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The effects of inspiratory muscle training on cardiorespiratory functions in juvenile idiopathic arthritis: A randomized controlled trial

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Abstract

Introduction: Although inspiratory muscle training (IMT) has proven effective in adult rheumatic diseases, its impact on juvenile idiopathic arthritis (JIA) remains unexplored. The present study aimed to investigate the effects of IMT in children with JIA.

Methods: Thirty-three children (13–18 years) with JIA were divided into two groups as exercise ($n = 17$) and control ($n = 16$). The exercise group performed IMT at home daily for 8 weeks. The initial IMT load was set as 60% of maximal inspiratory pressure (PI_{max}) and increased by %10 of the initial load every 2 weeks. The control group received no additional intervention. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FVC/FEV_1, PI_{max}, and maximal expiratory pressure (PE_{max}) were evaluated. Peak oxygen consumption (VO_{2max}), metabolic equivalents (METs), and maximal heart rate were measured with cardiopulmonary exercise test. Functional capacity and quality of life were assessed with 6-min walk distance and Pediatric Quality of Life Inventory 3.0 Arthritis Module. All participants were evaluated at baseline and post-treatment.

Results: FVC (↑0.20 (95% CI: 0.07/0.32) liters), FEV_1 (↑0.14 (95% CI: 0.02/0.25) liters), PI_{max} (↑19.11 (95% CI: 9.52/28.71) cmH_2O), PE_{max} (↑12.41 (95% CI: 3.09/21.72) cmH_2O), VO_{2peak} (↑158.29 (95% CI: 63.85/252.73) ml/min), and METs (↑0.92 (95% CI: 0.34/1.49) [ml/kg/min]) significantly improved only in the exercise group ($p < .05$). The difference over time in FVC, FEV_1, PI_{max}, VO_{2peak}, and METs were significantly higher in exercise group compared to control group ($p < .05$).

Conclusions: IMT seems to be an effective option for improving respiratory functions and aerobic exercise capacity in JIA.

KEYWORDS

aerobic capacity, pulmonary function, respiratory muscle exercise

All patients signed a written informed consent and the study was performed in compliance with Declaration of Helsinki. The Ethical approval for the study was obtained from the Ethics Committee of the Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital with 521 protocol number and 2021/07-05 decision number.

Clinical Trial Registration Number: NCT05482633

1 | INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term for the arthritis of childhood.[1,2] It is the most common pediatric rheumatic disease and affects up to 3.8–400 in every 100.000 children worldwide.[3] Even though the most prominent symptom of the disease is joint involvement, the effects of JIA are not limited to the joints. Fever, lymphadenopathy, skin rash, and chronic fatigue due to systemic inflammation are often observed in children with JIA and primary/secondary organ involvement including eyes, kidneys, heart, and lungs may also accompany to the clinical picture.[2,4]

Pulmonary complications are important aspects of the disease process and may lead to morbidity and mortality in adult patients with rheumatic diseases.[4,5] However, primary pulmonary involvement is reported less frequently in children with JIA (prevalence; 4%–8%).[6] On the other hand, evidence indicates that respiratory functions are affected in more than 50% of all JIA cases, even without radiological involvement.[4,5,7,8] Children with JIA may have deteriorated forced vital capacity (FVC), peak flow rate (PEF), and diffusion capacity compared to their healthy peers.[4,7] Moreover, the maximum inspiratory pressure (PI_{max}) and maximum expiratory pressure (PE_{max}), which are indicators of respiratory muscle strength were reported significantly lower in children with JIA.[4,7] Although the abnormality in pulmonary functions were identified, the underlying mechanisms were not established to full extent. Disease-modifying anti rheumatic drugs (DMARDs), and non-steroid anti-inflammatory drugs (NSAIDs) are known to affect pulmonary functions in both adults and children with rheumatic diseases.[9,10] Inspiratory muscle weakness was also suggested to be associated with decreased pulmonary functions.[4,7] Inactive lifestyle due to JIA accompanying the disease process may decrease exercise capacity, peripheral muscle strength, and quality of life (QoL).[11] Besides, children with JIA generally achieve less peak oxygen consumption (VO_{2peak}) in maximal cardiopulmonary exercise test.[12–15]

Inspiratory muscle training (IMT) aims to improve the function and strength of respiratory muscles through specialized exercises.[16] IMT was found effective on improving functional status, enhancing aerobic exercise capacity, decreasing disease activity, increasing respiratory muscle strength and vital capacity in adult patients with rheumatic disease.[17,18] Furthermore, IMT was demonstrated beneficial for increasing oxygen perfusion and muscle metabolism in both respiratory and extremity muscles, and inducing neural plasticity at respiratory synapses in different populations.[19] However, no previous studies utilized IMT in children with JIA. Therefore, the present study aimed to investigate the effects of IMT primarily on respiratory muscle strength, and secondarily on pulmonary functions, aerobic exercise capacity, functional capacity, and QoL in children with JIA.

2 | METHODS

2.1 | Study design

The present study was designed as a parallel, prospective randomized controlled trial with a pre-test, post-test design. Ethical approval was obtained from Ethics Committee of the Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol number: 521 and decision number: 2021/07-05). All the procedures were conducted in accordance with the Declaration of Helsinki. The procedure for the trial was registered before the study (clinicaltrials.gov, trial number: NCT05482633).

