Studies on physical performance and functional ability in juvenile idiopathic arthritis

Tim Takken

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Studies on physical performance and functional ability in juvenile idiopathic arthritis

Onderzoek naar het lichamelijke prestatievermogen en functionele mogelijkheden bij juveniele idiopathische artritis

(met een samenvatting in het Nederlands)

Proefschrift

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Tim Takken

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Promotoren:
Prof. Dr. P.J.M. Helders, Faculteit Geneeskunde, Universiteit Utrecht
Prof. Dr. W. Kuis, Faculteit Geneeskunde, Universiteit Utrecht

Copromotor:
Dr. J. van der Net, Universitair Medisch Centrum Utrecht

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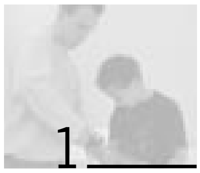
“It is easier to maintain good health through proper exercise,
diet and emotional balance
than to regain it once it is lost”.

Kenneth H. Cooper, MD, M.P.H.

Contents

Introduction



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Tim Takken

Introduction in Physical Fitness & General Health

In general, physical fitness consists of different components such as body composition, flexibility, strength, speed, and endurance. However, currently physical fitness has become synonymous with cardio-respiratory fitness (maximal oxygen consumption; VO_{2peak}). Physical fitness is dependent on both lifestyle factors such as physical activity levels and nutritional habits, as well as genetic factors.
More and more evidence becomes available indicating that physical active subjects have a lower mortality rate compared to sedentary persons. Ralph Paffenberger Jr was one of the first to describe this phenomenon in the now "almost classic" Harvard Alumni Study[1]. In the 16 years following this publication, many studies confirmed this finding. A few years ago the U.S. Centers for Disease Control and Prevention reviewed the literature in their landmark report "Physical Activity and Health: A Report of the Surgeon General"[2]. This report clearly showed that a low physical fitness is associated with a higher mortality rate, a higher risk in certain forms of cancer, obesity, decreased mental health, hypertension and a lower quality of life.

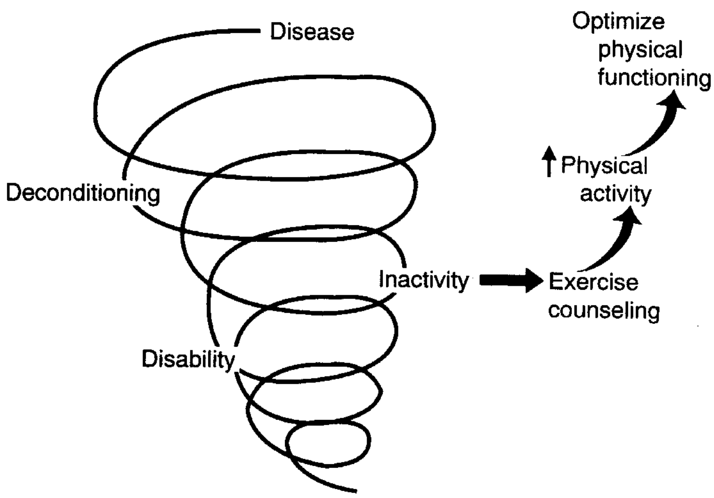

Figure 1.

The relationship between Disease, Deconditioning, Inactivity and Disability.
From Painter (3).

Most of the studies performed were based on exercise behaviors assessed using questionnaires[2]. Recently, Myers and colleagues examined 6213 consecutive men referred for treadmill exercise testing for clinical reasons during 6.2 years follow-up. The results indicated that every increase of physical fitness leads to a reduction in overall mortality in a clinical, adult male population[4]. Moreover, studies from the Cooper Institute for Aerobics Research indicated that physical fitness is of comparable importance in cardiovascular mortality with that of diabetes mellitus and other cardiovascular disease risk factors like smoking, cholesterol and hypertension[5].

For children and adolescents with a disability or chronic disease, physical fitness is at the least of equally importance[6]. Maintaining and improving physical fitness can assure that children and adolescents with a chronic disease will enter adulthood with a sound basis for their future health and an optimal physical function (See Figure 1.).

Age related decline in Physical Fitness

A literature review on North-American and European studies on aerobic physical fitness clearly showed the improvement in VO_{2peak} during childhood and the age

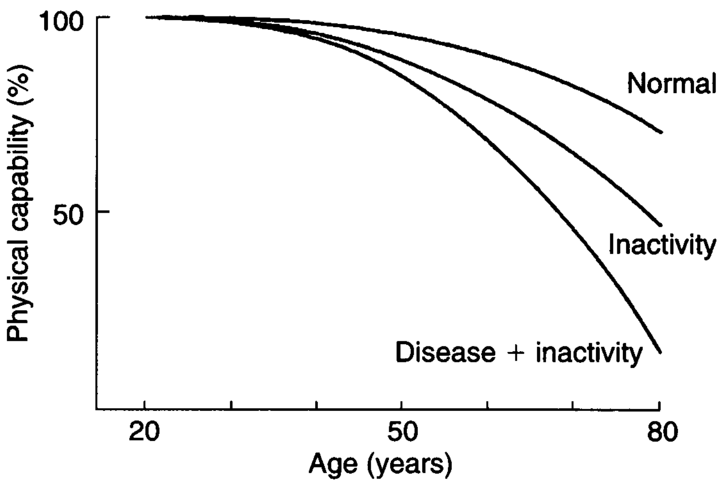

Figure 2.

The age related decline in exercise capacity in men and women.
From Ward (10).

related decline in VO_{2peak} in both men and women[7] (See Figure 2.). This decline started approximately at the age of 20 with a mean rate of 41 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$, irrespectively of gender. Additionally, women do have lower initial levels of VO_{2peak} (± 30%) when entering adulthood. This is not only the effect of a lower body fat mass, but also in absolute values, men out perform women. Thus women with a chronic disease with a pediatric onset such as juvenile arthritis, are at risk for a low VO_{2peak}, which can lead to an early disability when VO_{2peak} values reach critical thresholds for activities of daily living[8,9] (see also Chapter 4).

Physical fitness levels in patients with Juvenile Idiopathic Arthritis

Numerous studies have been performed to investigate the physical fitness levels of JIA patients and compared these results to reference values or with values from healthy control subjects. The most important findings from the physical fitness studies in JIA are summarized in Table 1. From these findings one can conclude that the physical fitness levels of JIA patients are diminished at least in the domain of muscle strength, muscle bulk, pulmonary function, anaerobic performance, sub-maximal endurance and VO_{2peak}. The studies examining VO_{2peak} are not displayed in Table 1, but are extensively reviewed in Chapter 4.

Trainability of children with Juvenile Idiopathic Arthritis

It is believed in the past that young children were not trainable in terms of improvements in VO_{2peak}. Some researchers found no improvements while others did[24]. Payne & Morrow systemically reviewed the literature and performed a meta-analysis on these data. They found that in healthy, active, children exercise training generates small to moderate effects (± 8%) on physical fitness (VO_{2peak})[24]. Rowland et al.[25] found for instance an improvement of 6.5 % in VO_{2peak} in healthy children after an exercise program (3 x week 30 min vigorous treadmill running). Patients with a chronic disease have low physical activity levels and are more detrained compared to healthy children[26,27]. Thus, in theory they have more potential to train (no ceiling effect, as is often suggested for the lower training effect in healthy active children). However, disease activity (inflammatory parameters) and medication (for example the effects of Cyclosporine A[28] and prednisone[29]) might diminish the trainability of the chronically ill child. Rowland[30] proposed that exercise training programs aiming to improve physical fitness for healthy children should incorporate adult guidelines for exercise intensity and duration (3 x week 30 min at 60 of heart rate reserve). The question arises whether adult guidelines are appropriate for chronically ill children? Klepper &

Table 1. Comparison of physical fitness variables between Juvenile Idiopathic Arthritis patients and controls.

Study	Assessed Variable	Used Method	Number of Patients	Findings
(11)	Skeletal muscle strength	Hand held dynamometer	20	↓
(12)		Hand held dynamometer	20	↓
(13)		Hand held dynamometer	11	↓
(14)		Computerized dynamometer	28	↓
(15)		NA	9	↔
(12)	Muscle bulk	Ultrasound	20	↓
(16)		Femoral muscle circumference	32	↓
(17)	Pulmonary function	Standard pulmonary function tests	31	↓
(18)	Anaerobic performance	WaNT	31	↔
(19)		WaNT	13	↓
(20)		50-meter run	20	↓
(21)		50-meter run	32	↓
(22)	Body composition	Skin folds	20	↔
(18)		Skin folds	31	↔
(22)	Sub maximal Endurance	9 min run walk test	20	↓
(23)		Heart rate during sub-maximal exercise	30	↑
(9)	VO_{2peak}	See Chapter 4		↓

Abbreviations: WaNT = Wingate anaerobic test; ↓ = decreased compared to healthy controls; ↔ = no difference between JIA patients and controls; ↑ = increased compared to healthy controls.

Giannini introduced some general guidelines for the training of children with juvenile arthritis and even described an example of a typical exercise training program[31].

One of the often asked questions is when to start a training program for children with juvenile arthritis. Klepper & Giannini[31] recommend children with chronic arthritis to start an individualized exercise program soon after diagnosis[31]. But should children train during active disease episodes? Research on adults with mild to moderate active rheumatoid arthritis[32,33] showed that exercise training did not increase disease activity. Fisher et al.[34] showed that immune parameters

Table 2. Training studies in Juvenile Arthritis patients

Study	No of Patients	Disease subclass	Age (years)	Gender	Duration	Program	Medium
Klepper (51)	25	26pjia	8-17	23f/2m	8wks 3 sessions /wk	2 sessions /week supervised, 1 session/wk @ home. Focused on aerobic exercise (fit ball)	Land-based
Baldwin (47)	12	NA	8.18 mean 11.7	10f/2m	2 x 20 wks (cross-over study)	2x 15 wks Pool: 2x15 min Land 30 min Focused on strength & mobilization hip and knee joints	1 pool group, 1 land based group
Bacon (52)	11	4ojia, 4pjia, 3sjia	4-13	7f/4m	6wks 2 sessions / wk	45 min structured act, 15 min play	Pool T: 27-28C
Oberg (15)	10	5ojia, 3pjia, 1sjia, 1pso	7-15, mean 10.4	7f/3m	3 months 2 sessions / wk	40 min, gymnastics, pool, focused on strength & endurance	Pool + land
Feldman (53)	9	pjia	8-11	NA	12 weeks 1 or 2 sessions /week	NA	Pool + land
Klepper (49)	5	NA	5-13	NA	6 wks (13 sessions)	60 min/session, focused on aerobics, strength and stretching	Land

	Supervision	Outcomes	Results
	PT, RN, ExPhys	Joint count, Articular severity Index Pain, Swelling, ROM, 9-min run walk	Joint count ↑; 9 min run walk ↑; Articular severity index ⇔; pain ⇔; swelling ⇔; ROM ⇔.
	PT	Tenderness Swelling Quadriceps circumference Strength	Pool therapy: quadriceps strength ↑; Home therapy: mobility ↑; Parents & patients: pool therapy was more beneficial and enjoyable than home therapy
	PT + RN	ROM, gait, balance, functional mobility of lower extremities	Hip rotation & flexion ↑; HR recovery after exercise ↑; Balance tests & times tasks ⇔ Gait ⇔
	PT	Isometric force, muscle endurance @ 40% of max torque, Surface EMG	Muscle strength quadriceps ↑; Muscle strength trapezius ⇔; EMG ↑ (normalized towards control)
	PT	Energy cost of locomotion, VO_{2peak}, Anaerobic performance	Efficiency of gait ↑; VO_{2peak} ⇔; Anaerobic performance ↑.
	PT	9 min run walk, 1 min sit up, sit & reach, skin folds, swelling, ROM, tenderness, pain, self esteem, pain perception	Joint count V; Articular severity ↑; pain perception ↑; 9 min run walk ↑; sit-up test ↑; self esteem ↑.

Table 2. Continued

Study	No of Patients	Disease subclass	Age (years)	Gender	Duration	Program	Medium
Moncur (48)	7	7pjia	NA	NA	12 wks	NA	Bicycle ergo-meter
Fisher (38-41, 44)	10	NA	6-14	NA	8 wks	Resistance training, 3/wk duration and intensity: NA	Land
Fisher (34)	19	NA	Mean 11.3	NA	8 wks	Resistance training, 3/wk duration and intensity: NA	Land

even improved after resistance training in children with JIA. These reports suggest that exercise can be started even when the disease process is not in remission and that exercise can be continued during episodes of active disease.

Exercise immunology in Juvenile Arthritis

There is a growing interest of exercise scientists in the field of immunology. With the improvement of research techniques it will become easier, cheaper and quicker to analyze effects of exercise training and/or physical activity levels on immune status. In the field of arthritis research only a few reports have been published on this topic[33,35], as most of the exercise studies focused on improvement in exercise capacity, functional ability, range of motion etc. In adult RA, a few papers have been published[33,35] including 2 review papers[36,37]. In Juvenile

Supervision	Outcomes	Results
NA	Joint count, abs + rel VO_{2peak}, exercise time.	Joint count ↑, abs VO_{2peak} ↑, rel VO_{2peak} ↑, exercise time ↑.
NA	Plasma lactate after MXT, neutrophils, inflammation, muscle function, VO_{2peak}, blood pressure, peakHR, functional status, pain, disability.	Plasma lactate ↑, neutrophils ↑, inflammation ↑, quadriceps & hamstrings strength ↑, hamstrings & quadriceps endurance ↑, contraction speed ↑, VO_{2peak} ↑, blood pressure ↑, peakHR ↑, functional status ↑, pain ↑, disability ↑.
NA	Strength, endurance, contraction speed, EMG activity, inflammatory mediators.	Strength ↑, endurance ↑, contraction speed ↑, EMG activity ↑, inflammatory mediators ↑.

