

ORIGINAL ARTICLE

Exercise tolerance in children with juvenile idiopathic arthritis after autologous SCT

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Children with juvenile idiopathic arthritis (JIA) often have significant physical impairment. A minority is unresponsive to combinations of medications, and a possible treatment of resistant JIA is intense immunosuppression followed by autologous hematopoietic SCT (ASCT). Children resistant to conventional therapy have a poor prognosis with regard to long-term outcome of joint function, exercise tolerance and quality of life. It has previously been shown that ASCT can induce long-term remissions in such children. The long-term effects of this treatment are still largely unknown. This retrospective study investigates the exercise tolerance and functional ability in children with JIA who have undergone ASCT compared to healthy subjects. Ten children with JIA who received ASCT between 1997 and 2003 participated in this study. Patients were tested during their regular clinical follow-up. Exercise tolerance was determined using a maximal exercise test. Functional ability was measured using the Childhood Health Assessment Questionnaire and joint status. The study group showed significantly reduced exercise tolerance compared to healthy subjects. Functional ability and joint status were also decreased in patients after ASCT. Children with JIA postASCT have impaired exercise tolerance even 9 years postASCT.

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Introduction

Children with juvenile idiopathic arthritis (JIA) often have significant physical impairment.¹ JIA is the most common rheumatic disease in children and is characterized predominantly by idiopathic peripheral arthritis.² Children with JIA experience joint swelling, pain and limited joint mobility, which contribute to decreased physical activity, fitness and functional capacity, thereby increasing the risk for physical impairment from long-term disease.^{3–6} Peak oxygen uptake ($\dot{V}O_{2peak}$) attained during a graded maximal exercise to volitional exhaustion is considered by the World Health Organization as the single best indicator of exercise tolerance.⁷ A decreased $\dot{V}O_{2peak}$ is associated with a higher mortality rate, a higher risk of cardiovascular disease and different forms of cancer, decreased mental health, diabetes, hypertension and a lower health-related quality of life.^{8,9} A relatively high $\dot{V}O_{2peak}$ at baseline and an improvement of $\dot{V}O_{2peak}$ over time result in a marked reduction in mortality in an adult patient population.¹⁰

Some children with systemic or polyarticular JIA are unresponsive to combinations of nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs such as methotrexate, prednisone and biologicals such as etanercept and kineret.¹ These children have severe joint destruction, growth retardation, osteoporosis, psychosocial problems and reduced health-related quality of life or employment disadvantage.^{2,11,12} Recently, autologous SCT (ASCT) has become an accepted treatment modality in children with JIA.¹³ This is based on the idea of intense immunosuppression with reinduction of immunological tolerance by regeneration of naive T-lymphocytes derived from reinfused hematopoietic progenitor cells.¹ Treatment may require immunoablative therapy for ASCT to remove the autoreactive lymphocytes followed by rescue with hematopoietic stem cells.¹² ASCT is therefore associated with transplant-related toxicities, such as muscle weakness, which may contribute to morbidity associated with the procedure itself.¹⁴ There are few studies that have substantiated the morbidity associated with ASCT or allogeneic SCT (HSCT) in children. Larsen *et al.*¹⁵ reported on exercise tolerance in a cross-sectional study of a group of children with cancer before and after HSCT compared to healthy controls. Both treatment groups had lower exercise

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duration, total work performed and $\dot{V}O_{2peak}$ values, and lower ventilatory thresholds (VTs) than control subjects, indicating impaired cardiopulmonary or muscular function.¹⁵ Patients surviving more than 3 years had significantly lower peak cardiac output and stroke volume than patients surviving less than 3 years.¹⁵ A possible etiology for these findings is toxicity from the anthracyclines, CY and radiation exposure. Toxicity may be related to a developmentally important effect on the growing myocardium or to the duration of compensatory adjustment to impaired organ system function.¹⁵ Eames *et al.*¹⁶ identified decreased peak aerobic capacity in children who have undergone an ASCT at age <18 years.