2.2 | Patients

Patients who were diagnosed with JIA according to ILAR criteria[20] by a pediatric rheumatologist and referred to the Department of Physiotherapy and Rehabilitation in Izmir Katip Celebi University between May 2021 to May 2022 were assessed for eligibility. Patients who were 13–18 years old, using the same biological drug with the same frequency and dosage for at least 3 months, and had a history of arthritis in at least one of the joints in lower extremity were invited to participate in the study. Exclusion criteria were having an extra condition/involvement that would affect the ability to perform assessments or test results, having participated in a structured physiotherapy/exercise program in the last 6 months, having a regular exercise habit (at least three times a week), having active disease status, primary involvement of pulmonary or cardiac tissues, or having systemic JIA subtype.

2.3 | Sample size

The sample size was calculated by using the effect size (Cohen's $d = 1.02$) of the difference between the intervention and control groups in PI_{max} (primary outcome measure) from a similar previous study conducted by Bieli et al.[21] on the priori sample size calculation section of the G*Power 3.1.9.4 (Kiel University, Germany) software. An assumed type I error rate of 5% and an assumed type II error rate of 20% revealed a total of 34 patients (17 in each group, with an allocation ratio of 1:1) was sufficient.

2.4 | Procedures

Patients were evaluated at the beginning before randomization (baseline assessment) and after the end of 8 weeks (post-treatment assessment). Demographic information including physical characteristics (sex, age, weight, height), education, exercise habits, and disease-related data (JIA subtype, medication, and time since diagnosis) were recorded on a structured form. All measurements were performed by the same physiotherapist.

The Numerical Rating Scale (NRS) was used to assess the severity of pain and morning stiffness for the previous week at the baseline assessment.[22,23] Patients were asked to score their level of pain during resting and activity separately. The duration of morning stiffness was recorded in minutes.

2.5 | Primary outcome measurements

2.5.1 | Respiratory muscle strength

PI_{max} and PE_{max} were evaluated using a portable spirometer and respiratory pressure test device (Cosmed Pony FX, Rome, Italy). American Thoracic Society/European Respiratory Society (ATS/ERS) guide for respiratory muscle testing was followed for the testing procedure.[24] Both PI_{max} and PE_{max} were measured in sitting position. Patients wore a nose clip and were asked to close their lips tightly around the mouthpiece to prevent any air leakage. PI_{max} was evaluated at the residual volume and PE_{max} was evaluated from total lung capacity. Patients were instructed to demonstrate their best effort and sustain it for 1–3 s. Measurements were repeated 3–10 times until achieving a difference of less than 5% between two consecutive measurements. The highest PI_{max}/PE_{max} result was recorded as cmH_2O with higher values indicating better PI_{max}/PE_{max}.

2.6 | Secondary outcome measurements

2.6.1 | Pulmonary function test

FVC, FEV_1, and FEV_1/FVC were evaluated using a portable spirometer and respiratory pressure test device (Cosmed Pony FX, Rome, Italy) following the ATS/ERS guideline for spirometry testing.[25] FVC and FEV_1 were expressed as liters and FEV_1/FVC were expressed as percentages.

2.6.2 | Maximal aerobic exercise capacity

A mechanical treadmill ergometer and cardiopulmonary exercise testing device (CPET) (Cosmed Quark CPET, Rome, Italy) was used to perform a Bruce Protocol.[26,27] CPET was calibrated before each test according to the manufacturer's instructions. The patients were familiarized with the treadmill testing by walking at a comfortable pace (3 km/h, no inclination) for 3 min before the actual test. The CPET started at 2.74 km/h and an incline gradient of 10%. Speed and inclination were increased gradually every 3 min.[28] Respiratory gases were collected via breath-by-breath method during the test with a metabolic card (Cosmed Quark CPET Metabolic Card, Rome, Italy). Collected data through gas exchange were averaged every 15 s and the best values were used to calculate: peak oxygen consumption ($VO_{2peak,}$ ml/min) and peak metabolic equivalent (METs, ml/kg/min). Peak heart rate ($HR_{peak,}$ pulse/min) and heart rate reserve (HRR, pulse/min) were recorded with a heart rate sensor (Garmin, Polar H10) placed under the pectoral muscles with a vertical reference to the sternum notch. VO_{2peak} adjusted by bodyweight ($VO2_{peak}$/bodyweight) and peak heart rate ($VO2_{peak}/HR_{peak}$) values were also calculated.

2.6.3 | Lower extremity related functional capacity

Lower extremity functional capacity was evaluated using 6-Minute Walk Distance (6MWD).[29] The procedure was performed according to ATS guideline. Patients were instructed to walk as fast as possible without running for 6 min on a 30-m flat corridor of which the turning points were marked with colored tape. The total distance covered in 6 min was recorded as the patient's outcome.

2.6.4 | Quality of life

Pediatric Quality of Life Inventory (PedsQL) 3.0 Arthritis Module was used to evaluate QoL.[30] PedsQL is a disease-specific questionnaire administered separately to the patient (Child Self-Report) and the parent (Parent-Proxy Report). Both forms contain a total of 22 identical items in five different subscales: pain and suffering (four items), daily activities (five items), treatment (seven items), anxiety (three items), and communication (three items). Each item is scored on a 5-point Likert scale with zero (0) meaning the absence of a problem and four (4) meaning that the problem is almost always present. The item scores are reversed to calculate the total score and transformed into a score between 0 and 100 with higher scores indicating a better QoL. PedsQL is valid and reliable for Turkish language.[30]

2.7 | Randomization

Randomization was performed by an individual who was not involved in the recruitment or treatment of patients and was blinded to the results of baseline assessments. Index cards with a random group assignment were prepared before the beginning of the study and placed in opaque envelopes to ensure concealment. Following the baseline assessments, patients selected a random envelope and were allocated into one of two groups to either receive IMT (exercise group) or to receive no additional interventions (control group).