Abbreviations: ojia = oligoarticular juvenile idiopathic arthritis; pjia = polyarticular juvenile idiopathic arthritis; sjia = systemic juvenile idiopathic arthritis; pso = psoriatic arthritis; NA = not available; PT = physical therapist; RN = registered nurse; ExPhys = exercise physiologist; EMG = electromyogram; peakHr = peak heart rate; VO_{2peak} = peak oxygen consumption; ROM = range of motion; ↑ = improvement; ⇔ = no improvement; ↓ = worsening.

Idiopathic Arthritis only two research projects are reported from the University of Buffalo, NY. This work, to date only published as abstracts[34,38-44], suggest that resistance exercise training can improve not only muscle function, but also immune function in patients with juvenile arthritis.

Rationale for exercise

In adults with RA the major reason for their low ‘physical fitness’ is probably their lack of physical activity (deconditioning)[45] due to soreness and pain in muscles and joints[46] and the availability of technology supporting a sedentary lifestyle. Adults stated that they better could perform activities of daily living after a physical training program[46], i.e. their functional status had been improved.

There is a need to search for the rationale for an exercise program for children. For example Joan Baldwin[47] of the Hospital for Sick Children, Toronto, Canada reported the results of her training study for juvenile arthritic kids, three years before the first adult research from Stockholm, Sweden[45] was published. Baldwin did not mention the reasons why she started the research. However, it shows that she did not start because of the promising results in the adult rheumatoid arthritis population, but initiated the training program because of the assumed need for exercise and conditioning in the juvenile arthritis patient group. Moncur et al. (1990) used the adult results as a rationale for their research[48], the same is true for the research of Susan Klepper[49].
Before we started this research project there were only a few papers on the topic of exercise/training in juvenile arthritis. The body of evidence from pediatric studies is very small compared to the available number of studies on adult RA patients. The training studies available in current literature, both full report publications as well as abstracts are summarized in Table 2. Our recently published pilot study[50] will be described in Chapter 2, our randomized study in Chapter 7. Summarizing the available literature, 108 children with Juvenile Idiopathic Arthritis patients have been trained in nine different studies. In general, three modalities can be distinguished: land-based training, aquatic training and bicycle ergometer training. In all modalities effects have been found. However, most studies used different outcome measures. For reasons of comparison, we need an established core set of variables for assessing the effectiveness of therapeutic interventions in JIA. All studies included assessments in the domains of pathology and impairment within the disablement process, such as range of motion, pain and joint count. But performance variables (functional limitation and disability) are all measured using different methods. A standardized set of measures would facilitate the comparison of different studies and exercise intervention, by that showing which are the most effective ones.

Aims and Outline of this Thesis

As shown in the first part of this introduction, there is little known on the effectiveness of fitness training for children with JIA. Our first aim was to develop a save, enjoyable and practically executable exercise program with great adherence for children with JIA, and to investigate the effect of this program not only on the domain of physical fitness, but also on functional ability and quality of life.

In the consecutive studies, the physical fitness of JIA patients was studied and also its relationship with functional ability and physical activity was explored.

In the first Chapter a brief introduction on physical fitness and physical training is given. In Chapter 2, we described the findings of our pilot study with 10 JIA patients. We developed our aquatic fitness training program using the experiences of this pilot study. During this pilot study we also investigated the willingness of parents and patients to participate in a training study. Chapter 3 deals with the reliability of the assessment of the maximum oxygen consumption (the gold standard for physical fitness) and gives a description of our experiences of exercise testing in this patient group. The comparison of the exercise capacity of JIA patients with healthy peers is reviewed in Chapter 4.
The relationship between functional ability and different indices of both aerobic and anaerobic physical fitness is described in Chapter 5; the association between physical activity and physical fitness in Chapter 6. The effects of our physical training study on physical fitness, joint status, functional ability and quality of life in JIA patients are provided in Chapter 7. A summary in English and the general discussion can be found in Chapter 8, while a Dutch summary is provided in Chapter 9.

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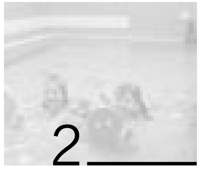

2

Do juvenile idiopathic arthritis patients benefit from an exercise program? A pilot study.

Tim Takken
Janjaap van der Net
Paul J.M. Helders

Arthritis & Rheumatism (Arthritis Care and Research). 2001;45(1):81-85.

Abstract

Objective

The current study aimed to investigate whether an aerobic aquatic training program could improve the functional ability, endurance and health related quality of life of JIA patients if added to the standard care.

Methods

Ten patients participated in a 15-week aquatic training program in a warm pool. There were 4 assessments, using the following instruments: Childhood Health Assessment Questionnaire (CHAQ), the 6-minute walking test and the Juvenile Arthritis Quality of Life Questionnaire (JAQQ).

Results

There were only significant changes in the JAQQ due to the lower score on the General Symptoms subscale.

Conclusion

It was concluded that an aquatic training program had no significant effects on the CHAQ and 6-minute walking test, but influenced the score on the JAQQ of these JIA patients. Further study is underway to investigate these effects in a more controlled research design.

Introduction

It is known from studies with adults with rheumatoid arthritis that they benefit from exercise[1]. There is some evidence that children with juvenile idiopathic arthritis (JIA) can benefit from exercise as well[2,3]; at least there is evidence that exercise does not exacerbate the arthritis[4,5].

Children with a rheumatic disease, and other chronic diseases, often live an inactive life. This leads to deconditioning and functional deterioration, which again promote an inactive lifestyle[6]. A training program could prevent the deconditioning due to hypoactivity and break the vicious circle, thus preventing this major risk factor for comorbidity[7]. Until recently, the main focus of exercise interventions for patients with a rheumatic disease was to study adverse effects on inflammation and joint disease and the effects on physical fitness. Previous research found that children with arthritis benefit from an aquatic exercise[2,3,8]. Recently, Klepper[4] found that land-based exercise could improve physical fitness in JIA patients. But whether exercise could influence patient-centered outcome measures (i.e., functional ability and health-related quality of life) in JIA patients is relatively unknown. Therefore the aim of the current study was to investigate whether an aerobic aquatic training program could improve not only the endurance of JIA patients but also the functional ability and health-related quality of life if added to the usual medical and physical therapeutic care.

Methods

The study started in January 1999. Twenty-five patients (age range 5-12 years) who lived within 25 km of our hospital and were diagnosed with JIA (International League of Associations of Rheumatology criteria[9]) in the pediatric immunology/rheumatology outpatient clinic were asked to participate in a pilot study. Ten patients with JIA, all females, and their parents agreed to participate in the study. The parents signed their informed consent during the first visit to our department. The patient characteristics are shown in Table 1.

Joint status was assessed by the number of tender and swollen joints. Tenderness and swelling were scored for the following joints: temporomandibular, sternoclavicular, shoulder, elbow, wrist, thumb, knee, ankle, and toes. Joint mobility was scored on the Pediatric Escola Paulista de Medicina Range of Motion Scale (*p*EPMROM[10]). The *p*EPMROM 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 metacarpophalangeal], 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 10. Both joint status and joint mobility were scored by the same senior pediatric physical therapist with 20 years of experience in pediatric rheumatology (JvdN). The Dutch translation of the Childhood Health Assessment Questionnaire (CHAQ), Pediatric Rheumatology International Trials Organization (PRINTO) version, was used as a self-administered pencil and paper questionnaire for the parents (proxy), as an index of functional ability. The CHAQ[11] has been adapted from the Stanford Health Assessment Questionnaire so that at least one question in each domain is relevant to children aged 0.6 to 19 years. The CHAQ was recently cross-culturally adapted and validated for the Dutch language by the PRINTO group[12]. The question with the highest score within each domain (range 0 to 3; able to do with no difficulty = 0, able to do with some difficulty = 1, able to do with much difficulty=2, unable to do=3, time frame was last week) determined the score for that domain, unless aids or assistance was required (raising the score for that domain to a minimum of 2). The mean of the scores on the eight domains provided the CHAQ disability scale (range 0 to 3).

Endurance was measured with the 6-minute walking test, as recommended for patients with arthritis[13]. The 6-minute walking test was performed on an 8-meter track in a straight corridor. The patients were instructed to walk at their own chosen walking speed from one side of the corridor to the other, turn and walk back. The total distance covered in six minutes was calculated as the counted “repetitions” and multiplied by 8 meters. Time was measured with a stopwatch. During the test standardized verbal encouragements from the test-leader were used to encourage the subjects.

Health-related quality of life was assessed with a Dutch translation of the Juvenile Arthritis Quality of Life Questionnaire (JAQQ). The JAQQ is a recently developed disease-specific health-related quality of life questionnaire for children with arthritis[14]. The JAQQ was administered to the patients. The JAQQ consists of 74 items divided into five subclasses (gross motor function, fine motor function, psychosocial function, general symptoms and pain). The children scored each item on a 7-point Likert-scale according to how often they encountered problems during the last 14 days (none of the time = 1, hardly any of the

Table 1. Subject characteristics.

Subject	Age	DS	YA	NSTJ	*p*EPMROM	Medication	PT
1	10	sjia	7.4	0	0.0	-	+
2	10	sjia	2.3	2	0.1	pre mtx nsaid	-
3	10	ojia	5.5	5	0.1	dmard nsaid	-
4	7	ojia	5.5	2	0.1	nsaid	-
5	9	pjia	2.7	4	0.6	dmard nsaid	+
6	8	pjia	6.8	7	0.65	pre mtx nsaid	+
7	12	pjia	6.5	11	0.1	dmard nsaid	+
8	10	ojia	7.6	3	0.8	nsaid	+
9	12	sjia	7.8	2	0.4	mtx nsaid cyc	+
10	5	ojia	4	1	0.0	nsaid	

Abbreviations: DS = Disease subclass; YA = total years of arthritis; NST J= number of swollen and tender joints; EPMROM = score on the pediatric EPMROM; PT = physical therapeutic care; f = female; ojia = oligoarticular JIA; pjia = polyarticular JIA; sjia = systemic JIA; pre = prednisone; mtx = methotrexate; nsaid = non steroid anti inflammatory drugs; dmard = disease modifing anti rheumatic drugs; cyc = cyclosporine; + = yes; - = no. All subjects were female.

time = 2, some of the time = 3, half of the time = 4, most of the time = 5, almost all of the time = 6, all of the time = 7). Pain was measured on a 10 cm double anchored visual analog scale (VAS). In the original article the JAQQ was only scored on 5 particular items of interest per domain. This approach results in a different questionnaire on each occasion for each patient and makes group statistics difficult to interpret[15]. Therefore, the score on the JAQQ was calculated as (a) the sum of the scores on all 74 items of the questionnaire, (b) the score on its subscales, and (c) the VAS for pain. A higher score indicates a worse health-related quality of life.

The children in this study received a 15-week aerobic aquatic training program. The exercise groups (2-4 patients) were supervised by a pediatric physical therapist (JvdN) and an exercise physiologist (TT). The training took place in a heated swimming pool (temperature of water ± 32°C). The training activities were predominantly such exercises as swimming, aerobics, and ball games. Lessons were based on the same framework. The training started with a warm-up, followed by a conditioning part. After this conditioning part a small rest period was included. This period was followed by a second conditioning part. The training ended with a cooling down. The warming up, rest and cooling down period consisted of low-intensity swimming, aquarobics, play, flexibility exercises or ball games. The conditioning parts consisted mainly of high-intensity swimming, diving, walking through the water, aquajogging, or splashing with the legs. The duration and intensity of both conditioning parts increased stepwise during the program. During the training sessions the heart rates of the children were measured using a portable heart rate monitor (Polar Accurex Plus, Polar Oy, Kempele, Finland) to get an impression of the training intensity and prevent overreaching. The children received one training session per week, each lesson lasting 60 minutes.

There were four measurements; baseline (mean of two assessments), after seven weeks of training, immediately after fifteen weeks and three months after the end of the training program.

Statistical analysis was performed with SPSS 8.0 for Windows (SPSS, Chicago, Ill). The non-parametric Friedman test[16] was used for analyzing the four repeated measurements on all the measures (CHAQ, 6-minute walking test, and JAQQ). When the differences between the groups appeared to be significant ($P<0.05$), the Wilcoxon signed-rank test was used to detect the significant differences. The study was approved by the human ethical committee of the University Medical Center Utrecht, Wilhelmina Children's Hospital.

Results

The attendance during the training sessions was 85%. The major reasons for absence were disease, no available transportation and other social peer activities. At the fourth measurement, because of nonadherence of one patient, the respective parents returned the CHAQ by mail. The mean CHAQ disability scale showed a trend to improve from 1.21 (SD ± 0.6, baseline) to 1.16 (SD ± 0.6) after the training program. Three months after finishing, the CHAQ disability scale decreased to baseline level (1.21; SD ± 0.6) as shown in Figure 1. However, these changes were not statistically significant.

The covered distances during the 6-minute walking test, baseline, during, and immediately after the end of the training program, and three months after the end of the training program were 440 meters (SD ± 54.0), 415,6 meters (SD ± 33.7) 436 meters (SD ± 50.4), and 436 meters (SD ± 50.4). The changes are shown in Figure 2. The values did not differ significantly from baseline and from each other. One patient was not able to accomplish the 6-minute walking test in the

Figure 1.

Box plot of the scores in functional ability (disability scale of the CHAQ) during the 4 assessments. Differences between the measurements are not statistically significant. Measurements: baseline, after seven weeks of training, immediately after fifteen weeks and three months after the end of the training program. The whiskers represent the highest and lowest values within 1.5 times the inter quartile range (box length, IQR). The lower horizontal line of the box indicates the 25^{th} percentile. The upper-horizontal line indicates the 75^{th} percentile. The mid horizontal bar in the box indicates the median.

second, third, and fourth assessments because of arthritis-related problems in the ankle. Two others patients did not accomplish the 6-minute walk on the fourth assessment because of pain and fatigue. One patient did not comply with the fourth assessment.