These findings underscore the need to study exercise tolerance in children treated with ASCT. Moreover, these reports indicate that decreased cardiopulmonary performance postASCT increases the risk for physical impairment from long-term disease and are based on findings in a patient population with malignant diseases. Reports of exercise tolerance in nonmalignant diseases have not been presented to date. Investigation of the exercise tolerance in children with JIA postASCT has not been previously undertaken. Long-term rheumatological outcome expressed as the Pediatric Rheumatology International Trials Organisation (PRINTO) score has been published recently.¹⁷ The purpose of this retrospective study is therefore to describe the exercise tolerance and functional ability in children and adolescents with JIA who have undergone ASCT.

Methods

Patients

Thirteen children with JIA at our hospital had received an ASCT in the past. Patients were examined during their regular clinical follow-up. JIA was diagnosed by a pediatric rheumatologist using the Europeans League Against Rheumatism and later by the International League against Rheumatism criteria.¹⁸ Patients were divided into different subclasses by sex, age, time postASCT and two types of JIA; polyarticular JIA: five or more joints affected with arthritis without systemic manifestations; and systemic JIA: characterized by intermittent fever, rheumatic rash and arthritis. Thirteen children with JIA had received an ASCT for refractory JIA between 1997 and 2003. In this retrospective analysis, only 10 children performed at least one exercise test postASCT. Two patients died after the ASCT and one patient was considered too obese to perform exercise testing. Most of these children performed more than one exercise test postASCT. The most recent data available of their clinical characteristics and tests are displayed in Tables 1 and 2. Almost all the patients performed their last exercise test in 2006/2007. One patient was not able to perform an exercise test in 2006/2007 because of an exacerbation of JIA (after a 9-year disease-free period). The clinical parameters and results of her most recent available data from 2004 were therefore included in Table 1. Joint count, physician global assessment, erythrocyte sedimentation rate and medication use after ASCT have been published previously.^{1,13}

Table 1 Patient characteristics and physical impairment scores

Patient	Sex	Age	Age at ASCT	Years postASCT	Relapse years postASCT	Height (Z-score)	Weight (kg) (Z-score)	BMI (Z-score)	JIA subclass	CHAQ (in %)	Pain score (in %)	pEPM-ROM (in %)	Swollen joints (in %)
1	M	17.6	9.3	8.3	No	1.81 (-0.10)	65 (0.04)	19.8 (-0.95)	sJIA	0	0	0	0
2	F	16.2	6.5	9.6	7.3 years postASCT	1.40 (-4.69)	44 (-1.76)	22.4 (0.74)	sJIA	21.8	35.0	40	0
3	M	14.6	8.4	6.2	1.9 years postASCT	1.48 (-0.36)	34 (-2.65)	15.5 (-2.09)	pJIA	11.1	0	6.7	7.4
4	F	20.0	10.1	9.8	No	1.50 (-3.55)	46 (-1.75)	20.4 (-0.53)	sJIA	3.4	5.0	13.3	0
5	F	14.9	7.8	7.1	9.1 years postASCT	1.61 (-1.02)	53 (-0.30)	20.4 (0.25)	pJIA	31.0	35.0	30	0
6	F	17.8	10.6	7.3	No	1.6 (-1.94)	57 (-0.35)	22.3 (0.30)	sJIA	1.1	0.0	0	0
7	M	10.7	5.1	5.5	1.4 years postASCT	1.13 (-4.50)	22 (-2.23)	17.2 (0.11)	sJIA	4.8	30.0	26.7	20.4
8	M	19.0	10.4	8.63	No	1.64 (-2.00)	56 (-0.95)	20.82 (-0.48)	sJIA	19.0	0	20	0
9	M	20.7	11.3	9.37	0.5 years postASCT	1.63 (-2.12)	46 (-2.06)	17.31 (-2.15)	sJIA	35.6	10.0	56.7	7.4
10	F	16.1	13.1	3.0	No	1.56 (-2.19)	55 (-0.73)	22.6 (0.79)	sJIA	17.9	0	46.7	0
Mean ± s.d. (Z-score)		16.76 ± 2.95	9.26 ± 2.37	7.48 ± 2.14		1.5 ± 0.18 (-0.2 ± 1.6)	47.8 ± 12.5 (-1.3 ± 0.9)	19.9 ± 2.5 (-0.4 ± 1.1)		14.6 ± 12.6	11.5 ± 15.5	19.9 ± 17	4.5 ± 6.8

Abbreviations: ASCT = autologous SCT; BMI = body mass index; CHAQ = Childhood Health Assessment Questionnaire; F = female; JIA = juvenile idiopathic arthritis; M = male; pEPM-ROM = pediatric Escola Paulista de Medicina Range of Motion scale; pJIA = polyarticular JIA; sJIA = systemic JIA.

