was asked to inhale and exhale as fast as possible for 10 s to achieve maximal ventilation. Each child performed each assessment three times, with their highest score being recorded [19].

b. Assessment of physical fitness

The 6-min walk test, a submaximal oxygen consumption level test, was used to evaluate functional capacity in children. The child rested for 10 min and then was instructed to walk on 20 m without obstructing. To guarantee the safety of the children and to get an accurate distance measurement, the therapist observed the child closely using a stopwatch for 6 min. They were given 6 min to walk as many repetitions of the course as feasible. A chair was positioned every 5 m distance if the child could not walk while the stopwatch was not stopped. The test was terminated if the child could no longer precede the test [20].

The energy expenditure index (EEI) has been utilized to evaluate energy expenditure based on heart rate and oxygen consumption by assessing walking efficiency at different velocities. The child was instructed to rest to allow the heart rate to reach the resting level. The pulse oximeter was used to measure the resting heart rate before the test. The child was instructed to walk for 5 min at a comfortable speed with a stopwatch to identify the time. At the end of the test, the walking heart rate and the distance were assessed. The walking speed was calculated by dividing distance/time. The EEI = (walking Heart Rate – resting Heart Rate)/walking velocity [21].

The pediatric balance scale, a modified form of the Berg Balance Scale designed to evaluate functional balance among school-aged children, was utilized to evaluate the balance. The scale consists of 14 items (including get to stand, stand to sit, stand on one foot, reach forward, and alternate foot placing on a stool) and examines static and dynamic components. Every task was demonstrated and given instructions as written in the manual [22]. The child received a practice trial on every item; if the child could not complete the task, 1 s of the practice trial was done. Physical cues were used to clarify both verbal and visual instructions. Many items were used, including specific types of equipment like (small benches, rulers, and stopwatches). The test

was scored utilizing 0 – 4 scales, 0 (least function) to 4 points (maximum function), with a maximal scoring of 56 points scores of 0 to 20 represent high risk of falling, of 21 to 40 represent moderate risk, and of 41 to 56 represent good balance. Each item was described in detail in the manual, and multiple trials were conducted on many items. The performance of each child was graded using the minimum criteria, which indicates the highest performance. The child had to stay in a specified position with several items for the indicated time. If the time or distance needed were not reached, further points were deduced.

Statistical analysis

The Windows version of IBM's Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS, Chicago, IL, USA) was used for all statistical analysis. Means, standard deviations, absolute numbers, and percentages were calculated using descriptive analysis. The Shapiro-Wilk tests performed to ensure the normality of the data showed that the distributions of all outcome variables were normal. A Pearson correlation coefficient test was used to analyze the correlation between pulmonary functions and fitness. All statistical tests were performed at the $p < 0.05$ level of significance.

Results

Thirty-four children with β-thalassemia participated in this study. Table 1 lists the general characteristics of the study group. The results revealed that a moderate positive significant correlation existed between pulmonary functions (tidal volume (TV), VC, forced vital capacity (FVC), forced expiratory volume in 1st s (FEV1), MVV, and peak expiratory flow (PEF), and functional capacity, with Pearson correlation coefficients (r) of 0.526, 0.432, 0.382, 0.376, 0.675, and 0.420, respectively. Moreover, a moderate positive significant correlation was observed between balance and pulmonary functions (TV, VC, FVC, FEV1, MVV, and PEF), with Pearson correlation coefficients (r) of 0.393, 0.365, 0.487, 0.440, 0.577, and 0.475, respectively. Additionally, there were moderate negative significant correlations between EEI and pulmonary functions (TV, VC, FVC, FEV1, and PEF), with Pearson correlation coefficients (r) of -0.376, -0.577, -0.395, -0.427, and -0.466, respectively, except MVV which had a weak negative non-significant correlation ($p > 0.05$, Table 2).