The mean JAQQ subscale scores improved by 16 % (NS), 19 % (NS), 16 % (NS), 12 % (P<0.05) and 17 % (NS), respectively, for physical function, psychosocial function, general symptoms, and the VAS for pain after the end of the training program compared with baseline. The overall score on the JAQQ is shown in Figure 3. The improvements in the JAQQ during the training program (assessments 1, 2, and 3) were not statistically significant. However, the relapse after the training program (the differences between assessments 3 and 4) reached statistical signifi-

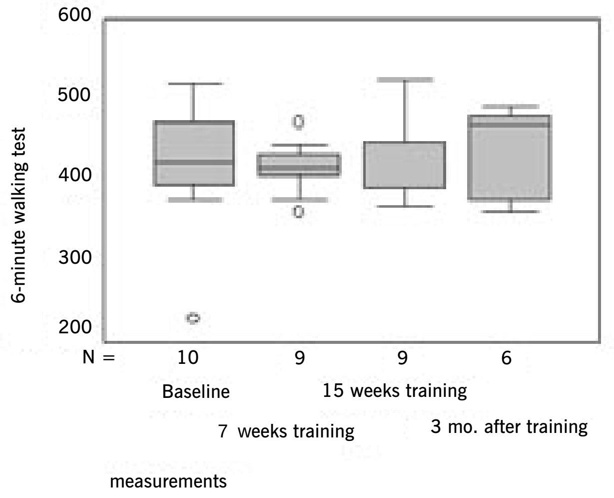

Figure 2.

Box plot of the scores on the 6-minute walking test during the 4 assessments. Differences between the measurements are not statistically significant. Measurements: baseline, after seven weeks of training, immediately after fifteen weeks and three months after the end of the training program. The O symbol indicates an outlier between 1.5 and 3 times the interquartile range from the box. (For explanation of box plot see legend to Figure 1.)

cance. Two patients did not accomplish the JAQQ on the fourth assessment. One patient did not comply with the fourth assessment, and one patient failed to complete the entire questionnaire.

Figure 3.

Box plot of the score changes in health-related quality of life (mean score on the total JAQQ) during the 4 assessments. The differences between the third and fourth assessments are significantly different. Measurements: baseline, after seven weeks of training, immediately after fifteen weeks, and three months after the end of the training program. The * symbol indicates an extreme lying more than 3 times the interquartile range from the box. (For explanation of box plot see legend to Figure 1.)

Discussion

Our main interest was to investigate whether a 15-week aerobic aquatic training program could improve the functional ability, endurance, and health-related quality of life of JIA patients if added to the common medical and physical therapeutic care.

The high attendance rate of the current training program reflected good adherance of the parents and patients to our training intervention. It also reflects the high interests of parents and patients with JIA in adapted physical activity programs, which may be a more effective and economic method of providing therapeutic and recreational exercises to this population.

The lack of change of the CHAQ disability scale could be explained by the fact that the CHAQ was originally developed as a discriminative instrument for disability and not as an outcome measure for effect studies[8]. Flato and colleagues[17] concluded that the Norwegian version of the CHAQ was sensitive to clinical change. However, the way in which the CHAQ disability scale is calculated (the highest score within a domain determining the score of that domain, the requirement of aids or assistance raising the score on that domain to a minimum of 2) makes it difficult to detect changes in functional ability in the "home situation".

Recently, the 6-minute walking test was proposed as a potential outcome measure for hydrotherapy[18]. However, our subjects did not improve as to the distance they covered. It is difficult to explain the results for the 6-minute walking test, because these sorts of tests not only depend on physical fitness but are also highly influenced by pain, fatigue, motivation, muscle strength, and encouragement[19]. Further experience will reveal its validity.

The JAQQ subscale scores on the gross motor function and fine motor function confirmed the results from the CHAQ disability score, indicating that there were no significant changes in functional ability. Our program was also not able to significantly improve the psychosocial function domain and pain. On the other hand, the general symptoms domain improved, and the change was statistically significant; thus, the patients encountered fewer disease signs and symptoms during the exercise program. This has been confirmed in a land-based aerobic intervention as well[4]. However, it has been questioned whether a separate analysis on the different domains within one quality of life instrument is appropriate[20]. The results on the JAQQ might have been different if this instrument had been used in the original manner. In that approach patients can pick or add items of interest in each domain of the JAQQ.

The trend to an improvement of the overall health-related quality of life score during the training program is in accordance with the existing literature on adults with a chronic disease[20]. Surprisingly, this improvement did not reach statistical significance. This could be explained by the large differences in response between subjects due to the heterogeneous patient population and the small sample size that we used for this study. The decreased health-related quality of life in the 3 months after the end of the training program suggests that JIA patients can benefit from an exercise program or a more active lifestyle.

The changes in the outcome of our measurements can be explained by the exercise program, the seasonal influences, the repeated-measurements design of our study[21], the limited number of patients, or a combination of these factors. A randomized design, a control group, and a larger number of patients are necessary to take these factors into account.

Conclusion

In conclusion, an aquatic training program positively influenced the health-related quality of life of JIA patients, but it had no significant effects on endurance and functional ability. Further study should investigate these effects in a randomized design and with a larger number of patients.

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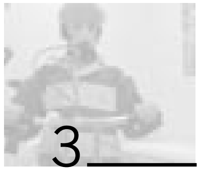
Aerobic exercise testing in juvenile rheumatoid arthritis (JRA) patients



3

Tim Takken
Janjaap van der Net
Paul J.M. Helders

Clinical Exercise Physiology 2002 4(1): 38-43

Abstract

Purpose

The purpose of this study was threefold (i) to examine the feasibility of maximum exercise testing in JRA patients, (ii) compute the error of measurement of maximum exercise tests, and (iii) characterize the functional aerobic impairment of these patients.

Methods

Twenty-three patients diagnosed with JRA (age 6-14) performed 2 graded, maximum exercise tests using an electronically braked cycle ergometer and metabolic cart to volitional exhaustion, two months apart.

Results

In total 46 exercise tests from 23 children were available for analysis. We faced no complications during the tests. Standard error of measurement between the first two assessments was 9.5 %. The majority of the patients had an impaired maximal oxygen uptake (in $L{\cdot}min^{-1}$), with an average functional aerobic impairment of 24 % (range: 8 % above predicted to 61 % lower than predicted). When corrections were made for body mass, the average functional aerobic impairment was 22 %, ranging from 65 % above predicted to 69 % lower than predicted.

Conclusion

Maximal exercise testing of our study population of JRA patients was feasible. There were large variations in aerobic impairment between JRA patients, which makes a generalization about aerobic fitness in this population difficult. Using maximum exercise tests, JRA patients with a low aerobic fitness can be identified and a physical training program can be initiated.

Introduction

Aerobic exercise testing is commonly employed to determine aerobic fitness in pediatric patients with various conditions, and has proven to be a valuable tool in measuring a patient's exercise capacity in a variety of diseases such as heart disease, asthma and cystic fibrosis[1]. In Juvenile Rheumatoid Arthritis (JRA) however, aerobic exercise testing is rarely employed. Surprisingly, since children with a rheumatic disease, and other chronic diseases, often live an inactive life. In JRA, pain, joint swelling, and limited range of motion can aggravate this lifestyle. A sedentary lifestyle leads to deconditioning and functional deterioration, which again leads to an impairment in aerobic functioning and promotes an inactive lifestyle[2]. Moreover, a low aerobic fitness is a major risk factor for comorbidity[3,4].

A systematic review revealed only seven published reports[5-11], describing the aerobic fitness of approximately 170 patients in the pediatric age group (< 18 years). However, these patients were predominantly adolescents. None of these publications reported any problems in assessing aerobic fitness of JRA patients. However, maximal aerobic exercise testing in healthy children[12,13], and in adult patients with arthritis[14] is in some cases difficult or not even possible. Therefore, we studied the feasibility in JRA patients between 6 and 14 years of age.

For intervention studies it is relevant to measure the reliability of an outcome measure. High reliability ensures detection of small to moderate effects. This strongly depends on the within-subject variability. Giannini and Protas[8] report a high within-subject variability between tests in only 10 children with JRA.

For intervention studies it is also important to have test-retest statistics of outcome measures with approximately the same time interval between the tests as you intend to have in your experiment[15]. To date, there are no reliability statistics available for maximal exercise tests in JRA longer than two weeks.

Differences exists in the literature about the aerobic fitness of JRA patients. Schröter et al.[11], and Malleson et al.[10] found no differences in maximal oxygen consumption (VO_{2max}) between JRA patients and healthy age and sex-matched controls. Data from Giannini and Protas[7,8], Klepper[16], Golebiowska et al.[5,6] and Hebestreit et al.[9] suggest that JRA patients have an impairment in aerobic fitness. None of these studies describes whether the differences were clinically relevant. Moreover, it is possible that the above mentioned reports[5-11] found a lower aerobic fitness because their patients terminated the exercise test before reaching a 'true' maximal effort, as VO_{2max} can only be measured at the end of a real maximal exercise test[1] (MXT). However, only a minority of children reaches a plateau of VO_2 during such a test[13]. Consequently, several objective and subjective criteria are required to determine if a true maximal effort has been achieved[17]. In the currently published reports, the criteria for determining maximal effort are not defined. Therefore, the lower aerobic fitness found in some of the published reports might be a result of a prematurely terminated and, thus, sub maximal exercise test and not merely the result of deconditioning.

The purpose of this study was threefold: (i) to examine the feasibility of maximum exercise testing in JRA patients, (ii) compute the error of measurement of maximum exercise tests, and (iii) characterize the functional aerobic impairment of JRA patients.

Methods

Patients

Twenty three patients (age 6 to 14 yr, 6 male / 17 female) participated in this study. Patients were assessed on two occasions two months apart. JRA was diagnosed by a pediatric rheumatologist, and the patients were divided in three distinct types of JRA: oligoarticular JRA (OJRA; arthritis present in four or fewer joints); polyarticular JRA (PJRA; 5 or more joints affected with arthritis without systemic manifestations); systemic JRA (SJRA; characterized by intermittent fever, rheumatoid rash, and arthritis). The characteristics of the patients at baseline are presented in Table 1.

All patients were receiving a local and/or a systemic arthritis related therapy consisting of non-steroid anti-inflammatory drugs and/or disease modifying anti-rheumatic drugs and/or immunosuppressive drugs/steroids in the last 6 months prior inclusion. The mean disease duration in this patient group (mean ± SD) warrants early as well as late disease effects. The wide range of the body mass index and VO_{2peak} values shows the variation in physique of JRA-patients. Winter presented compelling arguments to question the validity of using ratio scaling to remove the influence of body size from independent performance measures[18]; we

[1] 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.

Table 1. Subjects' characteristics.

JRA Patients (N=23)	
Age (years: mean ± SD)	10.0 (± 2.1)
Body Mass Index (in kg · m^{-2}: mean ± SD)	17.9 (± 3.1)
Weight (in kg: mean ± SD)	35.7 (± 10.7)
Σ7-Skinfolds (in mm: mean ± SD)	103.5 (± 44.7)
Disease Subclass	11 OJRA / 10 PJRA / 2 SJRA
pEPMROM (mean ± SD)	0.18 (± 0.21)
Number of Swollen Joints (mean ± SD)	2.6 (± 2.9)
Years of Arthritis (in years: mean ± SD)	5.7 (± 2.3)

Legend: pEPMROM = Pediatric Escola Paulista de Medicina Range of Motion Scale.

therefore report both absolute values ($L \cdot min^{-1}$) and relative values ($ml \cdot kg^{-1} \cdot min^{-1}$) of VO_{2peak}.
All subjects were recruited from the pediatric rheumatology outpatient clinic of the Wilhelmina Childrens Hospital, University Medical Center Utrecht, the Netherlands. Parents gave their informed consent for participating in the study. All procedures were approved by the local medical ethical committee.

Maximal Exercise Test (MXT)

Subjects performed a MXT using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The seat height of the ergometer was adjusted to the patient's leg length. Three minutes of unloaded cycling preceded the application of resistance to the ergometer. Thereafter, the workload was increased by the constant increment of 20 Watts every 3 minutes. This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the experimenters. During the MXT, subjects breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Mijnhart, Bunnik, the Netherlands). Expired gas was passed through a flowmeter, an oxygen (O_2) analyzer and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (Ve), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER) from conventional equations. Heart rate (HR) was measured continuously during the MXT by a bipolar electrocardiogram. Ratings of perceived exertion (RPE) were recorded during exercise on a Borg CR-10 scale[19]. The question was asked "How hard are you exercising?" Subjects gave an answer on a scale of 0-10, 0= nothing; 10= very very hard, maximal. Maximal effort occurred when one of 3 criteria were met: RPE of 10, HR > 180 bpm, or RER > 1.0. Peak oxygen consumption was taken as the average value over the last 30 sec during the MXT. Percentage functional aerobic impairment (FAI) was calculated as: FAI = [(predicted VO_{2peak} - observed VO_{2peak}) / predicted VO_{2peak}] x 100[20]. Predicted VO_{2peak} values were obtained from established values from age- and sex- matched historical Dutch controls[21].

Anthropometry

The patient's body mass and height was determined using an electronic scale and a measuring stick. Body composition was assessed using the sum of seven skinfolds method according Pollack et al.[22]. The measurements were taken at 7 sites (at the right side of the body); triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf and thigh by the test leader in accordance with the American College of Sports Medicine guidelines[23].

Joint range of motion was assessed using the pediatric Escola Paulista de Medicina range of motion scale (pEPMROM)[24]. Ten joint movements (cervical spine [rotation]; shoulder [abduction]; wrist [flexion and extension]; thumb [flexion metacarpophalangeal]; 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 the joint score at each movement divided by 10, providing a final range of scores for joint movement from 0 to 3.