2.8 | Interventions

Following the randomization, the participants in the exercise group underwent an IMT program. The Powerbreathe Classic LR (POWERbreathe International Ltd., Southam, UK) was used for IMT.[31] The device allows training resistances between 10 cmH_2O and 90 cmH_2O. Initial training resistance was determined as 60% of the PI_{max} measured at baseline (e.g., if the measured PI_{max} was 70 cmH_2O, initial training resistance was set as 42 cmH_2O). The intensity as 60% of PI_{max} was determined based on two purposes: (1) obtaining of the most possible improvements in an 8-week period due to dose–response relationship of the exercise and (2) avoiding respiratory fatigue[32] as indicated in previous studies supporting moderate intensities being more feasible in children.[33] The patients

performed the first session under the supervision of physiotherapist giving the intervention and the rest of the sessions were performed at home by the patient without supervision. In the first session, the patient and parents were educated on how to perform IMT, how to use the Powerbreathe Classic LR device, and how to adjust the resistance. The patients were followed up by video and/or audio calls by the physiotherapist once every 2 weeks for 8 weeks. The workload was increased by 10% of the start load at the end of the second, fourth, and sixth weeks (e.g., 0–2 weeks: 50 cmH_2O, 2–4 weeks: 55 cmH_2O, 4–6 weeks: 60 cmH_2O, 6–8 weeks: 65 cmH_2O). The patients were informed to call the researchers if they could not tolerate the increased workload. In this case physiotherapist and patient re-determined the workload.

The IMT was performed while patients were sitting. Patients breathed through the Powerbreathe Classic LR for five breaths, rested for 4–5 spontaneous breaths, and continued this cycle until they reached a total of 30 breaths with the device, and completing 30 breaths with the device was called a session. Patients were informed to close their lips tightly around the mouthpiece and the nose clip was placed on nose wings to prevent any air leakage during training. IMT program was performed as daily for 8 weeks with two sessions a day.[34]

Participants in the control group continued their routine medical treatments for 8 weeks. No changes were made in the medication (type, dosage, or frequency) of the patients in both groups during the study.

2.9 | Statistical analysis

The Statistical Package for Social Science for Windows version 20.0 program (SPSS 20.0) was used for the statistical analysis. Shapiro-Wilk test, histograms, detrended-Q plot graphs, kurtosis, and skewness were screened to examine the normality of the distribution. Categorical variables were presented as numbers and percentages. Continuous data was expressed as mean (standard deviation) or mean and 95% confidence interval (CI) for normally distributed variables and as median and interquartile range between 25th and 75th quartiles (IQR 25/75) for non-normally distributed data.

The independent samples *t*-test (student's *t*-test) was used to detect between-group differences in comparison of normally distributed variables and Mann-Whitney U test was used for comparing non-normally distributed variables. The paired samples t-test and Wilcoxon signed ranks test were employed to examine the significance of within-group changes over time for normally and non-normally distributed variables, respectively. The Chi-Square test or Fisher's Exact test were used to compare categorical demographic data. The effect sizes were calculated using Hedge's *g*.

Intention-to-treat analysis was performed, assuming the measurement outcomes of the participants did not change for patients who did not attend the post-treatment assessment. A *p*-value of <0.05 was considered statistically significant for all analyses.

3 | RESULTS

A total of 102 patients with JIA were invited to the study and 40 of them met the eligibility criteria. The study was completed with 33 children with JIA (Figure 1). Seventeen patients (12 males) with a mean age of 15.12 (2.23) years were in the exercise group, and 16 patients (11 males) with a mean age of 15.7 (1.59) years were in the control group. The participants in the exercise group performed two sessions of IMT for 4.74 (0.78) days per week which accounts for an adherence rate of 68.2% and no adverse effects were reported. An intention-to-treat analysis was performed for two patients (one in the exercise group, and one in the control group). No between-group differences were detected regarding physical, demographic or disease-related characteristics at baseline ($p > .05$, Table 1).

FVC, FEV_1, PI_{max}, and PE_{max} significantly increased following the intervention, while no significant change-over-time within-group differences were observed for FEV_1/FVC in the exercise group ($p < .05$, Table 2). No within-group differences were detected in the control group regarding, pulmonary function test results, or respiratory muscle strength measurements ($p > .05$, Table 2). Comparison of mean difference over time between groups indicated that the increases in FVC and PI_{max} were greater in the exercise group than control group ($p < .05$, Table 2), while no significant between-group differences ($p > .05$, Table 2) for FEV_1, FEV_1/FVC, and PE_{max}.

$VO2_{peak}$, $VO2_{peak}$/body weight, METs, and $VO2_{peak}/HR_{peak}$ significantly increased following the intervention ($p < .05$, Table 3), while no significant change-over-time within-group differences were observed for HR_{peak} and HRR in the exercise group ($p > .05$, Table 3). No within-group differences were detected in any of the CPET parameters in the control group. Comparison of mean difference over time results between groups indicated that the increases in $VO2_{peak}$, $VO2_{peak}$/body weight, METs, and $VO2_{peak}/HR_{peak}$ were greater in the exercise group than the control group ($p < .05$, Table 3), while the comparison of mean difference over time results for HR_{peak} and HRR resulted in no significant between-group differences ($p > .05$, Table 3).