Tab. 1. Descriptive statistics for variables of the study group

Variables	Mean ± SD	Maximum	Minimum	95% CI		Z-score		
				Upper limit	Lower limit	Mean ± SD	Maximum	Minimum
Age (years)	8.52 ± 1.52	10	6	8	9.06	0 ± 1	-1.66	0.97
Weight (kg)	26.8 ± 6.94	52	19	23.75	28.6	0 ± 1	-1.03	3.72
Height (m)	129.58 ± 11.01	159	113	125.75	133.43	0 ± 1	-1.51	2.67
BMI (kg/m²)	15.32 ± 1.52	20.6	13.4	14.79	15.84	0 ± 1	-1.26	3.5
Haemoglobin (g/dl)	7.20 ± 0.54	8	6.2	7.39	7.01	0 ± 1	-1.84	1.46
Functional capacity (m)	330.82 ± 49.50	419.8	220.2	313.71	347.95	0 ± 1	-2.25	1.81
Balance	54.41 ± 2.24	56	47	53.63	55.19	0 ± 1	-3.3	0.71
EEI (beats/m)	26.29 ± 9.50	44.3	13.2	22.98	29.61	0 ± 1	-1.38	1.9
Tidal volume (L)	0.62 ± 0.35	1.4	0	0.5	0.74	0 ± 1	-1.73	2.28
Predicted tidal volume (L)	2.17 ± 0.51	3	1.5	1.99	2.35	0 ± 1	-1.23	1.58
Vital capacity (L)	1.02 ± 0.38	1.8	0.3	0.89	1.16	0 ± 1	-1.79	2.14
Predicted vital capacity (L)	1.98 ± 0.35	2.8	1.5	1.87	2.11	0 ± 1	-1.52	2.42
Forced vital capacity(L)	1.08 ± 0.33	1.6	0.5	0.96	1.2	0 ± 1	-1.77	1.59
Predicted forced vital capacity(L)	1.92 ± 0.33	2.7	1.4	1.8	2.03	0 ± 1	-1.5	2.43
Forced expiratory volume in 1st second (L)	1.05 ± 0.33	1.6	0.5	0.93	1.17	0 ± 1	-1.69	1.63
Predicted forced expiratory volume in 1st second (L)	1.75 ± 0.32	2.5	1.3	1.65	1.87	0 ± 1	-1.35	2.39

Maximal voluntary ventilation (L/min)	27.97 ± 9.97	49	14.7	24.5	31.46	0 ± 1	-1.33	2.11
Predicted maximal voluntary ventilation (L/min)	61.44 ± 11.03	87.9	46.6	57.59	65.28	0 ± 1	-1.35	2.39
Peak expiratory flow (L/min)	2.41 ± 0.94	4.2	0.8	2.07	2.74	0 ± 1	-1.75	1.93
Predicted Peak expiratory flow (L/min)	3.87 ± 0.66	5.4	2.9	3.64	4.11	0 ± 1	-1.42	2.35

BMI- body mass index, EEI- energy expenditure index, SD- standard deviation

Tab. 2. Correlation of pulmonary functions and physical fitness in children with β-thalassemia

Variables	Functional capacity		Balance		EEI (beats/min)	
(Person coefficient - probability)	(r)	(p)	(r)	(p)	(r)	(p)
TV (L)	0.526	0.001*	0.393	0.021*	–0.376	0.028*
VC (L)	0.432	0.011*	0.365	0.034*	–0.577	0.001*
FVC (L)	0.382	0.026*	0.487	0.003*	–0.395	0.021*
FEV1(L)	0.376	0.029*	0.440	0.009*	–0.427	0.012*
MVV(L/min)	0.675	0.001*	0.577	0.001*	–0.291	0.095
PEF (L/min)	0.420	0.003*	0.475	0.004*	–0.466	0.005*

EEI- energy expenditure index, FEV1- forced expiratory volume in 1st second, FVC- forced vital capacity, MVV- maximal voluntary ventilation, p- p-value, PEF- peak expiratory flow, r- Pearson correlation coefficient, TV- tidal volume, VC- vital capacity, *- statistically significant result ($p < 0.05$)