Statistics

All data were entered and analyzed in SPSS 9.0 for Windows. The standard error of measurement (SEM) was computed as the square root of the sum of the squared differences between corresponding measurements divided by twice the sample size[25]. Comparison of the VO_{2peak} of JRA patients with historic controls was computed as the percentage of the FAI (see Methods section). Differences between patients and reference values was tested with a paired samples T-test, differences between disease subgroups (OJRA and PJRA) were tested using an independent samples T-test ($\alpha = 0.05$).

Results

Feasibility

In total 46 exercise tests from 23 children were available for analysis. The data of the cardiopulmonary responses are shown in Table 2. Three children were omitted from the analysis because they were too scared to wear a facemask. We faced no complications during the tests. Table 3 shows the number of patients fulfilling the criteria for peak exercise (RPE=10 or RER>1, or HR>180) during both exercise tests. Two patients did not attain the RER>1 criterion in both tests. These patients stated on both occasions that they terminated the MXT due to local muscle fatigue. During the second testing occasion we faced some technical problems with the connection between the ECG-apparatus and the metabolic cart; therefore, there were no maximal heart rate data available for six MXTs.

Table 2. Descriptive statistics for peak cardiopulmonary values during the MXT.

	MXT 1			MXT 2		
	Mean	Sd	Range	Mean	Sd	Range
VO_{2peak} (in $L \cdot min^{-1}$)	1.12	0.38	0.47 - 2.03	1.14	0.34	0.53 - 2.0
VO_{2peak} (in $ml \cdot kg^{-1} \cdot min^{-1}$)	32.0	7.6	12.8 - 50.8	32.2	7.9	14.6 - 50.0
Peak HR	180	18.2	140 - 217	176	14.9	154 - 201
Peak RER	1.1	0.09	0.88 - 1.21	1.1	0.1	0.93 - 1.27
Peak RPE	8.7	2.3	4 - 10	9	1.7	5 - 10

Reliability

Standard error of measurement between the two assessments was calculated for the 23 patients. The calculated SEM was 9.5% (mean SEM: VO_2 0.16 $L \cdot min^{-1}$). The results of the individual VO_{2peak} attained during MXT 1 (in $L \cdot min^{-1}$) versus the differences in VO_{2peak} between MXT 2 and MXT 1 are presented in Figure 1. The random scatter around the zero level indicated that there were no learning effects between the two measurements.

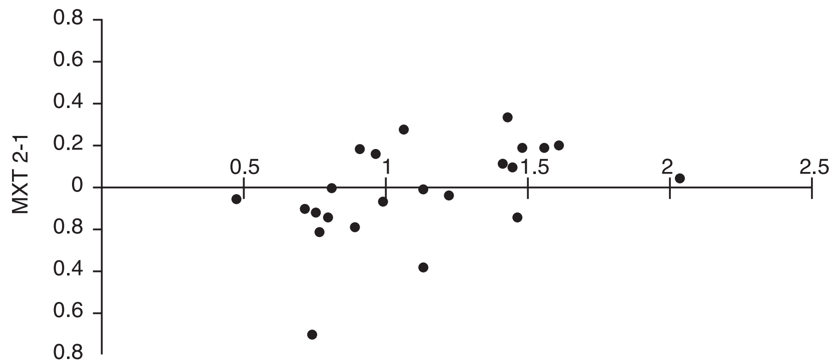


Figure 1.

VO_{2peak} attained in MXT 1 (in L · min^{-1}) versus the differences in VO_{2peak} between MXT 2 and MXT 1 (N=23).

Aerobic function

Figure 2 shows that in the majority of the JRA patients an impaired FAI was observed for absolute VO_{2peak} and relative VO_{2peak} (FAI > 0; $p < 0.001$). When absolute values of VO_{2peak} were compared, some of the OJRA patients had no impairment, and all PJRA and SJRA patients showed an impairment in FAI. Although there was a large difference between the OJRA and PJRA patients (FAI 18 % vs 27.8 %), this difference was not statistically significant ($p = 0.2$).

Table 3. Number of patients fulfilling each 'maximum criterion'.

Criterion	Number of Patients	
HR > 180	13	6
RER > 1.0	19	19
RPE = 10	13	15

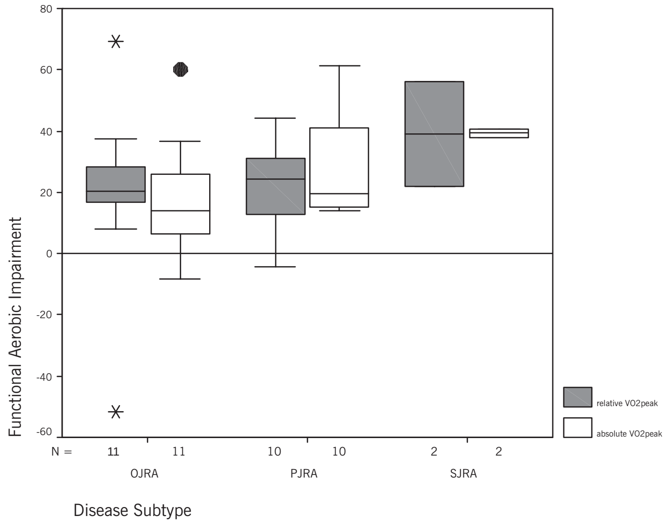


Figure 2.

Box-plot of the Functional Aerobic Impairment of oligoarticular JRA, polyarticular JRA and systemic JRA patients for both relative VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) and absolute VO_{2peak} ($L \cdot min^{-1}$).

Positive values of FAI indicates an impairment in aerobic fitness, negative values of FAI indicates an above average aerobic fitness.

The bars represent the highest and lowest values within 1.5 times the interquartile range (box length; IQR). The lower horizontal line of the box indicates the 25th percentile. The upper horizontal line indicates the 75th percentile. The mid horizontal bar in the box indicates the median. The ● symbol indicates an outlier between 1.5 and 3 IQR from the box, the * symbol indicates extremes lying over 3 times IQR from the box.

Relative VO_{2peak} values gave almost similar results of FAI as the absolute VO_{2peak} values; however, the differences between OJRA and PJRA group were less pronounced (FAI 19.7 % vs 22.6 %; p = 0.7). One OJRA patient, who was very lean, his results lied within the normal range when VO_{2peak} was expressed in absolute values of VO_{2peak}, but became an outlier when the VO_{2peak} was related to body mass. The three subgroups showed a large variation in magnitude of the impairment of physical fitness (see Figure 2).

Discussion

Since the body of knowledge of exercise testing in patients with JRA is limited, we investigated the feasibility of aerobic exercise testing in JRA patients, the error of measurement of MXTs, and the functional aerobic impairment of JRA patients.

Feasibility

The most frequently attained maximum criterion was RER > 1. This might be due to the fact that the JRA patients were deconditioned, and did rely more on carbohydrates as energy source at the same exercise intensity compared to healthy children. The higher peak post-exercise blood lactate levels of JRA patients compared to healthy controls found by Golebiowska et al.[5] confirms this hypothesis. The maximal oxygen uptake criteria are originally developed for the testing of healthy adults[17]. It is questionable whether these criteria are applicable to JRA patients. It seems that JRA patients are attaining a maximal effort at a lower peak HR with concurrently higher RER values as compared to healthy children.

It is important to know why patients have to terminate a MXT. Once the underlying limitation is apparent, effective interventions can be started to improve exercise capacity.

Limited range of motion did not restrict the bicycling activity of our patients to an extend that the MXT was impossible to continue to volitional exhaustion. Muscle weakness is a common characteristic in JRA patients[26,27]. Skeletal muscle weakness is associated with reduction in the cross-sectional area of muscle[27,28]. The suggestion of muscle weakness is also supported by data from Giannini and Protas[7,8] showing that peak HR of a group of juvenile arthritis patients during an MXT is significantly lower than peak HR of healthy controls, indicating that JRA patients terminated the MXT before reaching the maximum capacity of their cardiovascular system.

Pulmonary function abnormalities have also been reported in patients with JRA[29], but only in effort-dependent tests (e.g. forced vital capacity and peak expiratory flow). Peak expiratory and inspiratory power was reduced compared to healthy controls[29]. The authors concluded that the abnormal pulmonary function most likely was caused by weakness of the respiratory muscles. Thus, the limiting factor in exercise capacity of JRA patients might be muscular strength, and not the restricted joint range of motion, nor the capacity of the cardiovascular and pulmonary system.

Reliability

The standard error of measurement in our tests (9.5 %) was slightly lower than earlier reported coefficients of variability of 12 %[8] in children with JRA during MXTs. Our error level was somewhat higher than observations in healthy children[30]. The absolute SEM of VO_{2peak} was 0.16 $L \cdot min^{-1}$, and is well within the quality range of certified exercise physiology laboratories[31], and shows the reliability of our MXTs.

Aerobic function

Our observations showed that there are marked differences in impairment in aerobic fitness between patients and disease subclasses. The more severely diseased (PJRA and SJIA) patients had a slightly more pronounced impairment in aerobic fitness than the OJRA patients. This suggests that physical fitness might be affected by the number of joints involved in the arthritis. This finding is in accordance with the results of Malleson et al.[10], who found a negative association between disease severity and physical fitness in JRA patients. A possible explanation is that the more severely diseased patients have longer periods of inactivity resulting in a more decreased physical fitness.

The majority of the MXTs indicated a small impairment in aerobic fitness. On the other hand, these data show the importance of exercise testing, since especially children with PJRA and SJRA are at risk for a low aerobic fitness. To improve their aerobic fitness (lowering this risk factor for co morbidity), they must be identified and a physical training program must be started, in addition to their medical and physical therapeutical treatment, to enhance an active lifestyle. It is our experience that parents and patients with JRA are highly interested in adapted physical training programs for providing therapeutic and recreational exercises[32], and so far no negative effects of exercise programs have been reported[33,34].

Clinical implications

These data showed that maximal exercise testing of our study population of JRA patients was feasible. The SEM of MXTs in this patient group was well within the values generally accepted for exercise physiological measurements of VO_{2peak}. Because of the large differences in functional aerobic impairment between JRA patients, range: 65% above predicted to 69% lower than predicted, a generalization about the aerobic fitness in this population is difficult. Using maximum exercise tests, JRA patients with low aerobic fitness can be identified and exercise interventions can be initiated.

Conclusion

Maximum exercise testing was possible in this population of JRA patients, and can be a valuable tool in identifying patients with an impairment in aerobic fitness.

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Aerobic fitness in children with juvenile idiopathic arthritis: a systematic review

4

Tim Takken
Arlette Hemel
Janjaap van der Net
Paul J.M. Helders

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Abstract

Objective

To determine whether children with Juvenile Idiopathic Arthritis (JIA) have a 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) could be pooled in a meta-analysis. The VO_{2peak} of the JIA patients was 21.8 % (95 % CI: 13.7, 29.9) lower than healthy children ($p < 0.0001$).

Conclusions

The results of the meta-analysis suggest that children with JIA have a moderate-to-large impairment in physical fitness as represented by maximal oxygen consumption compared to healthy children.

Introduction

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 other known causes are excluded. In JIA seven 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 VO_{2peak} between JIA-patients and healthy age and sex matched controls. Data from Giannini & Protas[5,6], Klepper[7], Golebiowska et al.[8,9] and Hebestreit et al.[10] have suggested that JIA patients have a 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})[1] attained during a graded maximal exercise to volitional exhaustion (MXT) is considered as the single best indicator of aerobic physical fitness by the WHO[11] and can be reliably performed in JIA patients[6,12].

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

[1] 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.

Methods

Search strategy

Publications were selected based on a literature search from 1966 until October 2001 using the Medline, Cinahl, Embase and Sportdiscus database. Search terms "physical fitness", "exercise testing", "exercise", "exercise capacity", "exercise tolerance", "Juvenile Rheumatic Arthritis", "Juvenile Chronic Arthritis", "Juvenile Idiopathic Arthritis" were used. References of the 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. Only publications, in which directly measured values of VO_{2peak} (in $ml \cdot kg^{-1} \cdot min^{-1}$) were published, including a description of used methods, patient and control subject characteristics were included in this study. Data were extracted from the publications and entered into Review Manager 4.1 (Update Software, Oxford, U.K.). 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.

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 two means divided by an estimate of the within-group standard deviation and can be considered as an effect size. Negative values for SMD indicates a lower physical fitness of JIA patients 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 meta-analysis, because of incomplete VO_{2peak} data (no values and standard deviations reported) and it was not clear whether these patients were not included in their 1992 publication. 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-minute 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 meta-analysis. Because the standard deviation of this study was not published, we estimated the standard deviation using the weighted-pooled standard deviation of the other four included studies. In total, 144 JIA-patients 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, using 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 were based on the same concept in all studies. All children exercised until fatigue prevented further work.

In Table 3 the results of the meta-analysis are displayed. There was a significant heterogeneity between the included studies ($p = 0.021$). The SMD of -1.13 indicated that JIA-patients 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 values, VO_{2peak} was 21.8 % (95 % CI: 13.7; 29.9; $p < 0.0001$) lower for the JIA patients.

Table 1. Characteristics of included studies.