Comparison of baseline and post-treatment of 6MWD or PedsQL scores demonstrated no within-group differences in both groups ($p > .05$, Table 4). No significant differences were detected when the mean differences in 6MWD or PedsQL scores were compared between groups ($p > .05$, Table 4).

A post-hoc power analysis using the mean difference over time results of PI_{max} revealed the study had sufficient power (94.55%).

4 | DISCUSSION

Our results suggest that 8 weeks of IMT seems beneficial to improve inspiratory muscle strength, vital capacity, and aerobic exercise capacity compared to no intervention in children with JIA. On the other hand, the IMT procedure employed in the present study did not lead to any significant improvements in lower extremity related functional capacity or QoL. To the best of our knowledge, the effects of IMT were investigated for the first time in JIA.

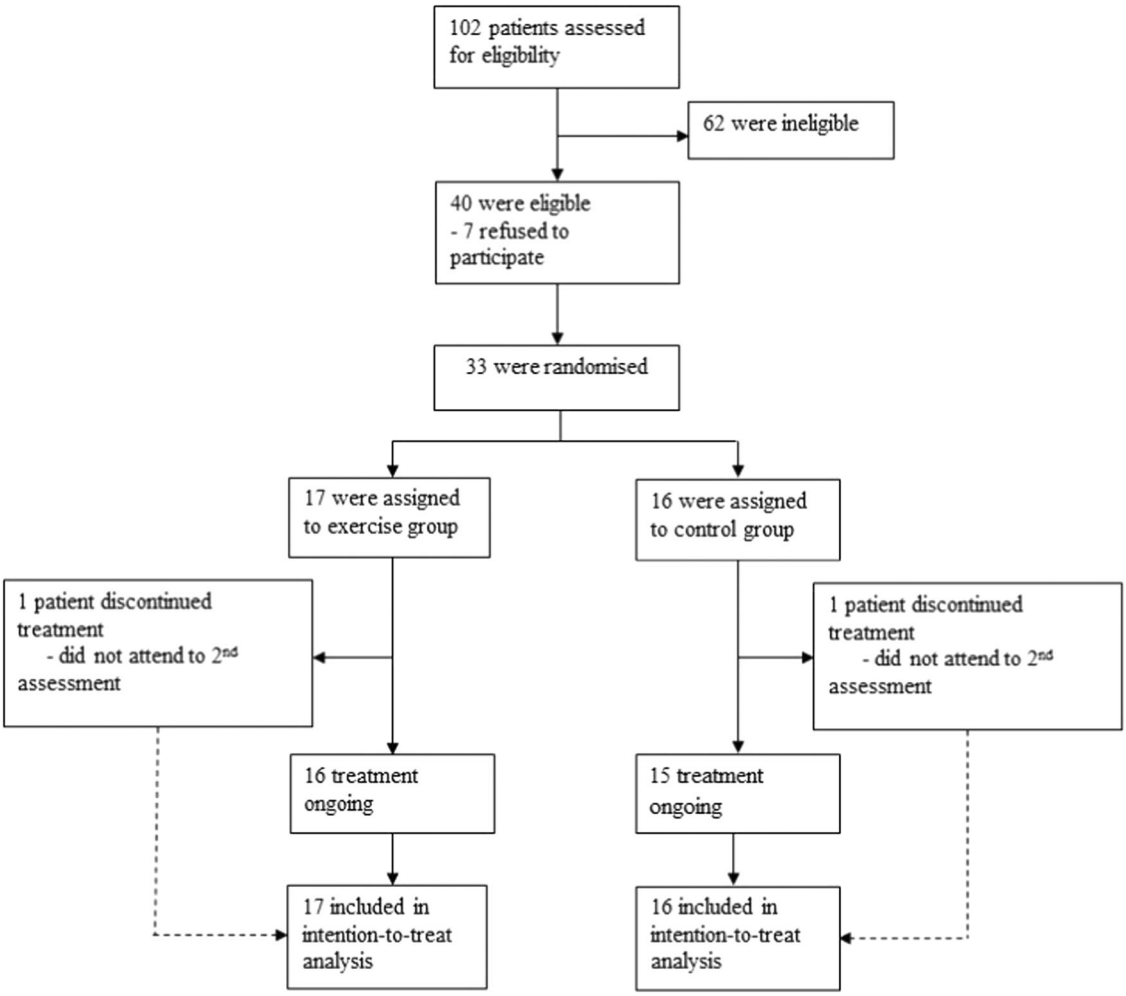

FIGURE 1 Flowchart of the study.

Respiratory involvement due to primary or secondary factors is a frequent and debilitating complication of rheumatic diseases. However, only two randomized controlled trials which were conducted in adult patients with ankylosing spondylitis have reported the effectiveness of IMT regarding rheumatic diseases.[17,18] Drăgoi et al. determined that the IMT program may improve VO_{2peak} and FVC.[17] Similarly, VO_{2peak} and FVC were improved in the present study. Basakci Calik et al.[18] also demonstrated that IMT can be effective in increasing inspiratory muscle strength, improving aerobic exercise capacity, and reducing disease activity. However, more clinical trials performed in different adult and childhood rheumatic diseases with robust designs may help to better understand the efficacy of IMT and boost its clinical usage in future.

Previous studies conducted in different populations have shown IMT to be effective in increasing PI_{max}, PE_{max}, FVC, and FEV_1 without a change in FEV_1/FVC ratio, similar to the results obtained in the present study.[35–37] This outcome likely has emerged due to the restrictive nature of pulmonary involvement in JIA.[4,5,7] FEV_1/FVC of patients was already well over 70% in both groups at baseline which suggest the absence of obstructive changes in pulmonary structures. While both FEV_1 and FVC increased at a similar rate in IMT group, FEV_1/FVC remained relatively constant.

