Aerobic Fitness in Children with Juvenile Idiopathic Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** To determine whether children with juvenile idiopathic arthritis (JIA) have lower physical fitness compared to healthy children, and to determine the clinical relevance of this impairment.
Methods. A systematic literature search was performed using MEDLINE, CINAHL, EMBASE and SPORTDiscus. The appropriate titles were identified and the data were extracted from these publications. The maximal oxygen consumption (VO_{2peak}; in $ml \cdot kg^{-1} \cdot min^{-1}$) during a maximal exercise test until volitional exhaustion was used as the main outcome for this review.
Results. Nine studies were identified in the literature. Data from 5 studies (144 patients) were pooled in a metaanalysis. The VO_{2peak} of the patients with JIA was 21.8% (95% CI 13.7, 29.9) lower than that of healthy children ($p < 0.0001$).
Conclusion. The results of the metaanalysis suggest that children with JIA have moderate to heavy impairment in physical fitness as represented by maximal oxygen consumption compared to healthy children. (J Rheumatol 2002;29:2643–7)

Key Indexing Terms:
EXERCISE CAPACITY
EXERCISE TOLERANCE
METAANALYSIS
JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the currently proposed international name for the classification of chronic childhood arthritis[1]. Diagnosis is confirmed when the onset of the arthritis is before the age of 16, the duration of the symptoms exceeds 6 weeks, and when other known causes are excluded. In JIA 7 distinct subtypes can be distinguished[1].

Children with JIA are believed to be less physically fit compared to healthy children[2]. The manifestations of this articular disease such as chronic joint pain and stiffness, synovitis, and deformity are thought to be related to low levels of physical activity.

In the literature some conflicts exist about the aerobic physical fitness of JIA patients. Schröter, *et al*[3], and Malleson, *et al*[4] found no statistically significant differences in maximal oxygen consumption (VO_{2peak}) between patients with JIA and healthy age and sex matched controls. Data from Giannini and Protas[5,6], Klepper, *et al*[7], Golebiowska, *et al*[8,9], and Hebestreit, *et al*[10] have suggested that JIA patients have statistically significant impaired aerobic fitness.

Moreover, the clinical relevance of the magnitude of the impairment is not often determined in these studies. The maximal oxygen consumption (VO_{2peak}) [maximal exercise tests with children and adolescents are usually terminated when the young person, despite strong verbal encouragement from the experimenters, is unwilling or unable to continue; the appropriate term to use is therefore peak oxygen consumption (VO_{2peak}), which represents the highest oxygen uptake during an exercise test to volitional exhaustion] attained during a graded maximal exercise to volitional exhaustion (MXT) is considered as the single best indicator of aerobic physical fitness by the World Health Organization[11] and can be reliably performed in JIA patients[6,12].

The purpose of our review was to determine whether aerobic physical fitness as measured during a graded maximal exercise test of children with JIA is different compared to healthy children and whether this difference might be clinically relevant.

MATERIALS AND METHODS

Search strategy. Publications were selected based on a literature search from 1966 until October 2001 using the MEDLINE, CINAHL, EMBASE, and SPORTDiscus databases. Search terms "physical fitness," "exercise testing," "exercise," "exercise capacity," "exercise tolerance," "juvenile rheumatic arthritis," "juvenile chronic arthritis," and "juvenile idiopathic arthritis" were used. References of selected publications were tracked to find additional publications on this subject.

Selection of publications and types of outcome measures. All publications were selected in which a description of one or more outcome variables, such as VO_{2peak}, VO_{2max}, maximum power output, exercise testing on a treadmill, or cycle ergometer, appeared. We included in this study only publications in which directly measured values of VO_{2peak} (in $ml \cdot kg^{-1} \cdot min^{-1}$) were published, including description of methods used and patient and control subject characteristics. Data were extracted from the publications and entered into Review Manager 4.1 (Update Software, Oxford, UK). Data from graphs were scanned on a computer and extracted using Datathief II 1.1 (Tummers, Eindhoven, The Netherlands) and accordingly entered into Review Manager 4.1.

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Statistics. DerSimonian and Laird random effects model was used for analyzing the results on VO_{2peak} because of the statistically significant heterogeneity between the studies. The data were pooled using standardized mean differences (SMD). SMD statistic is the difference between 2 means divided by an estimate of the within-group size and can be considered as an effect size. Negative values for SMD indicates a lower physical fitness of patients with JIA compared to healthy controls. An alpha level of $p < 0.05$ was considered statistically significant.