Study	JIA Patients/ Controls	Patients Age	Disease Subgroups	Ergometer	VO_{2peak} Determination	Protocol
Malleson 1996	30 / 15	8 - 17 yrs	OJIA, PJIA, SJIA, JSpA, Juvenile psoriatic arthritis	Cycle ergometer	Direct	15 Watt · min^{-1}
Golebiowska 1992	45 / 61	4 - 19 yrs	OJIA, PJIA, SJIA	Treadmill	Direct	Riopel†
Giannini 1992	30 / 30	7 - 17 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	25 Watt · 2 min^{-1}
Takken 2002	23 / RV	6 - 14 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	20 Watt · 3 min^{-1}
Giannini 1991	16 / 16	8 - 13 yrs	OJIA, PJIA	Cycle ergometer	Direct	25 Watt · 2 min^{-1}

Abbreviations: OJIA = oligoarticular JIA; PJIA = polyarticular JIA; SJIA = systemic JIA; JspA = Juvenile spondylarthropathy; † = Riopel protocol consists of keeping the treadmill belt speeds at 5.6 km · hr^{-1} and elevating the slope of the belt by 2° every minute until volitional exhaustion of the patient; RV= Reference Values.

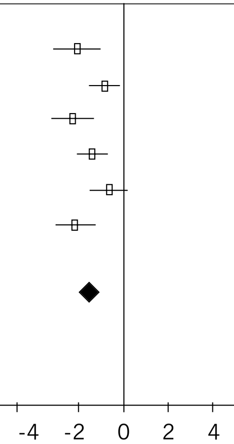
Table 2. Characteristics of excluded studies.

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

Abbreviations: HRPFT = Health Related Physical Fitness Test; OJIA = oligoarticular JIA; PJIA = polyarticular JIA; SJIA = systemic JIA ; JspA = Juvenile spondylarthropathy; NA = not available; † = Riopel protocol consists of keeping the treadmill belt speeds at 5.6 km/hr and elevating the slope of the belt by 2° every minute until volitional exhaustion of the patient; RV = Reference Values.

Table 3. Forrest-plot with the comparison of VO_{2peak} values of JIA patients with controls.

Study	JIA n	JIA mean(sd)	Control n	Control mean(sd)	SMD (95%CI Random)	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)
Golebiowkse 92 Boys	14	46.90 (8.37)	34	59.90 (7.13)		15.3	-1.70 (-2.42,-0.99)
Golebiowske 92 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							



n = number of subjects; mean (sd)= mean and sd of the VO_{2peak} (in ml·kg^{-1}·min^{-1}); SMD= standardized mean difference; weight (%) = the contribution of the study to the overall result; favours control = controls have a higher VO_{2peak} compared to JIA patients; favours 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.

Discussion

The purpose of this study was to determine whether children with JIA have a lower physical fitness compared to healthy children, and to determine the clinical relevance of this impairment.
The results of the meta-analysis suggests that JIA-patients have a significantly lower VO_{2peak} , which means that their physical fitness is lower than when compared to healthy children. However, there was a significant heterogeneity between studies, mainly caused by the study of Malleson et al.[4]. They did not find statistically significant differences between JIA-patients 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 this control group, because these control subjects might have an similar sedentary activity pattern as the JIA-patients, 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 statistical analysis showed a significant lower VO_{2peak} for JIA-patients compared to those reference values.

Physiology

What might cause the lower VO_{2peak} in JIA patients? VO_{2peak} is the product of cardiac output (heart rate x 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 · minute^{-1} (95 % CI -10, - 2.8) lower than in healthy controls during an MXT, indicating that some of the JIA patients terminated the exercise test before reaching the maximum capacity of their cardiovascular system. If the cardiovascular system was the limited 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 approximately 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 previously mentioned, the peak heart rate during a MXT is lower in JIA patients compared to healthy children. This indicates that the cardiovascular sys-

tem is not the limiting factor in oxygen uptake of JIA patients.
It is more likely, the limiting step is 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 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 an impaired lung function is the cause of the lower VO_{2peak}.
Muscular atrophy is also a common finding in JIA patients 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.
Muscular biopsy studies in children with JIA are, to our knowledge, not performed. Available evidence from studies with adult Rheumatoid Arthritis patients, suggests an atrophy in both type I and type II muscle fibers. The atrophy is most pronounced in the type II muscle fibers and can not be fully explained by disuse. It is suggested that muscle fibers are directly involved in the inflammation process[20]. Data from short-term and long-term 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, a 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

A SMD of -1.13 indicated a moderate-to-large impairment of physical fitness in JIA-patients. 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 a 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 physical 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 the deconditioning due to hypoactivity and break through the vicious circle, thus preventing this major risk factor for co morbidity.

The fact that JIA patients have an 8.6 $ml \cdot kg^{-1} \cdot min^{-1}$ lower VO_{2peak} might have large 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. Furthermore 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 approximately 20 years earlier compared to healthy control subjects. This could have a profound socio-economic impact when physical fitness is not maintained by physical training. Even more so for women, who have already a 30% lower VO_{2peak} compared to man[27].

Conclusions

In conclusion, this review showed that children with JIA have a moderate to large impairment in their VO_{2peak} compared to healthy children, indicating a 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. Long term exercise programs might be advisable for JIA-patients to improve physical fitness and reduce muscle atrophy.

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Relationship between functional ability and physical fitness in juvenile idiopathic arthritis (jia) patients

5

Tim Takken
Janjaap van der Net
Paul J. M. Helders

Submitted for publication

Abstract

Objective
To determine the existence of a relationship between aerobic and anaerobic physical fitness and functional ability in children with JIA.

Methods
Eighteen children with JIA (age 7 to 14 yr., 3 male / 15 female) performed an aerobic and anaerobic exercise test. Functional ability was concurrently assessed using the Childhood Health Assessment Questionnaire (CHAQ).

Results
A low relationship between aerobic fitness and functional ability was found. The correlations between anaerobic physical fitness and functional ability in JIA patients were strong. This is indicated a good relationship between anaerobic fitness and functional ability.

Conclusion
The strong association between anaerobic physical fitness and functional ability showed the importance of anaerobic physical fitness for children with JIA.

Introduction

Children with a chronic disease often have a lower physical fitness compared to healthy controls. They also have more problems in performing all kinds of activities of daily living (functional ability) compared to healthy controls. This finding also has been confirmed for children with JIA, they perform less activities of daily living, have a lower functional ability and aerobic and anaerobic physical fitness compared to active healthy children[1-5]. Bar-Or suggested a link between a low physical fitness and a low functional ability in pediatric chronic diseased patients[6]. However, little data exist linking physical fitness and functional ability in children with JIA. Only two studies exists suggesting a moderate relationship between isometric muscle strength and functional ability in juvenile arthritis patients[7,8]. No data exists whether aerobic and anaerobic physical fitness, as measured during a well-controlled laboratorium exercise test, could be related to functional ability in JIA patients.

Patients lacking the requisite physical fitness may not be able to perform various activities of daily living that are important determinants of independence. Therefore the purpose of this study was to determine the existence of a relationship between aerobic and anaerobic physical fitness and functional ability in children with JIA.

Methods

Patients

Eighteen patients (age 7 to 14 yr., 3 male / 15 female) participated in this study. JIA was diagnosed by a pediatric rheumatologist, and the patients were divided in three distinct types of JIA: oligoarticular JIA (OJIA; arthritis present in four or fewer joints); polyarticular JIA (PJIA; 5 or more joints affected with arthritis without systemic manifestations); systemic JIA (SJIA; characterized by intermittent fever, rheumatoid rash, and arthritis). The characteristics of the patients at baseline are presented in Table 1. All patients were receiving a local and/or a systemic arthritis related therapy consisting of non-steroid anti-inflammatory drugs and/or disease modifying anti-rheumatic drugs and/or immunosuppressive drugs/steroids in the last 6 months prior inclusion. All subjects were recruited from the pediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. Parents gave their informed consent for participating in the study. All procedures were approved by the local medical ethical committee.

Table 1. Patients Characteristics.

JIA Patients (N=18)	
Age (years: mean ± SD)	10.7 (± 1.7)
Body Mass Index (in kg · m^{-2}: mean ± SD)	18.5 (± 2.8)
Weight (in kg: mean ± SD)	39.1 (± 10.2)
Σ7-Skinfolds (in mm: mean ± SD)	110.3 (± 43.6)
Disease Subclass	9 OJIA / 7 PJIA / 2 SJIA
pEPMROM (mean ± SD)	0.2 (± 0.2)
Number of Swollen Joints (mean ± SD)	2.4 (± 3.1)
Years of Arthritis (in years: mean ± SD)	6.3 (± 2.3)

pEPMROM = Pediatric Escola Paulista de Medicina Range of Motion Scale.

Joint range of motion

Joint range of motion was assessed using the pediatric Escola Paulista de Medicina range of motion scale (pEPMROM)[9]. Ten joint movements (cervical spine [rotation], shoulder [abduction], wrist [flexion and extension], thumb [flexion metacarpophalangeal], 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 the mean joint score at each movement divided by 10, providing a final range of scores for joint movement from 0 to 3.

Anthropometry

The patient's body mass and height were determined using an electronic scale and a measuring stick. Body composition was assessed using the sum of seven skinfolds method according Pollack et al.[10] The measurements were taken at 7 sites (at the right side of the body); triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf and thigh by the test leader in accordance with the American College of Sports Medicine guidelines[11].

Aerobic Physical Fitness

The maximal oxygen consumption attained during a graded maximal exercise to volitional exhaustion (MXT) is considered as the single best indicator of aerobic physical fitness by the WHO[12] and is a reliable test in JIA patients[13]. Subjects performed a MXT using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The seat height of the ergometer was adjusted to the patient's leg length. Three minutes of unloaded cycling preceded the application of resistance to the ergometer. Thereafter, the workload was increased by the constant increment of 20 Watts every 3 minutes. This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the experimenters. During the MXT, subjects breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Mijnhart, Bunnik, the Netherlands). Expired gas was passed through a flowmeter, an oxygen (O_2) analyzer and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (Ve), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER) from conventional equations. Heart rate (HR) was measured continuously during the MXT by a bipolar electrocardiogram. Absolute peak oxygen consumption was taken as the average value over the last 30 sec during the maximal exercise test. Relative VO_{2peak} was calculated as absolute VO_{2peak} divided by body mass.

Anaerobic Physical Fitness

The Wingate anaerobic test (WaNT) as described by Bar-Or[14] was performed on a recently calibrated electromagnetic braked bicycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The ergometer was upgraded by the manufacturer to a maximal resistance of 800 Watt instead of the standard 400 Watt. The external resistance was controlled and the power output was measured using the Lode Wingate software package. The external load (torque; in N·m) was determined, dependent of bodyweight (at 0.53 × bodyweight and 0.55 × bodyweight for girls and boys respectively) according to the user manual. This test has been used in different pediatric patient groups, and has been shown to be reliable[15,16] and valid against other measures of anaerobic performance[17].

The seat height was adjusted to the patients leg length (comfortable cycling height). Thereafter the patients' feet were put in the Velcro toe-straps and the exercise protocol was explained. The patients were instructed to exercise for 1 minute at the cycle ergometer with an external load of 15 Watt at 50 Rpm's. Hereafter the sprint protocol started. The patients were instructed to cycle all-out for 30 seconds. Obtained variables (mean power and peak power) were corrected for the inertia of the mass of the flywheel.

Functional Ability

The Dutch translation of the Childhood Health Assessment Questionnaire (CHAQ) was used as a self-administered pencil and paper questionnaire for the parents (proxy), as an index of functional ability. The CHAQ[18] has been adapted from the Stanford Health Assessment Questionnaire so that at least one question in each domain is relevant to children aged 0.6 to 19 years. The CHAQ was recently cross-culturally adapted and validated for the Dutch language[2]. The question with the highest score within each domain (range 0 to 3; able to do with no difficulty = 0, able to do with some difficulty = 1, able to do with much difficulty = 2, unable to do = 3, time frame was last week) determined the score for that domain, unless aids or assistance was required (raising the score for that domain to a minimum of 2). The mean of the scores on the eight domains provided the CHAQ disability score (range 0 to 3).

Statistics

All data were entered and analyzed in SPSS 9.0 for Windows (SPSS, Chicago, Ill). Spearman's correlation coefficients were calculated to describe the relationships between aerobic an anaerobic physical fitness and the CHAQ disability score. Alpha level was set at $p < 0.05$ for all analyses.

Results

Descriptive statistics for the aerobic and anaerobic physical fitness tests and CHAQ disability score are displayed in Table 2. The wide range of subject characteristics shows the variation in physique of JIA patients and reflect an overall moderately impaired function.

Spearman's correlations between parameters of aerobic and anaerobic physical fitness and CHAQ disability scores and its subscales are displayed in Table 3 and show a low relationship between aerobic fitness and functional ability. On the other hand, the correlations between the two indices of anaerobic performance and functional ability in JIA patients were large for the CHAQ disability scores

Table 2. Descriptive statistics for peak values of the aerobic and anaerobic exercise tests.

	Mean	Sd	Range
Absolute VO_{2peak} (in $L \cdot min^{-1}$)	1.21	0.33	0.73 - 2.0
Relative VO^{2peak} (in $ml \cdot min^{-1} \cdot kg^{-1}$)	31.98	8.5	14.6 - 50.0
Peak Power WaNT (in Watt)	316.4	148.8	105 - 633
Mean Power WaNT (in Watt)	195.4	75.6	91 - 349
CHAQ Disability Score	0.81†		0.37 - 1.6*

† = Median; * = Interquartile range.

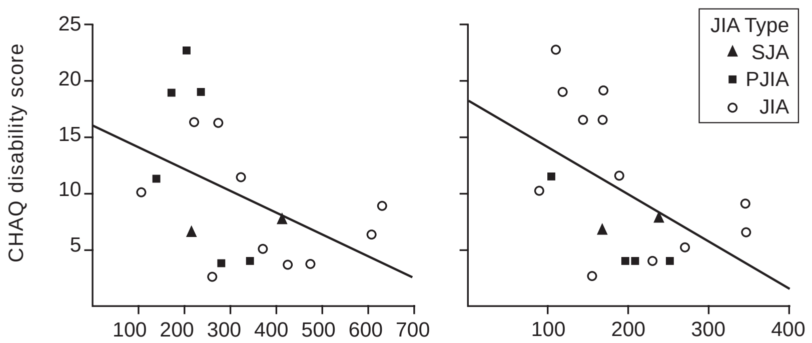

Figure 1A-B.