As expected, the most significant improvement following IMT was detected in PI_{max} with an increase of approximately 20% in the exercise group in the present study. This change seems to be parallel with the outcomes of previous studies performed in adult rheumatic diseases[17,18] and other reports that examined the effects of IMT on PI_{max} in various populations.[35–37] Although there is no confirmed mechanism, it is highly possible that this significant increase in PI_{max} is a result of adaptations in the musculoskeletal and peripheral nervous systems following long-term IMT. These adaptations may include increased perfusion/muscle metabolism in inspiratory muscles, transformation of muscle fiber type and/or neural plasticity at respiratory synapses in the central nervous system.[38] Although there was an increase of approximately 12% in the PE_{max} before and after the treatment in the exercise group, no between-group difference was detected for PE_{max} at the time of post-treatment assessment. IMT does not focus on improving expiratory muscles and a mean difference of 7.35 cmH_2O between groups in PE_{max} is possibly insufficient to demonstrate any statistical significance. Similarly, Basakci Calik et al. found IMT beneficial to significantly improve PI_{max}

TABLE 1 Baseline characteristics of groups.

	Exercise Group (n = 17) n (%), Mean (SD), or Median [IQR 25/75]	Control Group (n = 16) n (%), Mean (SD), or Median [IQR 25/75]	p
Sex (male)	12 (%70.6)	11 (%68.7)	.909[a]
Age (years)	15.12 (2.23)	15.7 (1.59)	.517[b]
Height (cm)	169 (12)	167 (12)	.814[b]
Weight (kg)	64.29 (19.22)	59.94 (13.20)	.457[b]
BMI (kg/m^2)	22.11 (4.65)	21.09 (3.07)	.513[b]
Duration of Education (years)	9.22 (1.88)	9.63 (1.73)	.543[b]
JIA Subtype			
Oligoarticular	3 (%17.6)	5 (%31.2)	.465[a]
Polyarticular	1 (%5.9)	2 (%12.5)	
ERA	13 (%76.5)	9 (%56.3)	
Time since Diagnosis (months)	24.41 (16.81)	26.0 (28.38)	.845[b]
Exercise Habit (no)	14 (%82.4)	12 (%75.0)	.606[a]
Biologic Drug			
Adalimumab	13 (%76.5)	11 (68.8)	.643[a]
Etanercept	2 (%11.8)	1 (%6.3)	
Tocilizumab	2 (%11.8)	3 (%18.8)	
Infliximab	0 (%0.0)	1 (%6.3)	
DMARD Use (no)	9 (%52.9)	10 (%62.5)	.728[c]
Morning Stiffness (rating)	0.0 [0.0/3.0]	0.0 [0.0/5.0]	.533[d]
Duration of Morning Stiffness (mins)	0.0 [0.0/15.0]	0.0 [0.0/27.5]	.581[d]
Pain at Rest (rating)	3.0 [0.0/4.5]	0.0 [0.0/3.75]	.402[d]
Activity Pain (rating)	1.0 [0.0/5.5]	0.0 [0.0/1.0]	.276[d]
Pulmonary Function Test			
FVC (l)	3.89 (0.92)	3.70 (1.04)	.582[b]
FEV_1 (l)	3.36 (0.80)	3.24 (0.89)	.701[b]
FEV_1/FVC (%)	85.47 (7.81)	86.56 (8.09)	.696[b]
Respiratory Muscle Strength			
PI_{max} (cmH_2O)	93.82 (37.05)	94.68 (36.28)	.947[b]
PE_{max} (cmH_2O)	96.05 (40.22)	92.12 (27.55)	.747[b]
Cardiopulmonary Exercise Test			
VO_{2peak} (ml/mins)	2138.29 (739.05)	2048.87 (790.94)	.739[b]
VO_{2peak}/Body weight (ml/mins/kg)	34.30 (7.75)	33.12 (8.46)	.679[b]
METs (ml/kg/mins)	9.80 (2.21)	9.46 (2.42)	.674[b]
HR_{peak} (pulse/min)	187.11 (20.36)	185.00 (20.03)	.771[b]
HRR (pulse)	17.76 (20.25)	19.50 (20.43)	.814[b]
VO_{2peak}/HR_{peak} ([ml/mins]/[pulse/min])	11.41 (3.74)	10.94 (3.63)	.715[b]
6-min Walk Distance (meters)	617.41 (98.38)	618.47 (100.56)	.978[b]
PedsQL Children's Module			
Pain and hurt	14.0 [9.0/16.0]	11.50 [8.25/14.0]	.780[d]
Daily activities	20.0 [19.0/20.0]	20.0 [17.25/20.0]	.752[d]

(Continues)

TABLE 1 (Continued)

	Exercise Group (n = 17) n (%), Mean (SD), or Median [IQR 25/75]	Control Group (n = 16) n (%), Mean (SD), or Median [IQR 25/75]	p
Treatment	24.0 [20.0/28.0]	22.50 [19.25/26.0]	.110[d]
Worry	10.0 [6.0/12.0]	8.50 [7.0/10.75]	.381[d]
Communication	12.0 [10.0/12.0]	12.0 [8.50/12.0]	.642[d]
Total	79.0 [64.0/86.0]	70.50 [62.50/80.50]	.224[d]
PedsQL Parents Module			
Pain and hurt	14.00 [8.0/16.0]	12.0 [6.50/14.0]	.590[d]
Daily activities	19.00 [18.0/20.0]	18.0 [16.0/20.0]	.724[d]
Treatment	24.00 [20.0/28.0]	21.0 [17.75/26.75]	.564[d]
Worry	9.00 [6.0/11.0]	8.0 [5.25/11.0]	.696[d]
Communication	12.00 [10.0/12.0]	12.0 [9.25/12.0]	.897[d]
Total	71.00 [64.0/82.0]	67.0 [57.0/79.25]	.468[d]

Note: Significance at $p < .05$.

