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

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Abstract

Introduction: Thalassemia, a genetic hemoglobinopathy, results from a defect in globin chain production. It is characterized by ineffective erythropoiesis, and complications related to multiple transfusions can lead to higher morbidity. Accordingly, this study examines 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 (17 boys and 17 girls) with β- thalassemia major, 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 following pulmonary functions were assessed using a spire spectrum neuro-soft spirometer: vital capacity (VC), maximal voluntary ventilation (MVV), forced expiratory volume in the first second (FEV1), and peak expiratory flow rate (PEF). Health-related physical fitness, as functional capacity, was measured by a 6-min walk test, with energy expenditure determined using the energy expenditure index (EEI). Skill-related fitness, as balance, was measured with a pediatric balance scale.

Results: Pulmonary function was found to be significantly positively correlated with functional capacity and balance in children with β- thalassemia major ($p < 0.05$).

Conclusions: Pulmonary rehabilitation is of significant value in children with β- thalassemia major.

Keywords: primary school children, physical activity, test-retest, motivation, knowledge.

Introduction

Thalassemia is an inherited autosomal recessive hematological disease characterized by a genetic defect in hemoglobin chains [1]. It is characterized by red blood cell malfunction, resulting in rapid hemolysis, decreased oxygen delivery to tissues, iron overload, and thus chronic anemia [2]. Patients with thalassemia receive periodic transfusions to increase the oxygen-carrying capacity of the blood. However, this could lead to generalized iron

overload in the body, particularly in the lungs, heart, liver, and endocrine glands [3]. The disease is generally categorized into three types according to clinical features and severity: thalassemia minor, intermediate, and major [4].

The World Health Organization considers thalassemia the most common inherited blood disorder, with an estimated 150 million carriers worldwide, and a high prevalence noted among children across the Middle East, the Mediterranean, and South Asia [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, with an estimated one thousand to one-and-a-half million live births are affected by thalassemia per year; this high figure has been attributed to the accumulation of harmful genes within families due to consanguineous marriage [7].

One severe form of thalassemia is β-thalassemia major, also known as Cooley's Anemia or Mediterranean Anemia. 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 initial signs 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, and recurring episodes of infection [8]. Alterations in blood parameters have a particularly strong influence on the respiratory system. Children with thalassemia major have been reported as having various problems with pulmonary function, including restrictive large-airway obstruction, diffusing impairment, and small-airway disease. Patients with thalassemia major may also experience lung abnormality due to iron accumulation from frequent transfusions. However, the underlying origin of this condition is unclear. Additionally, the systemic deficits associated with thalassemia major can result in a less active lifestyle, thus leading to an overall decrease in muscle strength and a corresponding drop in functional capacity [9]. Previous studies suggest 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." [11] Physical activity focused on fitness is the needed for children to find pleasure in various physical activities [12]. The two components of physical fitness are health and skill. Good health consists of cardiovascular fitness, body mass index (BMI), muscular strength, endurance and flexibility; in addition, competence refers to the ability to apply one's training, experience, knowledge and ability to safely complete a task [13]. Skill-focused fitness comprises enhanced agility, balance, coordination, strength, speed and reaction time [14].

The health potential of an individual is reflected in their physical fitness level, one component of which is their cardiorespiratory fitness, measured *inter alia* by heart rate after exercise [15]. A factorial analysis of energy capacities found both the ability to recover from exercise and heart rate during exercise to have an aerobic basis [16]. Thalassemic adults have been found to exhibit a marked decline in exercise capacity, most likely attributable to anemia, deconditioning, and an absence of exercise-induced hemoconcentration [17].

The physical health impacts of thalassemia can also include delayed puberty, growth retardation, and physical deformities. The patients are also characterized by low stature and bone abnormalities, which can lead to a negative self-image. In general, children with thalassemia have reduced muscle strength and flexibility and are less active than their healthier counterparts [18]. They may have joint pain, a reduced ability to exercise, and impaired physical function, all of which may contribute to diminished strength. Another consequence of thalassemia is pain, which may be becoming more prevalent among patients. Although the precise etiology of thalassemia discomfort is still unknown, it has been proposed that low hemoglobin levels, low bone mass and iron overload may play roles [19].