Relationship between functional ability (CHAQ disability score) and Peak Power (left panel) and functional ability (CHAQ disability score) and Mean Power on the WaNT (right panel).

and dressing/grooming and hygiene subscales and moderate for eating, walking and arising subscales. This indicated the good relationship between anaerobic fitness and functional ability.

The relationship between peak power on the WaNT and the CHAQ disability score is shown in Figure 1A and indicates a negative relationship between these

Table 3. Spearman correlation coefficients between Functional Ability and Physical Fitness.

	AbsoluteVO_{2peak}	RelativeVO_{2peak}	Peak Power WaNT	Mean Power WaNT
CHAQ Disability Score	-0.289	0.132	-0.528*	-0.527*
Subscales:				
Dressing and Grooming	-0.44	-0.020	-0.530*	-0.600*
Arising	0.004	0.28	-0.444	-0.475*
Eating	-0.469*	0.093	-0.464	-0.536*
Walking	0.003	0.307	-0.457	-0.473*
Hygiene	-0.452	0.2	-0.782*	-0.765*
Reach	0.079	0.153	-0.258	-0.299
Grip	0.14	0.199	-0.246	-0.224
Activities	-0.025	0.203	-0.380	-0.357

* = $p < 0.05$

variables. The relationship between mean power on the WaNT and the CHAQ is shown in Figure 1B, and also suggests a negative relationship between these two variables, with a floor effect at approximately 300 Watts. Patients with a lower anaerobic physical fitness show a higher degree of functional disability compared to the patients who perform better on the WaNT.

Discussion

The purpose of this study was to determine whether there is a relationship between aerobic and anaerobic physical fitness and functional ability in children with JIA. Although factors related to functional ability and disability could be explored using aerobic and anaerobic physical fitness tests, it is not common to perform these fitness tests in children with JIA, because most rheumatology health professionals are not trained in performing these kind of exercise tests. There is a paucity of research investigating the aerobic physical fitness of children with Juvenile Arthritis[5]; the anaerobic physical fitness of juvenile arthritic patients is even less investigated[3,4,19]. In juvenile arthritic patients, the relationship between aerobic and anaerobic physical fitness and functional ability has to our knowledge never been explored before.

Surprisingly no relationship could be observed between VO_{2peak} and CHAQ disability scores as the current goal for exercise programs for JIA patients is the improvement of aerobic physical fitness. The improvement in aerobic physical fitness might have more long-term benefits for these patients than short-term benefits in terms of an improved functional ability. On the contrary to aerobic physical fitness, there was a strong relationship between anaerobic physical fitness and functional ability. Especially dressing/grooming, hygiene and walking were correlated to anaerobic physical fitness. Thus children need a certain level of physical fitness for performing all kinds of activities of daily living. Observations of children's activity patterns are suggesting that the majority of these activities can be characterized by short intense bursts of activities[20]. An impaired physical fitness means that certain activities cannot be performed at the same pace as healthy children, or cannot be performed at all.

This type of activity patterns in children might explain the better relationship between anaerobic physical fitness compared to aerobic physical fitness. In adulthood, the activity patterns shift towards an aerobic activity pattern. This would make aerobic physical fitness more important with increasing age of the patients.

As shown in Figures 1A and 1B, there seems to be a floor effect in the relationship between anaerobic physical fitness and functional ability at around 300 Watt mean power over the 30 sec all-out sprint of the WaNT. The CHAQ seems to be insensitive to detect small levels of disability.

JIA patients often have a lower muscle bulk compared to healthy subjects[21-23]. This atrophy is still evident after some years without disease flares, and is more pronounced in children with a disease onset before the age of 3[23]. A lower muscle mass implies a smaller muscle mass to consume oxygen and to generate a certain power output during the 30 second sprint test. Suggestions for the cause of the diminished muscle mass are inactivity, disease activity, (inflammatory parameters such as TNF alpha[24]), and medication, (for example Cyclosporine A[25] and prednisone[26]).

Muscular biopsy studies in children with JIA are, to our knowledge, not performed. Available evidence from studies with adult Rheumatoid Arthritis patients, suggests an atrophy in both type I and type II muscle fibers, however the atrophy is most pronounced in the type II muscle fibers[27]. As the anaerobic exercise performance is heavily dependent on number and size of type II muscle fibers, it is not surprising that the anaerobic physical fitness of JIA patients is impaired.

This current finding does not imply that we should no longer focus on aerobic physical training programs. Recent (pilot) studies from both healthy children and patients with JIA are showing an improvement in anaerobic physical fitness after performing an aerobic training program[19,28,29]. Moreover, aerobic physical fitness is a strong indicator of functional ability and mortality in adulthood[30,31]. Long-term follow-up studies into adulthood might confirm this transition in the relationship between physical fitness and functional ability.

In conclusion, this study significantly adds to the body of knowledge on the relationship between physical fitness and functional ability in JIA patients. The strong association between anaerobic physical fitness and functional ability shows the importance of anaerobic physical fitness for children with JIA. These results may give further directions to exercise training interventions in this patient group. Further long-term follow-up studies are indicated to better understand the relation between physical fitness and functional ability with increasing age of patients.

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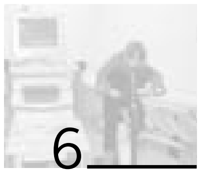
Physical activity and health-related physical fitness in children with juvenile idiopathic arthritis



6

Tim Takken
Janjaap van der Net
Wietse Kuis
Paul J.M. Helders

Submitted for publication

Abstract

Objective
The objective of this study was to get more insight into the interaction between daily physical activity and components of health-related physical fitness in children with Juvenile Idiopathic Arthritis.

Methods
Forty-nine patients (mean age 8.8 (± 2.2) years, 10 male / 39 female) participated in this study. Body mass, height, skin fold thickness, number of swollen joints and joint range of motion were determined. The maximal oxygen consumption (VO_{2peak}) was assessed during a graded maximal bicycle exercise test. Daily physical activity levels were measured using a Caltrac™ Activity Monitor, and a parental physical activity rating (PAL) on a 5-point Likert-scale.

Results
Partial correlation coefficients (to control for age) between physical activity and indices of health related physical fitness showed significant relationships between Caltrac™ motion counts and absolute VO_{2peak} ($r = 0.31$) and relative VO_{2peak} ($r = 0.34$), but not with the indices of body composition. There was also a significant correlation between PAL and relative VO_{2peak} ($r = 0.33$).

Conclusions
Physical activity was significantly related to cardio-respiratory fitness but not with body composition in children with Juvenile Idiopathic Arthritis. A longitudinal follow-up should reveal whether an active lifestyle protects for loss of aerobic fitness in this patient group.

Introduction

Health-related physical fitness of a patient is dependent on both lifestyle-related factors such as daily physical activity levels and nutritional habits, as well as genetic factors, and is an important indicator of health status. Health-related physical fitness consists of different components of which body composition and cardio-respiratory fitness (maximal oxygen consumption) are the most important ones.

A low physical fitness is associated with a higher mortality rate, a higher risk in certain forms of cancer, obesity, decreased mental health, diabetes, hypertension and a lower quality of life[1,2]. A recent study showed that every increase of maximal oxygen consumption gives a reduction in overall mortality in a clinical, adult population[3]. For children and adolescents with a disability or chronic disease, physical fitness is no less important[4]. Maintaining and improving physical fitness better prepare children and adolescents with a chronic disease for entering adulthood with a sound basis for their future health and prevent inactivity-induced diseases[2]. Children with Juvenile Idiopathic Arthritis (JIA) have lower activity levels than their healthy peers. They participate significantly less in strenuous activities compared to healthy peers[5].

This might cause the reduced cardio-respiratory fitness in children with JIA[6]. However, medication and inflammation-related factors might also contribute to this reduced exercise capacity. In the literature, data is lacking which could indicate as to whether there is a relationship between physical activity and physical fitness in JIA patients.

Therefore, the purpose of this study was to get more insight into the interaction between daily physical activity and components of health-related physical fitness in children with JIA.

Methods

Patients

Forty-nine patients (mean age 8.8 (± 2.2) years, 10 male / 39 female) participated in this study. JIA was diagnosed by a pediatric rheumatologist. The patients were divided in three distinct types of JIA: oligoarticular JIA (OJIA; arthritis present in four or fewer joints); polyarticular JIA (PJIA; 5 or more joints affected with arthritis without systemic manifestations); systemic JIA (SJIA; characterized by intermittent fever, rheumatoid rash, and arthritis). The characteristics of the patients are presented in Table 1. All patients were receiving a local and/or a systemic arthritis related therapy consisting of non-steroid anti-inflammatory drugs and/or disease modifying anti-rheumatic drugs and/or immunosuppressive drugs/steroids in the last 6 months prior to inclusion. All subjects were recruited from the pediatric rheumatology outpatient clinics of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands and the University Hospital Groningen, the Netherlands. Parents gave their informed consent for participating in the study. All procedures were approved by the local medical ethical committees.

Table 1. Subject characteristics.

	Min	Max	Mean	Sd
Age of Onset	0.9	10	4.3	2.7
Height (meters)	1.15	1.6	1.35	0.12
Weight (kg)	19	63	32.46	10.48
Number of Swollen Joints	0	8	1.6	2.1
EPMROM Score	0	0.9	0.17	0.21
CHAQ Disability Score	0	2	0.79	0.58
Disease Subclass	25 OJIA, 20 PJIA, 4 SJIA			

Anthropometry

The patient's body mass and height were determined using an electronic scale and a stadiometer. Body Mass Index (BMI) was calculated as weight · height^{-2}. Body surface area (BSA) was calculated according to the formula of Haycock et al.[7]. Subcutaneous adiposity was assessed using the sum of seven skin folds method (Σ7SF) according to Pollock et al.[8]. The measurements were taken at 7 sites (at the right side of the body); triceps, biceps, sub scapular, suprailiac, mid-abdominal, medial calf and thigh by the test leader (TT) in accordance with the American College of Sports Medicine guidelines[9]. The measurements were taken with Harpenden calipers (Baty International, Burgess Hill, Sussex, U.K.).

Joint range of motion

Joint range of motion was assessed using the pediatric Escola Paulista de Medicina range of motion scale (EPMROM)[10]. Ten joint movements (cervical spine [rotation], shoulder [abduction], wrist [flexion and extension], thumb [flexion metacarpophalangeal], 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 the mean joint score at each movement divided by 10, providing a final range of scores for joint movement (range 0-2).

Functional Ability

The Dutch translation of the Childhood Health Assessment Questionnaire (CHAQ) was used as a self-administered pencil and paper questionnaire for the parents (proxy), as an index of functional ability. The CHAQ[11] has been adapted from the Stanford Health Assessment Questionnaire so that at least one question in each domain is relevant to children aged 0.6 to 19 years. The CHAQ was recently cross-culturally adapted and validated for the Dutch language by the PRINTO group[12]. The question with the highest score within each domain (range 0 to 3; able to do with no difficulty = 0, able to do with some difficulty = 1, able to do with much difficulty=2, unable to do=3, time frame was last week) determined the score for that domain, unless aids or assistance was required (raising the score for that domain to a minimum of 2). The mean of the scores on the eight domains provided the CHAQ disability score (range 0 to 3).

Aerobic Physical Fitness

The maximal oxygen consumption attained during a graded maximal exercise to volitional exhaustion is considered as the single best indicator of aerobic physical fitness by the WHO[13] and is a reliable test in JIA patients[6]. Subjects performed a maximal exercise test using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). Five patients who did not fit on this ergometer were tested on a mechanically braked ergometer (Tunturi, Finland). The seat height of the ergometer was adjusted to the patient's leg length. Three minutes of unloaded cycling preceded the application of resistance to the ergometer. Thereafter, the workload was increased by the constant increment of 20 Watts every 3 minutes. This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the experimenters. During the maximal exercise test, subjects breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Mijnhart, Bunnik, the Netherlands). Expired gas was passed through a flow meter, an oxygen (O_2) analyzer and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (Ve), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER) from conventional equations. Heart rate (HR) was measured continuously during the maximal exercise test by a bipolar electrocardiogram. Absolute peak oxygen consumption was taken as the average value over the last 30 sec during the maximal exercise test. Relative VO_{2peak} was calculated as absolute VO_{2peak} divided by body mass.

Physical Activity

As index for the daily physical activity the children were asked to wear a Caltrac™ Activity Monitor (Muscle Dynamics Fitness Network, Inc, Torrance, Ca. USA) for 4 consecutive days (Friday, Saturday, Sunday and Monday). The Caltrac™ is a portable electronic accelerometer approximately the size and weight of a pocket calculator that is placed on the right hip and measures movements in the vertical plane. The Caltrac™ sums and integrates the absolute value of the acceleration versus time curve and derives a numerical count that is displayed on the monitor. The Caltrac™ was programmed with the following variables to overrule the internal program (Sex = 0, Age = 99, weight = 25, height = 36), in accordance with the recommendations of Sallis et al.[14] In this mode, body movements were expressed as motion counts. The number on the display was recorded twice daily, in the morning after rising and in the evening at bedtime. Motion counts were recorded each day and then averaged for the four days worn. The Caltrac™ has been used and validated in various studies of healthy[15,16] and diseased children including Juvenile Arthritis[5].

Additionally, parents were asked to rate their child's usual level of physical activity (PAL) on a 5 points scale: 1 = inactive, 2 = occasionally active, 3 = moderate active, 4 = active, 5 = very active, after Rowland[17].