Table 2 Maximal exercise test data in patients with JIA postASCT

Patient	HR _{peak} (beats/min) (Z-score)	RR _{peak} (Z-score)	$\dot{V}O_{2peak}$ (ml/min) (Z-score)	$\dot{V}O_{2peak}/kg$ (ml/min/kg) (Z-score)	W _{peak} (Watt) (Z-score)	$\dot{V}E_{peak}$ (l/min) (Z-score)	$\Delta\dot{V}O_{2}/\Delta W$ (ml O ₂ /W)	VT% of predicted $\dot{V}O_{2peak}$
1	190.0 (-0.47)	1.26 (1.00)	2679 (-1.55)	41.4 (-1.92)	280 (-0.77)	88.56 (-1.63)	8.14	45.0
2	193.0 (-0.01)	1.46 (2.75)	897 (-3.26)	20.4 (-3.78)	71 (-5.01)	46.0 (-1.88)	7.25	24.9
3	170.0 (-3.11)	1.16 (-0.67)	1219 (-3.70)	36.05 (-2.61)	98 (-5.37)	35.5 (-3.67)	10.36	22.4
4	195.9 (0.36)	1.21 (-0.42)	2086 (-0.29)	45.6 (1.29)	168 (-1.65)	70.6 (-0.42)	9.78	45.5
5	192.5 (-0.07)	1.23 (0.00)	1380 (-1.80)	26.05 (-2.67)	123 (-2.94)	53.5 (-1.24)	7.63	37.5
6	186.2 (-0.94)	1.27 (0.33)	1280 (-2.30)	22.4 (-3.34)	109 (-3.68)	44.2 (-2.10)	6.43	29.1
7	201 (1.18)	1.45 (2.50)	972 (-2.58)	42.8 (-1.50)	27 (-3.91)	45.0 (-1.46)	11.09	37.1
8	193.0 (-0.03)	1.37 (2.75)	1449 (-4.63)	25.95 (-5.01)	169 (-4.73)	55.5 (-3.89)	5.68	26.0
9	188.5 (-0.63)	1.32 (2.00)	1403 (-4.74)	30.5 (-4.10)	108 (-6.83)	56.5 (-3.82)	6.83	25.8
10	193.1 (-1.61)	1.30 (0.75)	1381 (-2.05)	27.4 (-2.38)	123 (-3.21)	37.5 (-2.42)	7.83	50.7
Mean ± s.d. (Z-score)	190.3 ± 8.2 (-0.8 ± 0.9) [#]	1.3 ± 0.1 (1.1 ± 1.3) [*]	1474 ± 531 (-2.7 ± 1.4) ^{**}	31.9 ± 9 (-2.9 ± 1.2) ^{**}	127 ± 68 (-3.8 ± 1.8) ^{**}	56.9 ± 16.2 (-2.3 ± 1.2) ^{**}	8.1 ± 1.8 ^{**}	34.4 ± 10.1 ^{**}

Abbreviations: ASCT = autologous SCT; HR_{peak} = peak heart rate; JIA = juvenile idiopathic arthritis; RR_{peak} = peak respiratory exchange ratio; $\dot{V}E_{peak}$ = peak minute ventilation; VT = ventilatory threshold; $\dot{V}O_{2peak}$ = peak oxygen uptake; $\dot{V}O_{2peak}/kg$ = peak oxygen uptake per body mass; W_{peak} = peak work load; $\Delta\dot{V}O_{2}/\Delta W$ = oxygen uptake work load relationship.
[#]P = 0.05; ^{*}P < 0.05; ^{**}P < 0.001.

All patients were recruited from the pediatric rheumatology clinic of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. All procedures were approved by the Medical Ethics Committee of our Institution.

Joint status

Joint status was assessed by an experienced pediatric physiotherapist during regular outpatient clinic visits and consisted of a joint count on swelling and a joint ROM score. Joint count on swelling was performed in 18 joints; temporomandibular, sternoclavicular, shoulder, elbow, wrist, fingers, knee, ankle and toes. This was scored on a 4-point scale (3 = heavy swollen joint) and (0 = no swollen joint) on two sides of the body, resulting in a maximal score of 54. Scores are presented as percentage of max.