Abbreviations: cm, centimetres; cmH_2O, centimetres water; ERA, Ethesitis-related arthritis; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; HR_{peak}, Peak heart rate; HRR, Heart rate reserve; IQR 25/75, Interquartile range between 25th and 75th percentiles; kg, kilograms; l, litres; MET, Metabolic Equivalent; mins, minutes; ml, mililiters; n = number of patients; PE_{max}, Maximal expiratory pressure; PI_{max}, Maximal inspiratory pressure; SD, standard deviation; VO_{2peak}, Peak oxygen consumption; %, percent.

[a]Chi-Square test.

[b]Independent samples *t*-test.

[c]Fisher's exact test.

[d]Mann-Whitney U test.

in adults with ankylosing spondylitis without a significant change in PE_{max}.[18] Thus, the effects of IMT on respiratory muscle strength in JIA seem to be similar to patients with adult rheumatic diseases.

One of the most noteworthy findings of the present study was the improvement in $VO2_{peak}$ and related measurements ($VO2_{peak}$/body weight, METs, and $VO2_{peak}/HR_{peak}$). $VO2_{peak}$ increased by 158.29 (63.85/252.73) ml/min in the exercise group. Drăgoi et al. also showed an increase in $VO2_{peak}$ of approximately 300 ml/min following IMT in adults with ankylosing spondylitis.[17] The lack of change in HR_{peak} and HRR may be associated with improvement in oxygenation through increases in inspiratory muscle strength and vital capacity. Improvements in PI_{max} and respiratory volumes were demonstrated to be associated with better pulmonary diffusion in previous studies,[39,40] and alveolar diffusion capacity was found to be an important determinant of VO_{2max}.[41] In this regard, the increase in inspiratory muscle strength following IMT may have increased the oxygen volume and diffusion in the lungs by enabling these muscles to become more active, particularly during maximal exercise. Outcomes of previous studies that observed an increase in FVC, PI_{max}, and $VO2_{peak}$ without an increase in HR_{peak} are also supporting the results of the present study.[42,43] Another potential reason for the observed increase in VO_{2max} could be that the patients became more accustomed to managing restricted breathing conditions following IMT.

No statistically significant difference was found in 6MWD between the treatment and control groups. Generally, 6-min walking test is considered as a submaximal field test used to estimate aerobic exercise capacity. However, Lelieveld et al. reported that 6-min walking test is inadequate for estimating VO_{2peak} in children with JIA and 6MWD is more of an indicator of joint status.[29] Consistently, although a significant improvement was obtained in $VO2_{peak}$ in exercise group, a similar change was not observed in 6MWD. We believe, the absence of joint pain and stiffness at the baseline was possibly the primary reason for this outcome. Besides, the mean 6MWD was similar to the estimated normative values[44] for healthy subjects in both groups at baseline. Thus, the lack of room for improvement may have also played a role in these insignificant improvements for 6MWD.

The improvements in the respiratory parameters did not lead to any significant changes in QoL in the present study. Previously Bayraktar et al. reported no significant change in QoL measured by the PedsQL 3.0 Arthritis Module following 8 weeks of water running,[13] while Mendonça et al. detected a significant improvement in QoL assessed by the PedsQL 4.0 General Module following a 6-month Pilates program in children with JIA.[45] These findings may suggest that the change in the QoL following exercise interventions may vary with the type of exercise, duration of intervention, and/or the evaluation method. Furthermore, QoL is a concept within the biopsychosocial model and can be influenced by many independent factors[46] such as age, body mass index, pain, joint status, sociocultural elements, and emotional status.[46–48] Accordingly, PedsQL 3.0 Arthritis Module questions the aspects of communication, worrying, satisfaction/confidence in general treatment, and basic activities of daily living.[30] Thus, the improvements in the

TABLE 2 Comparison of baseline and post-treatment respiratory parameters within and between groups.