Statistics

All data were entered and analyzed in SPSS 9.0 for Windows. Pearson's and Spearman's correlations were calculated where appropriate for finding associations. Partial correlation coefficients between physical activity and indices of health related physical fitness were calculated to control for age. Coefficient of variation of the Caltrac™ was calculated as the standard deviation in counts over the 4-day period divided by the average of the Caltrac™ motion counts over the 4-day period. A priori, an alpha of <0.05 was considered as statistically significant.

Results

The clinical and functional characteristics of the subjects on physical activity and physical fitness are shown in Table 2. The wide range of subject characteristics shows the variation in physique of JIA patients and reflect an overall moderately impaired function. In 4 children the data of the exercise test were missing. In one occasion this was due to the failure of the equipment, one patient was to sick to perform a maximal exercise test and two patients refused to wear a face mask during the maximal exercise test, therefore no ventilatory parameters could be obtained. The values we found for relative VO_{2peak} were lower compared to typical values for healthy children. Rowland[18] summarizing the literature, found typical values for VO_{2peak} in healthy children between 45 and 60 $ml \cdot kg^{-1} \cdot min^{-1}$. The range of VO_{2peak} values of our subjects was lower compared to these values. Results from a recent systematic review confirm this finding[19].
The Caltrac™ motion counts are lower compared to values found by Henderson et al.[5] They measured on average 123 $counts \cdot day^{-1}$ during a 3-day measuring period. Overruling the internal program of the Caltrac™ might cause these differences. It is not clear from their methods if Henderson et al.[5] used the same

Table 2. Subject characteristics on physical activity and physical fitness.

	Min	Max	Mean	Sd
VO_{2peak} ($L \cdot min^{-1}$)	0.39	2.0	1.07	0.32
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	14.6	50.39	33.9	8.5
BMI ($kg \cdot m^{-2}$)	14.12	25.24	17.27	2.82
BSA (m^2)	0.78	1.68	1.095	0.22
Σ7SF (mm)	41.17	246.7	98.2	47.17
Caltrac™ Counts	19	138	84.9	23.25
PAL	1	5	2.8	0.96

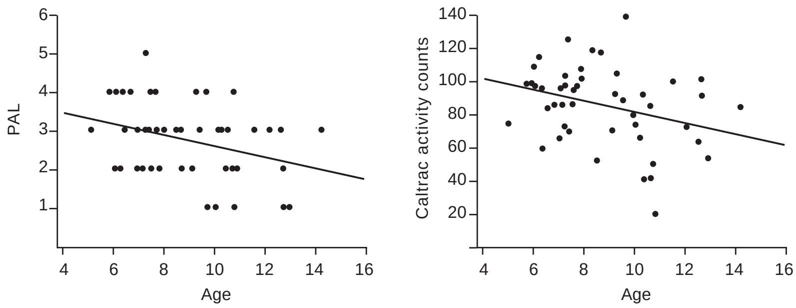


Figure 1A-B.

The relationship between physical activity and age. The left panel represents the relationship between age and Caltrac™ activity counts. The right panel shows the relationship between age and parental rated physical activity levels (PAL).

settings for the activity monitor. Sallis et al.[14] using the same monitors and setting found an average Caltrac™ activity count of 103 counts · day^{-1}, which is 22 % higher than the 84 counts · day^{-1} we found in this sample of JIA patients.
The average day-to-day variation in Caltrac™ motion counts (coefficient of variation) was 32 (± 15.4) %. The correlation between Caltrac™ motion counts and PAL was weak, r = 0.23 (p = 0.12). There was a significant inverse relationship between Caltrac™ motion counts, PAL and age (r = -0.31, p = 0.03; r = -0.33, p = 0.023 respectively) as shown in Figure 1. Therefore all correlations were controlled for age. It

Table 3. Partial correlation coefficients (controlled for age) between physical activity and health related physical fitness.

	Abs.VO_{2peak}	Rel. VO_{2peak}	BMI	BSA	S7SF	Weight	Height	EPMROM	Swollen Joints
Caltrac™ Counts	0.31*	0.34*	-0.05	-0.17	-0.13	-0.2	-0.16	-0.11	-0.16
PAL	0.24	0.33*	0.24	-0.08	-0.05	0.18	-0.13	-0.2	-0.33*

Abs.VO_{2peak} = Absolute VO_{2peak} (in L · min^{-1}); Rel. VO_{2peak} = relative VO_{2peak} (in ml · kg^{-1} · min^{-1}); * p<0.05.

was also typical for the activity level of JIA patients, that only one patient in this sample had a PAL rating of 5 (very active).

The relationship between physical activity and health-related physical fitness can be appreciated from Table 3. When controlled for age, there was still a significant relationship between physical activity and absolute and relative VO_{2peak}, but not with other anthropometrical variables, except for swollen joints and PAL.

Discussion

The main objective of this study was to determine whether there exists a relationship between physical activity and health-related physical fitness in patients with JIA. To our knowledge, this is the first study studying this relationship in JIA patients. There was a large variation in indicators of health-related physical fitness, this was also observed previously in a smaller sample of JIA patients[6]. Klepper et al. found also a larger variation in physical fitness in juvenile arthritis patients compared to healthy children. This variation might be due to differences in environment, genetics, disease course disease activity at time of the study, impairments and concurrent medication.

The current data of VO_{2peak} values of our subjects indicate that they have an impaired aerobic exercise capacity. This impairment in VO_{2peak} can have enormous effects on mortality in adult life. A recent publication showed that every increase of VO_{2peak} with 1 MET (Metabolic Equivalent = 3.5 ml · kg^{-1} · min^{-1}) results in a 12% decrease in mortality[3]. Improving physical fitness is a sound investment in future health.

Currently there is no gold standard for measuring physical activity. Many attempts have been made including doubly labeled water; heart-rate monitors, activity monitors, questionnaires, and recently Global Positioning System tracking devices. But all methods have their drawbacks, in terms of costs, practical usability, social acceptance, accuracy, etc.[20].

In this study physical activity was assessed by a short questionnaire and a simple accelerometer. The large day-to-day variability in the Caltrac™ activity counts shows the difficulties in assessing the physical activity of JIA patients. This high variability might as well reflect the day-to-day variations in disease activity and well being in patients with a rheumatic disease, a clinically well-known feature in JIA. Recent research investigated how many days are necessary for a reliable assessment of physical activities in children, and concluded that a 3 to 5 days

monitoring period including weekend days was sufficient[21]. Maybe a longer period is necessary in JIA patients because of this variability in disease activity and well being.
The physical activity levels decreased with age. This trend is also seen in cross-sectional[22] and longitudinal studies in healthy children[23]. However as JIA patients have already lower VO_{2peak} values at early ages, it should be encouraged to increase physical activity in this patient group, especially in the older age groups. When physical fitness was related to physical activity we found an increase in physical fitness with increasing physical activity levels. It is difficult to determine what is the cause and what is the effect, because physical fitness and physical activity are circular arguments. A decrease in physical fitness causes a low physical activity, which causes again a low physical fitness[24].
Our results indicated that body composition (weight, skin folds etc.) has much lower associations with physical activity compared to physical fitness. Body composition is not only dependent on physical activity (energy expenditure), but also dependent on eating habits (energy intake). The difference between energy expenditure and energy intake, combined with an individual genetic make-up, determines body composition. Occasionally (endocrine change e.g.) due to prednisone medication, both aspects are involved. In our study population prednisone treatment was administered in 3 patients. The correlation between PAL and swollen joints indicated that the more severe diseased children (larger number of swollen joints) were less active.
Morrow and Freedson[25] found in a review paper, only small relationships between physical activity and VO_{2peak} in healthy children with a typical correlation of 0.16 to 0.17. It has been suggested that healthy children have such a high level of physical activity, that extra physical activity will only result in a small improvement in VO_{2peak} (ceiling effect)[17,26]. Therefore, there is only a low to moderate the relationship between physical activity and VO_{2peak} in healthy children. However, chronically ill patients, have lower physical activity levels, and will not have this ceiling effect. In this patient group, the correlation between physical activity and VO_{2peak} is expected to be higher.
The correlation found in the current research is almost double compared to healthy children; we found moderate correlation of 0.3 between physical activity and VO_{2peak} in sick children. This indicates that physical activity is an important instrument for children with a chronic disease to become physical fit, and stresses the importance of creating exercise opportunities so patients with JIA could participate in (adapted) physical activities and sports. A low physical fitness has

major impact on health, and quality of life[2]. It has been shown from studies that from the second decade of life the VO_{2peak} decreases with 0.41 ml · kg^{-1} · min^{-1} yearly[27], implying that a lower physical fitness could also result in early disability to perform activities of daily living in later life[2,19].

In the past, there was much concern on the safety of physical exercise for children with JIA. Historically, bed rest formed the cornerstone of treatment in rheumatic diseases, and at the end of last century only mild graded exercise was applied in these children. Vigorous exercise was believed to have detrimental effects on disease activity and joint erosiveness[28]. However, Klepper[29] and Kirchheimer et al.[30] both found that children with JIA could safely participate in physical activities. Moreover, Klepper[29] showed that is save to involve children with JIA in vigorous weight-bearing exercise.

Klepper[29] performed an 8-week intensive weight-bearing exercise program in 25 children with polyarticular arthritis and found no disease exacerbations or deteriorations in joint swelling and tenderness score.

However, one must bear in mind that these patients do have a diminished load-bearing capacity because of their inflammatory disease and the immune suppressive medication. Exercise training might improve immune function[31], a training load which is too large might easily lead to overreaching or over training, as is often seen in athletes with a compromised immune system[32]. Medical specialists and health-care professionals should, therefore, find a balance between training load and load-bearing capacity of each individual patient. This and future longitudinal studies in this field should provide the tools for individual tailoring of exercise programs.

Conclusion

The data from this cross-sectional study suggest that activity patterns of JIA patients are decreasing between 5 and 14 years of age. Physical activity was significantly related to cardio-respiratory fitness but not with body composition. A longitudinal follow-up should reveal whether an active lifestyle protects for loss of aerobic fitness in this patient group.

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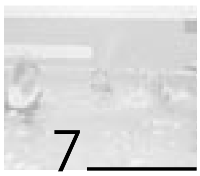

7

Aquatic fitness training for children with juvenile idiopathic arthritis

Tim Takken
Janjaap van der Net
Wietse Kuis
Paul J.M. Helders

Submitted for publication.

Abstract

Objective
To evaluate the effects of an aquatic training program for JIA-patients.

Methods
Fifty-four patients with JIA (age range 5 to13 years) participated in this study and were randomised into an experimental (N = 27) and a control (N = 27) group. The children in the experimental group received a training program consisting of a 1 hour a week supervised training program in a local pool of approximately 20 sessions. Effects were analysed on the following domains: functional ability, health-related quality of life, joint status and physical fitness.

Results
Although all measures improved more in the experimental group compared to the control group, none of the differences became statistically significant.

Conclusion
The current research found no significant effect of an aquatic fitness-training program in children with JIA. Since there were no signs for worsening in health status, one can conclude that this was a save exercise program.

Introduction

Patients with Juvenile Idiopathic Arthritis (JIA) show a decreased physical fitness compared to healthy children[1]. JIA patients perform also less strenuous physically activities compared to their healthy peers[2], and are often restricted in their activities of daily living. They may experience a limitation in functioning in one or more joints, stiffness or fatigue due to the arthritis. This may have considerable impact on the patients daily functioning. For decades, rest was thought to be, besides medication, the predominant treatment for children with JIA and adults with rheumatoid arthritis (RA)[3]. This attitude recently altered. In the past, major concerns were on the detrimental effects of physical exercise; now-a-days evidence is growing on the beneficial effects of regular exercise for arthritis patients[4,5]. Since aquatic therapy has been used for centuries to treat musculoskeletal disorders[4], and has proven to be save in adult RA patients[6], and a very enjoyable form of therapy for children[7], we developed an aquatic aerobic physical training program for JIA patients.
Previously published studies on the effects of physical training programs for JIA patients were small pilot studies[8-11], were not controlled by randomisation[7,12,13], and had small sample size. In a previous publication we described the pilot study for this larger randomised clinical trial[10]. In the previous conducted studies on this topic in JIA, the main focus was on improvements in physical fitness and on impairments like joint swelling and range of motion. None of the previous studies used contemporary, and recently validated, functional assessment tools (e.g. Childhood Health Assessment Questionnaire) as outcome measure for their study. As these instruments are more and more accepted as outcome measures in clinical trials in paediatric rheumatology, it is important for the comparison with other studies, to include these instruments as an outcome measure in an intervention study. Therefore, we studied the effects of an aquatic training program, on physical fitness, functional ability, joint status, and health-related quality of life in a randomised-controlled design.

Methods

Subjects

Fifty-four patients (40 girls, 14 boys) diagnosed with JIA, where recruited from the paediatric rheumatology outpatient clinics of the Wilhelmina Children's

Hospital, University Medical Center Utrecht, the Netherlands and the University Hospital Groningen, the Netherlands. Inclusion criteria were: diagnosed with JIA by a medical specialist (EULAR-criteria or ILAR-criteria[14]; a phase of remission without medication of no longer than 6 months in the absence of joint pain, tenderness, and/or morning stiffness and a erythrocyte sedimentation rate within normal limits. All patients were receiving a local and/or a systemic arthritis related therapy consisting of NSAID's and/or Disease Modifying Anti-Rheumatic Drugs and/or Immunosuppressive medication and/or steroids in the last 6 months prior inclusion.

Exclusion criteria were: a systemic disease with fever, low haemoglobin level and a general feeling of malaise; exercise contraindication by medical specialist; having received a bone marrow transplantation; and not feeling confident in water.

The characteristics of the patients are described in Table 1. The children and parents were informed of all aspects of the study, and written consent was obtained. The human ethical committees of the University Medical Center Utrecht/ Wilhelmina Children's Hospital and the University Hospital Groningen approved the study.