Due to the substantial long-term effects of continuous transfusion on growth, development, and nutrition, children with thalassemia may have decreased strength. Indeed, lower hemoglobin levels have been linked to a number of symptoms, including weariness, overall weakness, and decreased mental alertness, which may result in a worsened quality of life [20].

Currently, no data exists on the relationship between physical fitness and pulmonary functioning in Egyptian children with β-thalassemia, and there is an increasing need to fill this information gap. Current treatment strategies typically focus on medical care, but at the expense of physical rehabilitation. In order to enable early detection and more effective rehabilitation of pulmonary and fitness issues, the purpose of this study was to determine the relationship between pulmonary functions and physical fitness in children with β-thalassemia.

Materials and methods

Participants

The study included 34 children (17 boys and 17 girls) with blood transfusion-dependent β-thalassemia major (hemoglobin < 8 g/dL). All were recruited from Abo El-Reesh Al Mounira Hospital for Children. Their age ranged from six to ten years old, and their body mass

index ranged from 13.4-20.6 kg/m2. The exclusion criteria included the following: children with recent splenectomy or thoracic-pulmonary surgery, defined cardiorespiratory disorders, or 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: approval number P.T.REC/012/003478, approval date December 5, 2021. The study was registered on ClinicalTrials.gov (Registration number: NCT05494333). Before recruitment, all parents were informed about the study and gave their signed informed consent for their children to take part.

Sample size calculation

The sample size was calculated based on a pilot study of 13 children with thalassemia major. Assuming a two-tail exact correlation bivariate normal model, a sample size of 28 would be adequate to confirm any correlation among pulmonary functions and physical fitness in children with thalassemia major; this assumed 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. The calculation was performed using 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

Assessment of pulmonary functions

Pulmonary function was assessed using computerized spirometry Spiro-spectrum version (2000–2013), a quick and easy process. The weight and height of the children were determined based on weight and height scales. Three pulmonary tests were performed, including slow vital capacity (VC), forced expiratory, and maximal voluntary ventilation (MVV).

The participants sat in a chair set at an appropriate height with a back support to allow them to remain comfortable during testing. Each child was asked to take a few deep breaths as they blew a piece of paper. Following this, a clean mouthpiece with an attached flow sensor was placed in the child's mouth, and the nose was secured 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 it 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. A candle appeared on the test equipment screen and child was encouraged to blow it out. In the MVV test, the child was asked to inhale and exhale as quickly as possible for 10 s to achieve maximal ventilation. Each child performed each assessment three times, with their highest score being recorded [21].

Assessment of physical fitness

Functional capacity was assessed using the 6-min walk test, a submaximal oxygen consumption level test. The child first rested for 10 min and then was instructed to walk 20 m without obstacles. 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 the allow the child to take a rest if necessary, while the stopwatch was not stopped. The test was terminated if the child could no longer continue [22].

The energy expenditure index (EEI) was estimated based on heart rate and oxygen consumption while assessing walking efficiency at different velocities. The child was instructed to rest to allow the heart rate to reach resting level; resting heart rate was measured before the test using a pulse oximeter. The child was then instructed to walk for 5 min at a comfortable speed with a stopwatch to follow 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 by time. EEI was calculated as follows:

EEI = (walking Heart Rate – resting Heart Rate)/ walking velocity [23].

Balance was evaluated based on the pediatric balance scale a modified form of the Berg Balance Scale designed to evaluate functional balance among school-aged children. The scale consists of 14 items (including rise to stand, stand to sit, stand on one foot, reach forward, and alternate foot placing on a stool) and examines static and dynamic components.

Before each task was performed, the instructions were given as written in the manual [24] and these were accompanied by a demonstration. Physical cues were used to clarify both verbal and visual instructions. Furthermore, the child was allowed a practice attempt for every item; if the child could not complete the task, second practice trial was given. The tasks themselves used a variety of equipment, including small benches, rulers, and stopwatches. The test was scored on a five-point scale from 0 (least function) to four points (maximum function). Out of a maximum of 56 points, scores of 0 to 20 represent a high risk of falling, 21 to 40 represent a moderate risk, and 41 to 56 represent good balance. Briefly, the child had to remain in a specified position for the indicated time, as described in the manual. If the required time or distance were not achieved, points

were deducted. Each task was possibly performed a number of times. The performance of each child was scored based on the lowest criteria that described their best performance.