	Within groups								Mean differences (95% CI)			
	Exercise Group (n = 17) Mean (SD) (baseline)	Exercise Group (n = 17) Mean (SD) (post-treatment)	p^a value	ES	Control Group (n = 16) Mean (SD) (baseline)	Control Group (n = 16) Mean (SD) (post-treatment)	p^a value	ES	Exercise Group (n = 17)	Control Group (n = 16)	p^a value	ES
Pulmonary Function Test												
FVC (l)	3.89 (0.92)	4.09 (0.89)	**.003**	0.22	3.70 (1.04)	3.69 (1.06)	.849	0.01	0.20 (0.07/0.32)	−0.01 (−0.11/0.09)	**.010**	0.96
FVC (% of predicted)	90.64 (9.37)	96.11 (9.80)	**.004**	0.57	90.87 (10.32)	90.62 (10.21)	.851	0.02	5.47 (1.98/8.95)	−0.25 (−3.03/2.53)	**.011**	0.94
FEV_1 (l)	3.36 (0.80)	3.50 (0.75)	**.017**	0.18	3.24 (0.89)	3.26 (0.96)	.775	0.02	0.14 (0.02/0.25)	0.02 (−0.11/0.14)	.124	0.55
FEV_1 (% of predicted)	90.50 (11.18)	94.70 (11.86)	**.025**	0.36	90.37 (10.04)	91.43 (11.20)	.565	0.09	4.2 (0.59/7.81)	1.06 (−2.78/4.91)	.215	0.44
FEV_1/FVC (%)	85.47 (7.81)	85.64 (6.74)	.868	0.02	86.56 (8.09)	88.3 (6.36)	.269	0.23	0.16 (−1.96/2.30)	1.74 (−1.50/4.98)	.389	0.30
Respiratory Muscle Strength												
PI_{max} (cmH_2O)	93.82 (37.05)	112.94 (31.26)	**.001**	0.56	94.68 (36.28)	96.25 (35.07)	.510	0.04	19.11 (9.52/28.71)	1.56 (−3.37/6.50)	**.002**	1.18
PI_{max} (% of predicted)	85.88 (22.80)	107.29 (19.98)	**.002**	0.99	90.56 (22.70)	92.93 (21.69)	.362	0.10	21.41 (9.49/33.33)	2.37 (−3.0/7.75)	**.005**	0.95
PE_{max} (cmH_2O)	96.05 (40.22)	108.47 (37.79)	**.012**	0.31	92.12 (27.55)	97.18 (28.99)	.124	0.17	12.41 (3.09/21.72)	5.06 (−1.55/11.68)	.187	0.47
PE_{max} (% of predicted)	70.11 (23.62)	80.35 (20.52)	**.018**	0.46	72.25 (19.91)	76.18 (17.03)	.090	0.21	10.23 (1.98/18.48)	3.93 (−0.69/8.57)	.175	0.48

Note: Bold: Significant at $p < .05$.

Abbreviations: CI, Confidence Interval; cm, centimeters; cmH_2O, centimeters water; ES, Effect Size; FVC, Forced vital capacity; FEV_1, Forced expiratory volume in the first second; l, litres; PE_{max}, Maximal expiratory pressure; PI_{max}, Maximal inspiratory pressure; SD, Standard Deviation; %, percent.

[a]Independent samples t-test.

TABLE 3 Comparison of baseline and post-treatment aerobic and functional capacity within and between groups.

	Within Groups Exercise Group (*n*=17) Mean (SD) (baseline)	Exercise Group (*n*=17) Mean (SD) (post-treatment)	*p*[a] value	ES	Control Group (*n*=16) Mean (SD) (baseline)	Control Group (*n*=16) Mean (SD) (post-treatment)	*p*[a] value	ES	Mean differences (95% CI) Exercise Group (*n*=17)	Control Group (*n*=16)	*p*[a] value	ES
Cardiopulmonary Exercise Test												
VO_{2peak} (ml/min)	2138.29 (739.05)	2296.58 (607.34)	**.003**	0.23	2048.87 (790.94)	2077.68 (690.84)	0.582	0.04	158.29 (63.85/252.73)	16.81 (−68.98/102.61)	**.026**	0.81
VO_{2peak}/Body weight (ml/min/kg)	34.30 (7.75)	37.58 (7.11)	**.005**	0.44	33.12 (8.46)	33.66 (9.7)	0.597	0.06	3.28 (1.14/5.42)	0.33 (−1.47/2.14)	**.034**	0.78
METs (ml/kg/min)	9.80 (2.21)	10.72 (2.01)	**.004**	0.43	9.46 (2.42)	9.62 (2.61)	0.412	0.06	0.92 (0.34/1.49)	0.06 (−0.35/0.48)	**.015**	0.88
HR_{peak} (pulse/min)	187.11 (20.36)	189.38 (17.70)	.054	0.12	185.00 (20.03)	186.18 (22.21)	0.555	0.06	3.47 (0.17/6.76)	1.18 (−3.0/5.37)	.367	0.32
HRR (pulse)	17.76 (20.25)	15.61 (17.69)	.112	0.11	19.50 (20.43)	19.56 (21.17)	0.978	0.01	−3.47 (-6.76/-0.17)	−1.18 (−5.37/3.0)	.367	0.32
VO_{2peak}/HR_{peak} ([ml/mins]/[pulse/mins])	11.41 (3.74)	12.0 (3.36)	**.012**	0.17	10.94 (3.63)	10.92 (3.68)	0.912	0.01	0.59 (0.18/1.00)	−0.02 (−0.37/0.34)	**.024**	0.82
6-min Walk Distance (meters)	617.41 (98.38)	626.94 (76.26)	.432	0.11	618.47 (100.56)	622.62 (96.79)	0.528	0.04	9.52 (-15.53/34.58)	4.25 (−9.78/18.28)	.704	0.18

Note: Bold significant at $p < .05$.

Abbreviations: CI, Confidence Interval; ES, Effect Size; HR_{peak}, Peak heart rate; HRR, Heart rate reserve; kg, kilograms; MET, Metabolic Equivalent; min, minute; ml, milliliters; SD, Standard Deviation; VO_{2peak}, Peak oxygen consumption.

[a]Independent samples *t*-test.

TABLE 4 Comparison of baseline and post-treatment quality of life within and between groups.