Joint mobility in children was based on the evaluation of joint range of motion and was scored on the pediatric Escola Paulista de Medicina Range of Motion scale (pEPM-ROM).¹⁹ The pEPM-ROM measures mobility in children with JIA based on the evaluation of joint range of motion. Ten joint movements: cervical spine (lateral rotation); shoulder (abduction); wrist (flexion and extension); thumb (flexion MTP); hip (internal and external rotation); knee (extension); and ankle (dorsiflexion and plantar flexion) were examined using a goniometer and classified on a 4-point Likert scale (0 = no limitation to 3 = severe limitation). The final score was calculated as the sum of each movement score divided by 20 and was given as percentage of the maximal range of motion. Both joint status and joint mobility were scored by the same senior pediatric physical therapist with over 25 years of experience in pediatric rheumatology.

Functional ability

Functional ability was measured with the Dutch translation of the Childhood Health Assessment Questionnaire (CHAQ).²⁰ This is a self-administrated pencil and paper questionnaire for the parents (proxy) that is used as an index of functional ability. The CHAQ has been adapted from the Stanford Health Assessment Questionnaire so that at least one question in each domain is relevant to children between ages 0.6 and 19 years.²¹ The CHAQ has been translated into Dutch and is culturally adapted and validated by the PRINTO group.²⁰ The CHAQ consists of 30 items in eight domains, the disability index, combined with two visual analog scales for pain and severity, forming the discomfort scale.¹⁹ The question with the highest score within each domain (range 0-3; able to do with no difficulty = 0, able to do with much difficulty, unable to do = 3, this last week) determined the score for that domain. The aid and assistance, which are normally scored in the CHAQ, were not used in this study because they did not contribute to the reliability and also did not increase the correlation with pain and disease severity in patients with JIA.²²

Maximal exercise test

Subjects performed a maximal exercise test to volitional exhaustion with gas-exchange measurements as described

previously.^{23,24} This test has been shown to be reliable in children with JIA.^{25,23} The exercise test was performed using an electromagnetically braked cycle ergometer (Lode Examiner; Lode BV, Groningen, the Netherlands). The seat height was adjusted to the patient's leg length. Unloaded cycling for 1 min precedes the application of resistance to the ergometer. The workload was increased every minute. The increase in workload (10, 15 or 20 W/min) was individually selected because of the large differences in exercise capacity between patients. The patient stopped cycling when exhaustion was reached despite strong verbal encouragement from the experimenters. During the test, the subjects breathed through a facemask connected to a calibrated metabolic cart (Jaeger Oxycon Pro; Viasys BV, Balthoven, the Netherlands). The expired gas was passed through a flow meter, an oxygen (O₂) analyzer and a carbon dioxide (CO₂) analyzer. The flow meter and the gas analyzer were connected to a computer that calculated breath-by-breath minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and respiratory exchange ratio (RER). Absolute peak oxygen consumption ($\dot{V}O_{2peak}$) and breath-by-breath minute ventilation ($\dot{V}E_{peak}$) were taken of an average value over the last 20 s during the maximal exercise test. The VT was determined using the criteria of an increase in both the ventilatory equivalent of oxygen ($\dot{V}E/\dot{V}O_2$) and the end-tidal pressure of oxygen (PETO₂), with no increase in the ventilatory equivalent of carbon dioxide ($\dot{V}E/\dot{V}CO_2$).²⁶ Heart rate (HR) was measured continuously during the exercise test by a bipolar ECG (Hewlett-Packard, Amstelveen, the Netherlands) and oxygen saturation (SaO₂%) by pulse oxymetry (Nellcor 200 E, Breda, The Netherlands). The peak workload (W_{peak}) was computed as follows:²⁷ $W_{peak} = PO_f + (t/60 \times D)$, where PO_f is the power output (W) of the last completed workload, t is the time (in sec) the last uncompleted workload was maintained, 60 is the duration (in sec) of each completed workload and D is the power output difference (W) between consecutive workloads. Predicted $\dot{V}O_{2peak}$ and W_{peak} values were obtained from established values from age- and sex-matched Dutch controls.²⁸ The reference values were obtained in a population of 336 healthy Dutch children and adolescents (158 boys and 178 girls) on an electromagnetic-braked cycle ergometer using an incremental workload protocol.²⁸