Discussion

Pulmonary function and functional capacity may be negatively impacted by β-thalassemia due to its potential effects on several body systems. Fatigue and decreased physical capacity are two problems that can affect children [23]. Despite the data availability about pulmonary function and physical fitness in children with thalassemia, there remains a shortage of their correlation. Accordingly, this study aimed to examine the correlation among pulmonary functions and functional capacity, balance, and energy expenditure in children with β-thalassemia major. Our results revealed that a moderate positive correlation was observed between pulmonary functions and both functional capacity and balance. Meanwhile, we demonstrated a moderate negative correlation with energy expenditure except for MVV, which had a weak negative non-significant correlation. The majority of pulmonary anomalies in the research population were of the mixed

type, restrictive and obstructive respectively. Moreover, Sohn et al. [24] have reported that different pulmonary dysfunction types were observed in thalassemic children, including restrictive, large-airway obstruction, diffusion impairment, and small-airway disease.

Our findings are in line with Purnama et al. [25], who correlated lung function to physical activity and aerobic capacity in normal adolescents. Their study concluded that adolescents of both sexes with a higher vital lung capacity had a better aerobic capacity and physical activity level. Additionally, Oyedeji et al. [26] have measured pulmonary function, functional capacity, and grip strength, revealing that a positive correlation existed between grip strength (which represented peripheral muscle strength), MVV, and functional capacity measured by 6-min walk distance.

A previous study by Beam and Adams [27] has shown that MVV was moderately correlated with standard clinical outcomes for assessing chronic obstructive pulmonary disease patients. Our results are consistent with Moreira et al. [28], who have stated that functional capacity showed a statistically significant positive correlation with PEF rate in obese patients. Obese individuals exhibited low flow rate and functional capacity due to alterations in pulmonary function. Anemia caused by iron deposition due to repeated blood infusion reduces lung capacity and delivers less blood and oxygen to the body. Consequently, the prevalence of fatigue-related impairments in functional capacity and recurrent pain, most frequently in the hip and lower-extremity regions, has risen. Individuals with chronic pain may experience functional state alterations and be more prone to choose a less active lifestyle. This can lead to less physical activity, a decline in tropism, and, eventually, a weakening of the peripheral muscles [29].

Another physical parameter that is very important in functional capacity is balance. Children with β-thalassemia demonstrated impaired postural balance compared to their normal peers [30]. Balance disorders in β-thalassemia major are due to multifactor as postural impairment (scoliosis, anterior pelvic tilt); the postural defects in children with β-thalassemia might be disease side effects such as low hematocrit, calcium, bone mineral density, bone marrow expansion, high level of ferritin and alkaline phosphate [31]. Because of decreased chest wall and lung compliance, a sedentary lifestyle increases the mechanical stress on compromised respiratory muscles. Fatigue, postural problems, and respiratory insufficiency [32] are some possible outcomes of excessive overuse of respiratory muscles. Restrictive breathing is the result of weak inspiratory muscles. Orthopnea and abdominal paradoxical movement appear among individuals having inspiratory muscle dysfunction because these individuals use accessory breathing muscles and gravity to assist diaphragmatic motion; the state of balance will be negatively impacted by this [33].

This study illustrated the positive relation between pulmonary function and balance in children with β-thalassemia major. Recent research by Kaygusuz et al. [34] has shown that patients

with diminished lung function also have diminished balance and coordination. In addition, Park et al. [35] have found a significant postural imbalance in patients with various lung diseases. The biomechanics of the body as a whole are influenced by alterations in the respiratory thorax, meaning that alterations in respiratory metabolism might affect the overall metabolism of the body. The results of the current study corroborate those of Kayacan et al. [36], who elucidated that boxing is a sport that necessitates force, discipline, and balance. In this context, muscular as well as bone strength are efficient parameters. Boxers that train intensively with aerobic methods have greater bone and muscle density because of their increased lung capacity.