	Within Groups Exercise Group (*n*=17) Median [IQR 25/75] (baseline)	Exercise Group (*n*=17) Median [IQR 25/75] (post-treatment)	*p*[a] value	Control Group (*n*=16) Median [IQR 25/75] (baseline)	Control Group (*n*=16) Median [IQR 25/75] post-treatment)	*p*[a] value	Mean differences Exercise Group (*n*=17) Median [IQR 25/75]	Control Group (*n*=16) Median [IQR 25/75]	*p*[a] value
PedsQL Child Self-Report									
Pain and hurt	14.0 [9.0/16.0]	14.0 [9.0/16.0]	.103	11.50 [8.2/14.0]	12.0 [8.5/16.0]	.062	0.0 [0.0/2.0]	0.5 [0.0/2.0]	.545
Daily activities	20.0 [19.0/20.0]	20.0 [20.0/20.0]	.461	20.0 [17.2/20.0]	20.0 [18.5/25.7]	.715	0.0 [0.0/0.0]	0.0 [0.0/0.5]	.711
Treatment	24.0 [20.0/28.0]	24.0 [22.5/28.0]	.105	22.50 [19.2/26.0]	20.0 [18.5/25.7]	.231	1.0 [0.0/2.0]	0.0 [−1.5/0.7]	.086
Worry	10.0 [6.0/12.0]	11.0 [7.0/12.0]	.124	8.50 [7.0/10.7]	10.0 [6.25/11.0]	.288	0.0 [0.0/2.0]	0.0 [0.0/0.7]	.711
Communication	12.0 [10.0/12.0]	12.0 [10.0/12.0]	.705	12.0 [8.5/12.0]	12.0 [8.7/12.0]	.180	0.0 [0.0/0.0]	0.0 [0.0/0.0]	.626
Total	79.0 [64.0/86.0]	81.0 [66.0/87.0]	.054	70.5 [62.5/80.5]	72.0 [63.2/83.2]	.130	2.0 [−1.0/6.0]	0.5 [0.0/4.0]	.470
PedsQL Parent-Proxy Report									
Pain and hurt	14.00 [8.0/16.0]	14.0 [10.0/16.0]	.054	12.0 [6.50/14.0]	12.5 [6.25/16.0]	.103	0.0 [0.0/1.0]	0.5 [0.0/2.0]	.520
Daily activities	19.00 [18.0/20.0]	19.0 [18.0/20.0]	.680	18.0 [16.0/20.0]	18.5 [16.0/20.0]	.832	0.0 [0.0/1.0]	0.0 [0.0/0.0]	.830
Treatment	24.00 [20.0/28.0]	24.0 [18.0/28.0]	.673	21.0 [17.75/26.75]	21.5 [18.5/26.7]	.438	0.0 [0.0/2.0]	0.0 [−0.7/1.5]	.740
Worry	9.00 [6.0/11.0]	9.0 [5.0/12.0]	.218	8.0 [5.25/11.0]	8.5 [5.3/11.0]	.059	1.0 [0.0/2.0]	0.0 [0.0/0.7]	.281
Communication	12.00 [10.0/12.0]	11.0 [10.0/12.0]	.461	12.0 [9.25/12.0]	12.0 [9.2/12.0]	.564	0.0 [0.0/0.0]	0.0 [0.0/0.0]	.740
Total	71.00 [64.0/82.0]	72.0 [63.0/84.0]	.233	67.0 [57.0/79.25]	68.5 [55.0/83.7]	.108	2.0 [−2.0/4.0]	0.5 [0.0/3.7]	.861

Note: Significance at $p < .05$.

Abbreviations: IQR 25/75, Interquartile range between 25th and 75th percentiles; n = number of patients.

[a]Mann-Whitney U test.

present study regarding cardiorespiratory parameters may have been inadequate to induce a significant change in a multifaceted concept such as QoL.

The IMT was performed as a home exercise which can be counted as both a limitation and strength. Access to supervised physiotherapy programs has been restricted due to COVID-19 pandemic restrictions and remote treatment methods have gained popularity. Other factors such as inadequacy of transportation facilities, adverse weather conditions, lack of motivation, and security-related problems may also require remote exercise programs to improve compliance/adherence to treatment. The compliance of daily IMT sessions was relatively low compared to studies including children with chronic respiratory conditions. The sample of the present study consisted of JIA patients without primary cardiorespiratory complaints. Consequently, the low level of importance given to IMT by the participants would have decreased the adherence rates. Additionally, performing IMT sessions in a face-to-face manner would have possibly enhanced the compliance rates. The distribution of JIA sub-types may also be another limitation of the present study. Twenty-two of the patients in our sample were diagnosed with enthesitis-related arthritis. This possibly occurred due to only including patients who had a history of arthritis in their lower extremities to prevent heterogeneity. However, this might still have an impact on the generalizability of the results.

5 | CONCLUSION

IMT as a home exercise program appears to be beneficial for improving inspiratory muscle strength, respiratory functions, and aerobic exercise capacity in children with JIA. These findings are important as a large part of children with JIA suffer from subclinical pulmonary involvement that presents with abnormalities in pulmonary function test and respiratory muscle weakness. Implementing IMT for patient management may help enhance the effectiveness of treatments in the clinical settings. Future research should focus on the optimal dosage of IMT for JIA patients.

AUTHOR CONTRIBUTIONS

Concept/idea/research design: Devrim Can Sarac, Deniz Bayraktar, Derya Ozer Kaya, Ozge Altug Gucenmez, and Deran Oskay. *Writing*: Devrim Can Sarac and Deniz Bayraktar. *Data collection*: Devrim Can Sarac, Deniz Bayraktar, and Ozge Altug Gucenmez. *Data analysis*: Devrim Can Sarac. *Project management*: Derya Ozer Kaya and Deran Oskay.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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