RESULTS

Nine publications were identified in the literature[3-10,12]. Four publications were excluded from this review because of insufficient or incomplete data. One of the studies[8] was also published in the Polish language[13]. The study from Golebiowska, *et al*[9] was excluded from the metaanalysis because of incomplete VO_{2peak} data [no values and standard deviations (SD) reported] and it was not clear whether these patients were not included in their 1992 publication[8]. In the publication of Schröter, *et al*[3] both patient characteristics and methods were lacking. Klepper, *et al*[7] only reported the results on the 9 min run-walk and did not report directly measured VO_{2peak} values. Hebestreit, *et al*[10] did not report VO_{2peak} values in $ml \cdot kg^{-1} \cdot min^{-1}$. The characteristics of the included studies are displayed in Table 1; the characteristics of the excluded studies are presented in Table 2.

One study reported values separately for girls and boys[8], these values were separately entered into the metaanalysis. Because the SD of the study was not published, we estimated the SD using the weighted pooled SD of the other 4 included studies. In total, 144 patients with JIA and 145 control subjects were included in this review.

Instrumentation. All included studies monitored ventilation, oxygen consumption, and carbon dioxide production during the exercise test, which used a calibrated metabolic cart (Table 1). In most studies (Table 1) the investigators used a cycle ergometer. Aerobic fitness and VO_{2peak} were measured during a continuous graded exercise test until the subject could not maintain the work rate, despite maximal encouragement of the investigators. In one study a treadmill was used as the ergometer[8].

Although there were differences in protocols and instrumentation between the publications, the measurement of VO_{2peak} values was based on the same concept in all studies. All children exercised until fatigue prevented further work.

In Table 3 the results of the metaanalysis are displayed. There was a significant heterogeneity between the included studies ($p = 0.021$). The SMD of –1.13 indicated that patients with JIA have a significant lower VO_{2peak} compared to healthy control subjects ($p < 0.00001$). In absolute values, their VO_{2peak} was 8.8 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 11.6, 6.0) lower. Expressed as a relative value, VO_{2peak} was 21.8% (95% CI 13.7, 29.9; $p < 0.0001$) lower for the patients with JIA.

DISCUSSION

Table 1. Characteristics of included studies.

Study	JIA Patients /Controls	Patient Ages, yrs	Disease Subgroups	Ergometer Type	VO_{2peak} Determination	Protocol
Malleson, 1996	30/15	8–17	OJIA, PJIA, SJIA, JSpA, JPsA	Cycle	Direct	15 W/min
Golebiowska, 1992	45/61	4–19	OJIA, PJIA, SJIA	Treadmill	Direct	Riopel†
Giannini, 1992	30/30	7–17	OJIA, PJIA, SJIA	Cycle	Direct	25 W/2 min
Takken, 2002	23/RV	6–14	OJIA, PJIA, SJIA	Cycle	Direct	20 W/3 min
Giannini, 1991	16/16	8–13	OJIA, PJIA	Cycle	Direct	25W/2 min

OJIA: oligoarticular JIA; PJIA: polyarticular JIA; SJIA: systemic JIA; JSpA: juvenile spondyloarthropathy; JPsA:juvenile psoriatic arthritis; W: watt; RV: reference values. † Riopel protocol consists of keeping the treadmill belt speed at 5.6 km/h and elevating the slope of the belt by 2° every minute until volitional exhaustion of the patient.

Table 2. Characteristics of excluded studies.

Study	JIA Patients/ Controls	Patient Age, yrs	Disease Subgroups	Ergometer Type	VO_{2peak} Determination	Protocol
Hebestreit, 1998	10/10	6–18	JSpA (HLA-B27+)	Cycle	Direct	NA
Klepper, 1992	20/20	6–11	PJIA	9 min run-walk	Estimation	HRPFT
Schröter, 1980	11/RV	NA	NA	NA	NA	NA
Golebiowska, 1991	25/19	10–18	OJIA, PJIA, SJIA	Treadmill	Direct	Riopel†