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Version 12.0, SPSS Inc., Chicago, IL, USA). Normal distribution of the data was confirmed using the Shapiro–Wilk test. Variables with normal distribution were expressed as means, s.d. and range; statistical comparisons between measurements were made by using the Mann–Whitney U -test. The data were also expressed as the percent of predicted values or as Z -scores. Z -scores were calculated using the difference between the score of each individual patient and the reference values for age and gender, divided by the s.d. of the reference values. Associations were calculated using Spearman correlations. For all tests, α levels <0.05 were considered as statistically significant.

Results

Most of these patients were adolescents (mean age 16.8 years) who had undergone ASCT more than 7 years before this study. Six children with JIA postASCT had a significantly decreased height compared to age-matched healthy children. Their body mass index was not significantly decreased, with the exception of one patient. Five children (50%) suffered from a relapse of JIA.

Childhood Health Assessment Questionnaire and pEPM-ROM scores are displayed in Table 1. Functional ability scores varied enormously, reflecting a wide variation in the physical functioning of JIA patients. Two patients had a CHAQ score of more than 30%, reflecting the serious loss of functional ability. Pain score in three patients was also higher than 30%, which indicates that they may suffer from pain during the exercise test. There was also a large variability in the joint range of motion. Three patients had major limitations in their joint range of motion. Four patients had active inflammation of the joints during the examination. All but one patient showed reduced functional ability, pain and limitations in their range of motion.

Maximal exercise test

All subjects completed the exercise testing without complications or arterial oxygen desaturation. Table 2 shows exercise test results. All but one patient had an HR_{peak} above 180; furthermore, all patients had an RER_{peak} higher than 1.0. In some cases, the RER_{peak} was significantly increased (>1.29; the upper limit for healthy children in our laboratory). This indicated that the patients made sufficient efforts during the test. Z scores for $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}/kg$ ranged from -0.3 to -4.7 s.d. and from 1.3 to -5.0 s.d., respectively. Z -scores for W_{peak} ranged from -0.7 to -6.8 .

$\dot{V}E_{peak}$ was very low as well; however, $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ were 102.4 ± 16.7 and 79.4 ± 15.5 percent of predicted scores, showing a normal ventilatory efficiency and overall ventilatory work. Fifty percent of patients showed a reduced oxygen uptake work rate slope ($\Delta\dot{V}O_{2peak}/\Delta WR$). The average VT was 34% of predicted $\dot{V}O_{2peak}$, which is below normal (lower limit for normal children is 42%²⁹).

Longitudinal changes in $\dot{V}O_{2peak}$

Patients performed one or more exercise tests (the mean number of tests was 3.2 ± 1.9 per patient, range: 1–6 tests). Longitudinal data ($\dot{V}O_{2peak}/kg$) are displayed in Figure 1. There was no significant correlation between time since ASCT and $\dot{V}O_{2peak}/kg$ (Figure 1).

Discussion

This study represents a clinical follow-up study of exercise tolerance and functional ability in patients with JIA postASCT. There are reports indicating that decreased cardiopulmonary performance postASCT increases the risk of physical impairment from long-term disease; however, these reports are based on findings in a patient population with malignant diseases. This is the first study that has

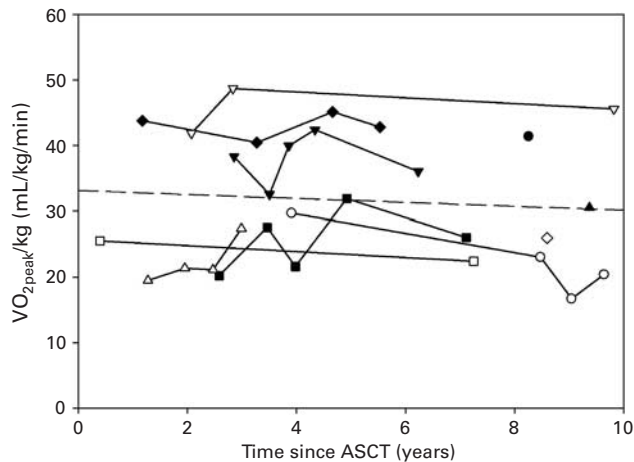


Figure 1 Longitudinal changes in $\dot{V}O_{2peak}/kg$ in relation with time since ASCT. The dotted line represents the regression line of all available data points. ASCT, autologous hematopoietic SCT; $\dot{V}O_{2peak}$, peak oxygen uptake.