The elevated erythropoiesis and heart activity associated with the chronic hemolysis observed in patients with thalassemia major leads to an increased metabolic demand for energy, minerals, and proteins. Thalassemia is not directly caused by oxidative stress; however, this stress does play a mediating role in several of them. Patients with thalassemia experience high oxidative stress levels due to two primary factors: the breakdown of unstable hemoglobin and iron overload [37]. Along with airway and parenchymal damage caused by chronic bacterial infection and an aggressive inflammatory reaction, these factors increase oxygen expenditure and breathing [38]. Therefore, this study revealed a moderate negative correlation with energy expenditure and pulmonary functions, which is consistent with Bell et al. [39], who have demonstrated a negative correlation between increasing resting energy expenditure and airway obstruction severity in patients with cystic fibrosis, as measured by the two primary variables (FEV1 and FVC). Our findings on the relation between EEI and MVV were inconclusive, showing only a weak and non-significant relation between the two variables. These findings contradict those of Andrello et al. [40], who have manifested that MVV has a stronger correlation with various outcomes of physical activity in everyday life, as well as that MVV has a statistical correlation with total energy expenditure. The difference in results may be due to different samples, age groups, or different methodologies. The increased resting energy expenditure is due to the higher requirement for oxygen by respiratory muscles. Chronic pulmonary impairment in cystic fibrosis has been related to a greater oxygen cost of breathing, which may be due to altered lung mechanics and structure. In vitro research has revealed that oxygen consumption, resting energy expenditure, and total energy expenditure may all be higher in infants with cystic fibrosis [41].

The outcomes of the present study furnish significant insights into the relationship between pulmonary functions and physical fitness among the studied children. Consequently, recommendations for pulmonary rehabilitation should be carefully contemplated. The incorporation of a cardiopulmonary exercise test in rehabilitation protocols allows for regular monitoring of oxygen saturation, exercise intensity, and heart rate. Adequate rest intervals between

activities are advisable to prevent fatigue. Additionally, integrated proprioception and postural correction techniques are recommended for balance training.

This is the first study among pediatric population which provide baseline information's regarding pulmonary functions and fitness in children with β-thalassemia helping the researchers build up on these results. Some limitations to this study should be recognized. The lack of previous studies investigating the relation between variables in children with thalassemia limits data comparison with other studies. Further research must be conducted on cardiopulmonary strength and fitness and their relation with functional and physical activity in these children. Future studies may be performed on larger samples in different age groups.

Conclusions

Collectively, pulmonary functions are significantly correlated with physical fitness in children with β-thalassemia. Therefore, appropriate intervention strategies should be supported, particularly physiotherapy, which may enhance the quality of life of this population.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Lin L, Chen D, Guo J, Zhou W, Xu X. Development of a capillary zone electrophoresis method for rapid determination of human globin chains in α and β-thalassemia subjects. Blood Cells Mol Dis. 2015; 55: 62–7.
2. Hossain M, Islam M, Munni U, Gulshan R, Mukta S, Miah M, et al. Health-related quality of life among thalassemia patients in Bangladesh using the SF-36 questionnaire. Sci Rep. 2023; 13(1): 7734.
3. Baghianimoghadam M, Sharifirad G, Rahaei Z, Baghianimoghadam B, Heshmati H. Health related quality of life in children with thalassaemia assessed on the basis of SF-20 questionnaire in Yazd, Iran: a case-control study. Cent Eur J Public Health. 2011; 19: 165–9.