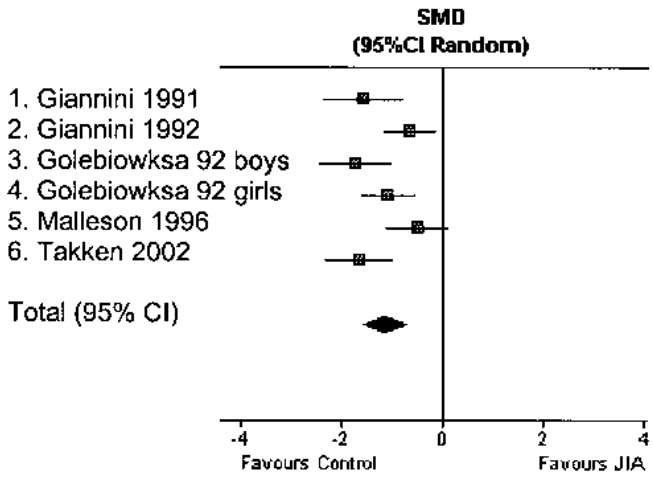
HRPFT: health related physical fitness test; OJIA: oligoarticular JIA; PJIA: polyarticular JIA; SJIA: systemic JIA; JSpA: juvenile spondyloarthropathy; NA: not available; RV: reference values. † Riopel protocol: keeping treadmill belt speed at 5.6 km/h and elevating slope of the belt by 2° every min until volitional exhaustion of the patient.

Table 3A. Comparison of VO_{2peak} values of JIA patients with controls.

Study	JIA, n	Mean (SD)	Control, n	Mean (SD)	Weight, %	SMD (95% CI Random)
Giannini, 1991	16	33.00 (8.20)	16	46.90 (9.40)	13.8	–1.54 (–2.34, –0.74)
Giannini, 1992	30	32.00 (8.80)	30	36.90 (6.50)	19.3	–0.63 (–1.14, –0.11)
Golebiowksa, 1992 Boys	14	46.90 (8.37)	34	59.90 (7.13)	15.3	–1.70 (–2.42, –0.99)
Golebiowksa, 1992 Girls	31	43.70 (8.37)	27	52.00 (7.13)	18.6	–1.05 (–1.60, –0.49)
Malleson, 1996	30	37.60 (8.40)	15	41.90 (9.80)	17.0	–0.48 (–1.10, 0.15)
Takken, 2002	23	32.24 (7.78)	23	41.77 (2.51)	16.1	–1.62 (–2.29, –0.95)
Total (95% CI)	144		145		100.0	–1.13 (–1.55, –0.71)

Test for heterogeneity chi-square = 13.14, df = 5, p = 0.022
Test for overall effect z = 5.24, p < 0.00001.

Table 3B. Forrest plot of VO_{2peak} values.



Mean (SD): mean and standard deviation of the VO_{2peak} (in $ml \cdot kg^{-1} \cdot min^{-1}$); SMD: standardized mean difference; weight (%): the contribution of the study to the overall result; favors control: controls have a higher VO_{2peak} compared to JIA patients; favors JIA: JIA patients have a higher VO_{2peak} compared to controls. Forrest plot with the SMD and error bars (95% CI) indicates the result of each individual study. The black diamond indicates the overall effect of all included studies.

The purpose of our study was to determine whether children with JIA have lower physical fitness compared to healthy children, and to determine the clinical relevance of this impairment. The results of the metaanalysis suggest that patients with JIA have a significantly lower VO_{2peak}, which means their physical fitness is lower compared to healthy children. However, there was a significant heterogeneity between studies, mainly due to the study of Malleson, *et al*[4]. They did not find statistically significant differences between patients with JIA and control subjects. As Malleson, *et al*[4] commented in their discussion, their control subjects were healthy friends of the JIA patients. There might be a selection bias in the control group, since the control subjects might have a sedentary activity pattern similar to the patients with JIA, making the control subjects deconditioned as well. Malleson, *et al*[4] also compared the VO_{2peak} of the JIA patients with established reference values. This comparison showed significantly higher VO_{2peak} values for healthy children, and a statistical analysis showed a significant lower VO_{2peak} for JIA patients compared to the reference values.

Physiology. What might cause the lower VO_{2peak} in JIA patients? VO_{2peak} is the product of cardiac output (heart rate × stroke volume) and the arterio – mixed venous oxygen difference (the Fick equation). Three studies[6,8,12] provided peak heart rate data. These studies (data not shown) show that peak heart rate is on average 6 $beats \cdot minute^{-1}$ (95% CI –10, –2.8) lower than in healthy controls during MXT, indicating that some JIA patients terminated the exercise test before reaching the maximum capacity of their cardiovascular system. If the cardiovascular system was the limiting factor in the exercise capacity of JIA patients, the heart rate would be taxed to a maximum, since stroke volume already reaches its maximum level at about 50–70% of VO_{2peak}[14].