Statistical analysis

All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS, Chicago, IL, USA) for Windows. Means, standard deviations, absolute numbers, and percentages were calculated using descriptive analysis. The Shapiro-Wilk tests performed to confirm 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 assuming a level of significance of $p < 0.05$.

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 significant moderately-positive correlation existed between functional capacity and the following pulmonary functions: tidal volume (TV), VC, forced vital capacity (FVC), forced expiratory volume in first second (FEV1), MVV, and peak expiratory flow (PEF) as shown in table 1.

Tab. 1. Descriptive statistics associated with the study group

Variables	Mean ± SD	Maximum	Minimum	95% CI		Z-score
				Upper limit	Lower limit	
Age [years]	8.52 ± 1.52	10	6	8	9.06	0.31
Weight [kg]	26.8 ± 6.94	52	19	23.75	28.6	-0.17
Height [m]	129.58 ± 11.01	159	113	125.75	133.43	-0.14
Body Mass Index [kg/m²]	15.32 ± 1.52	20.6	13.4	14.79	15.84	-0.20
Hemoglobin [g/dl]	7.20 ± 0.54	8	6.2	7.39	7.01	-1.84
Functional capacity [m]	330.82 ± 49.50	419.8	220.2	313.71	347.95	0.03
Balance [points]	54.41 ± 2.24	56	47	53.63	55.19	0.26
EEI [beats/m]	26.29 ± 9.50	44.3	13.2	22.98	29.61	-0.40
Tidal volume [L]	0.62 ± 0.35	1.4	0	0.5	0.74	-0.07
Predicted tidal volume [L]	2.17 ± 0.51	3	1.5	1.99	2.35	-0.32
Vital capacity [L]	1.02 ± 0.38	1.8	0.3	0.89	1.16	-0.11
Predicted vital capacity [L]	1.98 ± 0.35	2.8	1.5	1.87	2.11	-0.10
Forced vital capacity [L]	1.08 ± 0.33	1.6	0.5	0.96	1.2	-0.17
Predicted forced vital capacity [L]	1.92 ± 0.33	2.7	1.4	1.8	2.03	-0.20
Forced expiratory volume in 1st second [L]	1.05 ± 0.33	1.6	0.5	0.93	1.17	-0.25

Variables	Mean ± SD	Maximum	Minimum	95% CI		Z-score
				Upper limit	Lower limit	
Predicted forced expiratory volume in 1st second [L]	1.75 ± 0.32	2.5	1.3	1.65	1.87	-0.25
Maximal voluntary ventilation [L/min]	27.97 ± 9.97	49	14.7	24.5	31.46	-0.20
Predicted maximal voluntary ventilation [L/min]	61.44 ± 11.03	87.9	46.6	57.59	65.28	-0.25
Peak expiratory flow [L/min]	2.41 ± 0.94	4.2	0.8	2.07	2.74	-0.22
Predicted Peak expiratory flow [L/min]	3.87 ± 0.66	5.4	2.9	3.64	4.11	-0.18

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

Moreover, a significant moderately-positive correlation was also observed between balance and pulmonary functions (TV, VC, FVC, FEV1, MVV and PEF). Additionally, significant moderately-negative correlations were found between EEI and pulmonary functions (TV, VC, FVC, FEV1, and PEF). However, EEI demonstrated only an insignificant weakly-negative correlation with MVV ($p > 0.05$) (table 2).

Discussion

Pulmonary function and functional capacity may be negatively impacted by β-thalassemia through its potential effects on various parts of the body. Two problems that can have a particularly strong influence on children are fatigue and decreased physical capacity [25]. However, despite the wealth of data about pulmonary function and physical fitness in children with thalassemia, the relationship between them remains unclear. As such, the aim of this study was to examine the correlations between pulmonary functions and functional capacity, balance, and energy expenditure in children with β-thalassemia major.

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*
FEV_1 [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 ($p < 0.05$)

Our results indicate a moderate positive correlation between pulmonary functions and both functional capacity and balance. In addition, a moderate negative correlation was found between energy expenditure index (EEI) and pulmonary functions; however, it only demonstrated a weak negative non-significant correlation with MVV.

The majority of pulmonary anomalies recorded in the research population were of mixed type, followed by restrictive and then obstructive. Sohn et al. [26] also

report 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. [27], who found lung function to be correlated with physical activity and aerobic capacity in healthy 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, a study of pulmonary function, functional capacity, and grip strength by Oyedeji et al. [28] found a positive correlation between grip strength (representing peripheral muscle strength), MVV, and functional capacity measured by 6-min walk distance.