4. Chan K, Au C, Leung A, Li A, Li C, Wong M, et al. Pulmonary function in patients with transfusion-dependent thalassemia and its associations with iron overload. Sci Rep. 2023; 13(1): 3674.
5. Cao A, Galanello R. Effect of consanguinity on screening for thalassemia. N Engl J Med. 2002; 347(15): 1200–2.
6. Khodashenas M, Mardi P, Taherzadeh-Ghahfarokhi N, Tavakoli-Far B, Jamee M, Ghodrati N. Quality of Life and Related Paraclinical Factors in Iranian Patients with Transfusion-Dependent Thalassemia. J Environ Public Health. 2021; 2021: 2849163.
7. Farmakis D, Porter J, Taher A, Cappellini M, Angastiniotis M, Eleftheriou A, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022; 6(8): e732.
8. Cario H. [Diagnostics and treatment of alpha- and beta-thalassemias]. Dtsch Med Wochenschr. 2022; 147(19): 1250–8.
9. Panwar N, Gomber S, Dewan P, Kumar R. Pulmonary Dysfunction in Transfusion-Dependent Thalassemia and Response to Intensive Chelation Therapy. Indian Pediatr. 2022; 59(6): 451–4.
10. Parakh A, Dubey A, Chowdhury V, Sethi G, Jain S, Hira H. Study of pulmonary function tests in thalassemic children. J Pediatr Hematol Oncol. 2007; 29(3): 151–5.
11. Barnett L, Webster E, Hulteen R, De Meester A, Valentini N, Lenoir M, et al. Through the Looking Glass: A Systematic Review of Longitudinal Evidence, Providing New Insight for Motor Competence and Health. Sports Med. 2022; 52(4): 875–920.
12. Institute of Medicine (US). Informing the Future: Critical Issues in Health: Fifth Edition. Washington (DC): National Academies Press (US) [Internet]. 2009 [cited 2023 Nov 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK219850/
13. Cole C, Blackstone E, Pashkow F, Snader C, Lauer M. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med. 1999; 341(18): 1351–7.
14. Geraghty A, O'Brien E, Callanan S, Mehegan J, McAuliffe F. Cardiovascular fitness is associated with child adiposity at 5 years of age: findings from the ROLO longitudinal birth cohort study. BMC Pediatr. 2023; 23: 345.
15. Agostoni P, Cerino M, Palermo P, Magini A, Bianchi M, Bussotti M, et al. Exercise capacity in patients with beta-thalassaemia intermedia. Br J Haematol. 2005; 131(2): 278-81.
16. Mikelli A, Tsiantis J. Brief report: Depressive symptoms and quality of life in adolescents with thalassaemia. J Adolesc 2004; 27(2): 213–6.
17. Giardina PJ. Pain in thalassemia - an emerging complication. Thalass Rep. 2011; 1: e23.

18. Fung EB, Xu Y, Kwiatkowski JL, Vogiatzi MG, Neufeld E, Olivieri N, et al. Relationship between chronic transfusion therapy and body composition in subjects with thalassemia. J Pediatr 2010; 157(4): 641–7.
19. Ponce M, Sankari A, Sharma S. Pulmonary Function Tests. StatPearls [Internet]. 2022 [cited 2023 Nov 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482339/
20. Casano H, Anjum F. Six-Minute Walk Test. StatPearls [Internet]. 2023 [cited 2023 Nov 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576420/
21. Rose J, Gamble J, Lee J, Lee R, Haskell W. The energy expenditure index: a method to quantitate and compare walking energy expenditure for children and adolescents. J Pediatr Orthop. 1991; 11(5): 571–8.
22. Franjoine M, Gunther J, Taylor M. Pediatric balance scale: a modified version of the berg balance scale for the school-age child with mild to moderate motor impairment. Pediatr Phys Ther. 2003; 15(2): 114–28.
23. Li A. Respiratory function in patients with thalassaemia major: relation with iron overload. Arch Dis Child. 2002; 87(4): 328–30.
24. Sohn E, Noetzli L, Gera A, Kato R, Coates T, Harmatz P, et al. Pulmonary function in thalassaemia major and its correlation with body iron stores. Br J Haematol. 2011; 155(1): 102–5.
25. Purnama T, Sari D, Sastradimadja S, Arnengsih, Sungkar E, Shanti M, editors. Correlation between Level of Physical Activity, Aerobic Capacity and Body Mass Index with Vital Lung Capacity in Adolescence. Proceedings of the 11th National Congress and the 18th Annual Scientific Meeting of Indonesian Physical Medicine and Rehabilitation Association. 2019 Nov 20-23; Jakarta, Indonesia. Setubal: SCITEPRESS; 2019.
26. Oyedeji C, Hall K, Luciano A, Morey MC Strouse J. The Sickle Cell Disease Functional Assessment (SCD-FA) tool: a feasibility pilot study. Pilot Feasibility Stud. 2022; 8(1): 53.
27. Beam W, Adams G. Exercise Physiology: Laboratory Manual. 7th ed. New York: McGraw Hill; 2013.
28. Moreir G, Ribeir A, de Melo Carvalh P, de Carvalho Mir P, Freita I. Relationship between peak expiratory flow and impaired functional capacity in obese. Fisioterapia em Movimento. 2021; 34: e34105.
29. Henrot P, Dupin I, Schilfarth P, Esteves P, Blervaque L, Zysman M, et al. Main Pathogenic Mechanisms and Recent Advances in COPD Peripheral Skeletal Muscle Wasting. Int J Mol Sci. 2023; 24(7): 6454.