Another cause of the impaired VO_{2peak} might be a lower stroke volume of the heart. It is known from the literature that inactivity in children causes a decrease in stroke volume[15]. However, it is not clear whether this is the limiting step in oxygen transport in untrained children, because a decrease in stroke volume can be compensated at submaximal intensities by an increased heart rate. As mentioned, the peak heart rate during MXT is lower in JIA patients compared to healthy children. This indicates that the cardiovascular system is not the limiting factor in oxygen uptake of JIA patients.

The limiting step is more likely on the non-hemodynamic side of the Fick equation. Many possible causes can be distinguished with respect to this side of the equation. Pulmonary function abnormalities have also been reported in JIA patients[16], caused by weakness of the respiratory muscles. However, this was only found in effort dependent tests (e.g., forced vital capacity and peak expiratory flow). It is not likely that impaired lung function is the cause of the lower VO_{2peak}.

Muscular atrophy is also a common finding in patients with JIA, who have lower muscle bulk compared to healthy subjects[17-19]. This is still evident after some years without disease flares, and is more pronounced in children with a

disease onset before the age of 3[19].

A lower muscle mass implies a smaller muscle mass to consume oxygen. Also, a patient experiences fatigue at an earlier workload and will terminate the test earlier compared to healthy subjects. Suggestions for the cause of the lower muscle bulk are inactivity, medication, and disease activity.

Muscle biopsy studies in children with JIA are, to our knowledge, not performed. Available evidence from studies with adult rheumatoid arthritis suggests an atrophy in both type I and type II muscle fibers. The atrophy is most pronounced in the type II muscle fibers and cannot be fully explained by disuse. It is suggested that muscle fibers are directly involved in the inflammation process[20]. Data from short term and longterm training studies in RA patients and a training study in JIA patients[21] show that this muscular atrophy in both muscle fiber types can be reduced by dynamic exercise training[22,23]. Thus, part of the impairment in physical fitness might be caused by hypoactivity. The other part might be caused by medication and inflammation related factors.

Clinical relevance. SMD of –1.13 indicated a moderate to large impairment of physical fitness in patients with JIA. The wide confidence interval (impairment 21.8%, 95% CI 13.7, 29.9) indicates a large variation in physical fitness between JIA patients. This is in accordance with our own findings[12]. Due to lack of information we could not perform a subgroup analysis. Data from Takken, *et al*[12] and Malleson, *et al*[4] suggest a negative association between physical fitness and disease severity. This implies that more severely diseased children are more deconditioned and less physically fit.

Practical implications. Children with a rheumatic disease, and other chronic diseases, often show an inactive lifestyle. This leads to deconditioning and functional deterioration, which again promotes an inactive lifestyle[24]. A training program could prevent deconditioning due to hypoactivity and break the cycle, thus preventing this major risk factor for comorbidity.

That JIA patients have an 8.6 $ml \cdot kg^{-1} \cdot min^{-1}$ lower VO_{2peak} might have considerable consequences at an older age. The gerontology literature contains multiple reports suggesting a threshold in physical fitness (VO_{2peak}) for performing daily activities[25,26], below which it is not possible to perform these activities. Further, it is reported that there exists a 0.41 $ml \cdot kg^{-1} \cdot min^{-1}$ decline in VO_{2peak} per year from 18 years of age[27]. This means that JIA patients will reach this threshold about 20 years earlier compared to healthy control subjects. This could have a profound socioeconomic effect when physical fitness is not maintained by physical training. More so for women, who have already a 30% lower VO_{2peak} compared to men[27].

Our review showed that children with JIA have a moderate to heavy impairment in their VO_{2peak} compared to healthy children, indicating clinically relevant lower physical fitness. This impairment in physical fitness might be caused by an atrophy of the muscle fibers. However, this should be confirmed by muscle physiological studies in JIA patients. Longterm exercise programs might be advisable for patients with JIA to improve physical fitness and reduce muscle atrophy.