A previous study by Beam and Adams [29] found MVV to be moderately correlated with standard clinical outcomes for assessing chronic obstructive pulmonary disease patients. Our results are consistent with Moreira et al. [30], who found that functional capacity was significantly positively correlated with PEF rate in obese patients, and that 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 the delivery of blood and oxygen to the body. This in turn may result in an increased prevalence of fatigue-related impairments in functional capacity, as well as recurrent pain, most frequently in the hip and lower-extremity regions. Individuals with chronic pain may experience impaired functional states 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 [31].

Another physical parameter that has a significant influence on functional capacity is balance. Children with β-thalassemia demonstrate impaired postural balance compared to their healthy peers [32]. These balance disorders may be caused by multifactor postural impairment, such as scoliosis or anterior pelvic tilt; this can result from low hematocrit, calcium, bone mineral density, bone marrow expansion, and high levels of ferritin and alkaline phosphate associated with β-thalassemia [33]. In addition, a sedentary lifestyle can increase the mechanical stress placed on compromised respiratory muscles, resulting in decreased chest wall and lung compliance; the consequent excessive overuse of respiratory muscles also leads to fatigue, postural problems, and respiratory insufficiency [34].

If the inspiratory muscles are weakened, this can result in restrictive breathing. Individuals with inspiratory muscle dysfunction are also more likely to demonstrate orthopnea and abdominal paradoxical movement due to them using accessory breathing muscles and gravity to assist diaphragmatic motion. This will also adversely affect their state of balance [35].

Our findings indicate a positive relationship between pulmonary function and balance in children with β-thalassemia major. Recent research by Kaygusuz et al. [36] found that patients with diminished lung function also have diminished balance and coordination. In addition, Park et al. [37] report significant postural imbalances in patients with various lung diseases. Changes in the respiratory thorax influence the biomechanics of the body as a whole, and hence, alterations in respiratory metabolism can affect its overall metabolism. Our present findings corroborate those of Kayacan et al. [38] who report that boxers that train intensively with aerobic methods have increased lung capacity and hence greater bone and muscle density; being a sport that necessitates force, control and balance, clearly both muscular and bone strength are valuable characteristics for a boxer.

The chronic hemolysis observed in patients with thalassemia major leads to elevated erythropoiesis and heart activity, and thus an increased metabolic demand for energy, minerals, and proteins. Although thalassemia is not directly caused by oxidative stress, patients with thalassemia experience high oxidative stress levels, primarily due to the breakdown of unstable hemoglobin and iron overload [39]. These factors increase oxygen expenditure and breathing rate, as do the airway and parenchymal damage caused by chronic bacterial infection and an aggressive inflammatory reaction [40].

Our study revealed a moderate negative correlation between energy expenditure and pulmonary functions, which is consistent with Bell et al. [41], who also report 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 data on the relationship between EEI and MVV were inconclusive, showing only a weak and non-significant relation between the two variables. These findings contradict those of Pitta et al. [42], who investigated the relationship between MVV and total energy expenditure in patients with chronic obstructive pulmonary disease; they concluded that MVV has a stronger correlation with total energy expenditure and with various activity of daily life than EEI. The difference between our results may be due to different samples, age groups, or methodologies. Patients typically demonstrate increased resting energy expenditure due to a higher requirement for oxygen by the respiratory muscles. In cystic fibrosis, chronic pulmonary impairment has been related to a greater oxygen cost associated with 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 greater in infants with cystic fibrosis [43].

The outcomes of the present study offer 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 to provide baseline information regarding pulmonary functions and fitness in children with β-thalassemia and this data should serve as a basis for further research. Nevertheless, some limitations to this study should be recognized. Firstly, due to a lack of previous studies investigating children with thalassemia, no extensive comparison with other research is possible. Further research with larger samples and different age groups is needed to better understand cardiopulmonary strength and fitness in children with β-thalassemia, and their relationship with functional and physical activity.

Conclusions

Pulmonary functions in general are significantly correlated with physical fitness in children with β-thalassemia. Therefore, intervention strategies in this population should be supported by *inter alia* physiotherapy to enhance quality of life.

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Conflicts of interest

The authors declare no conflict of interest.

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