investigated peak cardiorespiratory capacity in children with a nonmalignant disease postASCT. The current data indicate that exercise tolerance (that is, $\dot{V}O_{2peak}$) was significantly impaired in the majority of children with JIA postASCT. Even when $\dot{V}O_{2peak}$ was corrected for body weight, it remained significantly reduced. However, there was a large variation in $\dot{V}O_{2peak}$ between patients. The lowest values were found in patients with relapsed JIA. The results of the current study compare well with the values found in children with polyarticular or systemic JIA.⁵ This raises the possibility that the severity of the disease and its consequences (hypoactivity) account for a major part of the poor exercise tolerance rather than the ASCT *per se*. However, the current results are lower compared to a group of adolescents with JIA.³

The $\Delta\dot{V}O_{2peak}/\Delta WR$ was positively related to $\dot{V}O_{2peak}$ and was reduced in our study population. Drinkard *et al.*³⁰ found oxygen uptake work rate slope values in healthy children of 10.8 ± 1.2 ml O_2 per W. The results of our study population indicate that there may be impairment in oxygen extraction capacity in the mitochondria of the skeletal muscles of children postASCT. This might be explained by a combination of systemic inflammation, relapse of the JIA, steroid myopathy and prolonged deconditioning as a result of decreased functional ability.

Another important exercise parameter is the VT. Work rates at levels above VT are associated with increased fatigue. Similar to $\dot{V}O_{2peak}$, the VT is related to muscle mass, muscle cellular energy level and oxygen carrying capacity of the blood. The results of our study population indicate that VT is significantly reduced. The reduced VT may be caused by the smaller muscle mass of our patients to consume oxygen during exercise.

Longitudinal changes in $\dot{V}O_{2peak}$

We found no relationship between $\dot{V}O_{2peak}$ and time since ASCT. This might indicate that there is no or limited recovery of $\dot{V}O_{2peak}$ after ASCT.

Larsen *et al.*¹⁵ suggested that the time postBMT may be a risk factor for impaired aerobic capacity and that it is probably related to toxicity of the therapy. Toxicity of medications such as CY might have influenced the development of the growing myocardium or duration of compensatory adjustment to impaired organ functioning.^{15,16} However, Hogarty *et al.*³¹ retrospectively investigated 33 patients postSCT using the results of exercise tests. They found that $\dot{V}O_{2peak}$ increased from 50% of predicted immediately postBMT to 69.3% of predicted at the end of 5 years of follow-up.³¹ In contrast with Larsen *et al.*,¹⁵ Hogarty *et al.*³¹ found no change in the cardiac index during exercise and suggested that myocardial injury postASCT is persistent but not progressive over the follow-up time of 6.1 years. Hogarty *et al.*³¹ suggested that the most likely explanation for an improved aerobic exercise capacity is an increase in oxygen extraction at the level of the exercising muscle, associated with recovery from a deconditioned state.

Some of our patients had major impairments in joint status and functional ability, impeding the ability to perform exercises at a sufficient intensity to have a reconditioning effect on the heart and muscles. Exercise programs may be advisable in JIA patients postASCT, but may be a challenge to design because of the impairments. The results of several studies in adults^{32,33} and children³⁴ showed that exercise training can improve exercise tolerance in patients after SCT for malignant disease. Moreover, several studies in patients with JIA have shown that exercise training is safe and feasible.^{35,36}

There are several limitations in this study; for instance, the study population was small. One must bear in mind that these 10 children with JIA and ASCT had participated in an experimental procedure and that there are only 41 children registered in the European Group for Blood and Marrow Transplantation in Europe.¹

In conclusion, this study shows that children with JIA postASCT have impaired exercise tolerance even 9 years postASCT. However, the spectrum of results is wide. Exercise training has been shown to be effective in other patient groups postASCT. An exercise program might therefore be advisable for patients with JIA postASCT to improve exercise tolerance.

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