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REFERENCES

1. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.
2. Singsen BH. Physical fitness in children with juvenile rheumatoid arthritis and other chronic pediatric illnesses. Pediatr Clin North Am 1995;42:1035-50.
3. Schroter K, Seidel U, Lorentz I, Lorentz K. Load-bearing capacity in school sports in juvenile rheumatiod arthritis [German]. Medizin Sport 1980;20:217-21.
4. Malleson PN, Bennett SM, MacKinnon M, et al. Physical fitness and its relationship to other indices of health status in children with chronic arthritis. J Rheumatol 1996;23:1059-65.
5. Giannini MJ, Protas EJ. Aerobic capacity in juvenile rheumatoid arthritis patients and healthy children. Arthritis Care Res 1991;4:131-5.
6. Giannini MJ, Protas EJ. Exercise response in children with and without juvenile rheumatoid arthritis: a case-comparison study. Phys Ther 1992;72:365-72.
7. Klepper SE, Darbee J, Effgen SK, Singsen BH. Physical fitness levels in children with polyarticular juvenile rheumatoid arthritis. Arthritis Care Res 1992;5:93-100.
8. Golebiowska M, Brozik H, Bujnowski T. Aerobic and anaerobic metabolism in children with juvenile chronic arthritis in relation to some clinical data. In: Coudert J, editor. Pediatric work physiology, children and exercise. Vol. XVI. Paris: Masson; 1992:175-7.
9. Golebiowska M, Brozik H, Bujnowski T. Maximal physical work capacity in adolescent girls with juvenile rheumatoid arthritis. In: Frenkl R, Szmodis I, editors. Children and exercise, pediatric work physiology. Vol. XV. Budapest, Hungary: National Institute for Health Promotion; 1991:52-7.
10. Hebestreit H, Muller-Scholden J, Huppertz HI. Aerobic fitness and physical activity in patients with HLA-B27 positive juvenile spondyloarthropathy that is inactive or in remission. J Rheumatol 1998;25:1626-33.
11. Shephard RJ, Allen C, Benade AJ, et al. The maximum oxygen intake. An international reference standard of cardiorespiratory fitness. Bull World Health Organ 1968;38:757-64.
12. Takken T, van der Net J, Helders PJM. Maximum exercise testing in juvenile rheumatoid arthritis (JRA) patients. Clin Exercise Physiology 2002;4:38-43.
13. Bujnowski T. Evaluation of maximal physical fitness in children with juvenile chronic arthritis [Polish]. Reumatologia (Warsaw) 1997;35:51-61.
14. Astrand P-O, Rodahl K. Textbook of work physiology. New York: McGraw-Hill; 1986.
15. Eriksson BO, Engstrom I, Karlberg P, Lundin A, Saltin B, Thoren C. Long-term effect of previous swim training in girls. A 10-year follow-up of the “girl swimmers”. Acta Paediatr Scand 1978;67:285-92.
16. Knook LM, de Kleer IM, van der Ent CK, van der Net JJ, Prakken BJ, Kuis W. Lung function abnormalities and respiratory muscle

weakness in children with juvenile chronic arthritis. Eur Respir J 1999;14:529-33.
17. Lindehammar H, Backman E. Muscle function in juvenile chronic arthritis. J Rheumatol 1995;22:1159-65.
18. Lindehammar H, Sandstedt P. Measurement of quadriceps muscle strength and bulk in juvenile chronic arthritis. A prospective, longitudinal, 2 year survey. J Rheumatol 1998;25:2240-8.
19. Vostrejs M, Hollister JR. Muscle atrophy and leg length discrepancies in pauciarticular juvenile rheumatoid arthritis. Am J Dis Child 1988;142:343-5.
20. Edstrom L, Nordemar R. Differential changes in type I and type II muscle fibres in rheumatoid arthritis. A biopsy study. Scand J Rheumatol 1974;3:155-60.
21. Oberg T, Karsznia A, Gare BA, Lagerstrand A. Physical training of children with juvenile chronic arthritis. Effects on force, endurance and EMG response to localized muscle fatigue. Scand J Rheumatol 1994;23:92-5.
22. Nordemar R, Berg U, Ekblom B, Edstrom L. Changes in muscle fibre size and physical performance in patients with rheumatoid arthritis after 7 months physical training. Scand J Rheumatol 1976;5:233-8.
23. Nordemar R, Edstrom L, Ekblom B. Changes in muscle fibre size and physical performance in patients with rheumatoid arthritis after short-term physical training. Scand J Rheumatol 1976;5:70-6.
24. Bar-Or O. Pediatric sports medicine for the practitioner. In: Katz M, Stiehm ER, editors. Comprehensive manuals in pediatrics. New York: Springer-Verlag; 1983:68.
25. Astrand P-O. From exercise physiology to preventive medicine. Ann Clin Res 1988;20:10-7.
26. Shephard RJ. Adapting physical activity to an aging population. Int J Sport Cardiol 1987;4:1-14.
27. Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. Aviat Space Environ Med 1990;61:3-11.