30. Pano G, Çina R, Murataj G, Kristuli A, Rusi D. Postural and balance evaluation in 18-30 years old albaniana β-thalassemia patients. J Hum Sport Exerc. 2016; 11: 251–258.
31. Papanastasiou A, Ellina A, Baikousis A, Pastromas B, Iliopoulos P, Korovessis P. Natural History of Untreated Scoliosis in beta-Thalassemia. Spine (Phila Pa 1976). 2002; 27(11): 1186–90.
32. Borrelli M, Terrone G, Evangelisti R, Fedele F, Corcione A, Santamaria F. Respiratory phenotypes of neuromuscular diseases: A challenging issue for pediatricians. Pediatr Neonatol. 2023; 64(2): 109–18.
33. Meysman M, Droogmans S. Orthopnea and pulmonary hypertension. Treat the underlying disease. Respir Med Case Rep. 2018; 24: 105–7.
34. Kaygusuz M, Oral Tapan O, Tapan U, Genc S. Balance impairment and cognitive dysfunction in patients with chronic obstructive pulmonary disease under 65 years. Clin Respir J. 2022; 16(3): 200–7.
35. Park E, Son Y, Johnson J, Yi K, Oh J-I. The Effects Of Multi-directional Exercise Training On Body Composition, Physical Fitness, And Mobility In Stroke Patients. Med Sci Sports Exerc. 2018; 50: 483.
36. Kayacan Y, İslamoğlu İ, Birinci M. Respiratory functions and anatomical balance in boxers. Spormetre. 2018; 16(4): 12–20.
37. Eren F, Koca Yozgat A, Firat Oğuz E, Neşelioğlu S, Firat R, Gürlek Gökçebay D, et al. A New Perspective for Potential Organ Damage Due to Iron-Mediated Oxidation in Thalassemia Major Patients. J Clin Med. 2023; 12: 2422.
38. Wang R, Zhou M, Ma H, Qiao Y, Li Q. The Role of Chronic Inflammation in Various Diseases and Anti-inflammatory Therapies Containing Natural Products. ChemMedChem. 2021; 16(10): 1576–92.
39. Bell S, Saunders M, Elborn J, Shale D. Resting energy expenditure and oxygen cost of breathing in patients with cystic fibrosis. Thorax. 1996; 51(2): 126–31.
40. Andrello A, Donaria L, de Castro L, Belo L, Schneider L, Machado F, et al. Maximum Voluntary Ventilation and Its Relationship with Clinical Outcomes in Subjects With COPD. Respir Care. 2021; 66(1): 79–86.
41. Vaisman N, Pencharz P, Corey M, Canny G, Hahn E. Energy expenditure of patients with cystic fibrosis. J Pediatr. 1987; 111(4): 496–500.