Design

Patients were stratified to disease subclass (two strata: an oligoarticular JIA group and a polyarticular (with or without systemic onset) JIA) and individually randomly assigned to the assessment only group (Con-group) or the training group (Exp-group) by an off-site data-manager. Three measurements were included in the study protocol, (T1) just before the start of the training program, (T2) 3 months after start, and (T3) immediately after the end of the training program. The investigators and the subjects were blinded for previous measurements at each stage of the evaluation; the investigators and subjects were not blinded for the group allocation of each subject.

Training program

All patients received the usual care and medical treatment during the study. The patients in the Exp-group received an aquatic group (2-4 children/group) exercise program, 1 hr a week, supervised by an instructed community physical therapist. If there was only one patient at a certain training location, the patient was allowed to bring a relative or friend to join the training program. The training took place in heated (30-33°C) community-based pools at twenty different locations throughout The Netherlands. The training program was conducted within a half-year period. Due to holidays, seasonal holidays and pool maintenance, the program consisted of approximately twenty training sessions on the different locations.

The program was available on paper and on instructional videotape, and consisted predominantly of aerobic exercises. Training sessions were based on the same framework. The training started with a warm-up, followed by an aerobic conditioning part, a short rest period, again followed by a second conditioning part. The training ended with a cooling-down. The warm- up, rest, and cooling down periods consisted of low intensity swimming, aquarobics, play, flexibility exercises, or ball games. The conditioning parts consisted mainly of high intensity swimming, diving, walking through the water, aqua jogging, or splashing with the legs. The duration and intensity of both conditioning parts increased stepwise during the program. During the training sessions the heart rates of the patients were measured using a portable heart-rate monitor (Polar Accurex Plus, Polar Oy, Kempele, Finland) to monitor the training intensity.

Functional ability

Functional ability was measured using the Childhood Health Assessment Questionnaire (CHAQ)[15] and the Juvenile Arthritis Functional Assessment Scale (JAFAS)[16]. The Dutch translation of the CHAQ[17] was used as a self-administered pencil and paper questionnaire for the parents (proxy). The CHAQ has been adapted from the Stanford Health Assessment Questionnaire so that at least one question in each domain is relevant to children aged 0.6 to 19 years. The questionnaire consists of 30 items divided into 8 domains. The question with the highest score within each domain (range 0 to 3; able to do with no difficulty = 0, able to do with some difficulty = 1, able to do with much difficulty = 2, unable to do = 3) determined the score for that domain, unless aids or assistance was required (raising the score for that domain to a minimum of 2). The mean of the scores on the eight domains provided the CHAQ disability scale (range 0 to 3) and was chosen as the primary outcome measure of this study.

The Juvenile Arthritis Functional Assessment Scale (JAFAS)[16] is a performance test assessing disability in children with JIA. This test includes 10 activities of daily living. Time to perform each individual item is recorded and compared to a reference time. Each item was scored on a scale from 0-2 (able to perform the task within reference time = 0, perform the task slower than reference time = 1, not able to perform the task = 2).

Health-related Quality of Life

Health-related quality of life was assessed with a Dutch translation of the Juvenile Arthritis Quality of Life Questionnaire (JAQQ)[18] and the Child Health Questionnaire (CHQ)[17].

The JAQQ is a recently developed disease-specific health-related quality of life questionnaire for children with arthritis[18]. The JAQQ was administered to the patients; it consists of 74 items divided into five subclasses (gross motor function, fine motor function, psychosocial function, general symptoms, and a pain assessment section). The patients scored each item on a 7-point Likert-scale according to how often they encountered problems during the last 14 days (none of the time=1, hardly any of the time=2, some of the time=3, half of the time=4, most of the time=5, almost all of the time=6, all of the time=7). The score on the JAQQ was calculated as the sum of the five highest scores in each domain of the JAQQ. A higher score indicates a worse health-related quality of life.

The Child Health Questionnaire Parent-Form 50 (CHQ)[17] is a parent proxy report of assessing general health. A Dutch translation of the CHQ was used in this study[17]. The questionnaire consists of 50 items in 14 dimensions. From these dimension a summery can be calculated for physical (CHQ-PhS) and psychosocial health (CHQ-PsS). The CHQ was administered to the parents; a higher score reflects a better health status of the child.

Joint Status

Joint status was assessed by the number of tender and swollen joints and the range of motion. Tenderness and swelling were scored for the following joints: temporomandibular, sternoclavicular, shoulder, elbow, wrist, thumb, knee, ankle, and toes. Joint mobility was scored on the Paediatric Escola Paulista de Medicina Range of Motion Scale (pEPMROM)[19]. The pEPMROM measures mobility in children with JIA based on the evaluation of joint range of motion. Ten joint movements (cervical spine rotation, shoulder abduction, wrist flexion and extension, thumb flexion [metacarpophalangeal], 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, 3 = severe limitation). The final score was calculated as the sum of each movement score divided by 20.

Physical Fitness

The physical fitness of the patients was assessed using a maximal exercise test (MXT) and a sub maximal 6-minute walking test.

Subjects underwent a MXT on an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, and The Netherlands). The patients who did not fit on this ergometer were tested on a mechanically braked ergometer (Tunturi, Finland). The seat height was adjusted to the patient's leg length. Three minutes of unloaded cycling preceded the application of resistance to the ergometer. Thereafter, the workload was increased in constant increments of 20 watts every 3 minutes. This protocol continued until the patient stopped due to volitional exhaustion, despite strong verbal encouragement from the experimenters. During the test the subjects breathed through a facemask (Hans Rudolph Inc., Kansas City, MO) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Breda, The Netherlands). Expired gas was passed through a flow meter, an oxygen (O_2) analyser, and a carbon dioxide (CO_2) analyser. The flow meter and gas analysers were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER) from conventional equations (Jaeger Masterlab Software, Jaeger, Breda, The Netherlands). Heart rate (HR) was measured continuously during the maximal exercise test by a bipolar electrocardiogram. Absolute peak oxygen consumption (VO_{2peak}) was taken as the average value over the last 30 seconds during the maximal exercise test.

Sub maximal endurance was measured using the 6-minute walking test, as recommended for patients with arthritis[20]. The 6-minute walking test was performed on an 8-meter track in a straight corridor. The patients were instructed to walk at their own chosen walking speed from one side of the corridor to the other, turn, and walk back. The total distance covered in 6 minutes was calculated as the counted "repetitions" and multiplied by 8 meters. Time was measured with a stopwatch. During the test standardised verbal encouragements from the test leader were used to encourage the subjects. Before the assessment of physical fitness, anthropometric measurements were taken: height, weight and skin fold thickness, as previously described[21].

Statistical analysis

All data were entered into SPSS data entry 3.0 and analysed using SPSS-base 10.0 for Windows (SPSS Inc, Chicago, Ill.). General Linear Model (repeated measures ANOVA group (2)x time (3)) was used to analyse the effects of the aerobic aquatic training program. Greenhouse-Geisser Epsilon was used for adjusting the degrees of freedom when the sphericity assumption was not met. Alpha level < 0.05 was considered as statistically significant.

Results

Descriptive characteristics of the subjects at baseline are presented in Table 1. No significant differences were found at baseline between the Exp-group and Con-group on CHAQ, JAFAS, JAQQ, CHQ-PsS, CHQ-PhS, joint status, and physical fitness levels.

The patients conducted a mean number of 19.6 ± 3.9 training sessions. There was one dropout during the training program; one boy (13 years old with an OJIA onset type) stopped the training program after 15 training sessions. Since he still met the 75% criteria of 20 sessions, his data were not excluded from the analysis.

Table 1. Subject characteristics of the study participants.

Groups	Age	Weight	Height	Skin folds	Onset type	Gender
Exp-group	8.66±2.3	31.9±10.1	1.34±0.1	86.0±43.5	11 ojia, 15 pjia, 1 sjia	11 m / 16 f
Con-group	8.88±1.9	30.3±9.1	1.33±0.1	80.7±27.36	12 ojia, 14 pjia 1 sjia	3 m / 24 f

Values are mean ± standard deviation, age in years, weight in kg, height in meters, skin folds = sum of 7 different skin fold sites, ojia = oligoarticular JIA, pjia = poliarticular JIA, sjia = systemic JIA, m = male, f = female.

Functional ability

For the CHAQ and the JAFAS, mean scores and standard deviations of each group are at baseline are presented in Table 2. A lower score on both instruments means better performance on functional ability and functional skills. Table 2 shows F-values of the main effect of time, and the main effect of group x time interaction. No significant effects were found, however the Exp-group improved 27% in CHAQ score, while the Con-group improved only 5%.

The scores on the JAFAS were very low (a mean score of 0.15 at baseline for the EXP-group). The range of the JAFAS is from 0 to 2, a score of 0.15 is very close to the lowest possible score on this instrument, this phenomenon, a so-called floor-effect, would make improvement on this instrument hardly possible.

Health-related quality of life

JAQQ and CHQ-50 (divided into a physical summary and a psychological summary), mean scores, standard deviations, and the F-values of the main effect of time, and the main effect of group x time interaction are presented in Table 3.
There was a trend for the Con-group to deteriorate in JAQQ-score (-15%), as the Exp-group remained stable throughout the intervention period (0% change). However differences between the two groups did not reach statistical significance.
The Exp-group showed small improvement overtime on both CHQ summaries (8.4% and 7% respectively), while the Con-group decreased slightly (PhS -4%) or remained stable (0% PsS). These changes were almost reached statistically significance.

Joint status

Mean scores, standard deviations, and the F-values of the main effect of time, and the main effect of group x time interaction of both swollen and tender joints, and pEPMROM are presented in Table 4. The number of swollen and tender joints decreased in the Exp-group (-55%), while the number of swollen and tender joint increased in the Con-group (+21%). These differences were almost statistically significant (p=0.07).
For the range of motion (pEPMROM), there were no significant changes over time as both groups showed a very small decrease over time (18 and 30 % for swollen and tender joints, and pEPMROM respectively).

Physical fitness

Results on VO_{2peak} and the distance covered on the 6-minute walking test, mean scores, standard deviations, F-values of the main effect of time, and the main effect of group x time interaction are presented in Table 5. VO_{2peak} remained stable during the training period for both the Exp-group (0% change) and Con-group (-3% decrease). The 6-min walk improved slightly (+3%; non-significant) in the experimental group, while it did not change in the Con-group.

Table 2. Mean scores and standard deviations for both groups, and statistics of the analysis of variance for the functional ability instruments CHAQ and JAFAS.

	Assessment			Effect			
	T1 M (SD)	T2 M (SD)	T3 M (SD)	Time		Group x Time	
CHAQ†				F	Sig.	F	Sig.
Exp-group	0.65±0.54	0.56±0.39	0.47±0.45	2.3	0.1	1.03	0.35
Con-group	0.875±0.77	0.79±0.74	0.83±0.79				
JAFAS				F	Sig.	F	Sig.
Exp-group	0.14±0.12	0.14±0.14	0.13±0.12	2.2	0.11	0.6	0.55
Con-group	0.22±0.36	0.24±0.35	0.19±0.34				

(T1): Baseline =, before the start of the training program, (T2) = 3 months after start, (T3) = immediately after the end of the training program, M = mean, SD = standard deviation, F = F-value, Sig = P-value, * $p< 0.05$, ** $p< 0.001$, † = adjusted using Greenhouse-Geisser Epsilon.

Table 3. Mean scores and standard deviations for both groups, and statistics of the analysis of variance for the health-related quality of life instruments JAQQ and CHQ.

	Assessment			Effect			
	T1 M (SD)	T2 M (SD)	T3 M (SD)	Time		Group x Time	
JAQQ†				F	Sig.	F	Sig.
Exp-group	12.4±5.6	11.5±4.7	10.6±5.2	1.57	0.22	1.71	0.19
Con-group	14.3±5.0	14.6±5.4	14.34±5.9				
CHQ-PhS†				F	Sig.	F	Sig.
Exp-group	48.79±11.14	51.89±7.25	52.87±7.42	0.69	0.47	2.67	.085
Con-group	44.27±13.11	44.04±14.95	42.42±15.8				
CHQ-PsS				F	Sig.	F	Sig.
Exp-group	50.24±7.27	52.24±7.48	53.58±5.31	1.62	0.2	2.09	0.13
Con-group	49.32±8.98	50.28±7.46	48.91±8.24				

(T1): Baseline =, before the start of the training program, (T2) = 3 months after start, (T3) = immediately after the end of the training program, M = mean, SD = standard deviation, F = F-value, Sig = P-value, * = $p < 0.05$, ** = $p < 0.001$, † = adjusted using Greenhouse-Geisser Epsilon.

Table 4. Mean scores and standard deviations for both groups and statistics of the analysis of variance for the joint status: number of Swollen and Tender Joints and pEPMROM.

		Assessment		Effect			
	T1 M (SD)	T2 M (SD)	T3 M (SD)	Time		Group x Time	
Swollen & Tender joints				F	Sig.	F	Sig.
Exp-group	2.5 ± 2.7	2.2 ± 2.5	1.11 ± 1.3	0.92	0.41	2.7	0.07
Con-group	2.9 ± 4.7	3.6 ± 5.1	3.6 ± 4.9				
*p*EPMROM				F	Sig.	F	Sig.
Exp-group	0.11 ± 0.19	0.15 ± 0.26	0.13 ± 0.22	3.0	0.08	0.3	0.06
Con-group	0.23 ± 0.39	0.22 ± 0.42	0.3 ± 0.45				

(T1): Baseline = before the start of the training program, (T2) = 3 months after start, (T3) = immediately after the end of the training program, M = mean, SD = standard deviation, F = F-value, Sig = P-value, pEPMROM = Escola Paulista de Medicina range of motion scale, * $p < 0.05$, ** $p < 0.001$.

Table 5. Mean scores and standard deviations for both groups, and statistics of the analysis of variance for physical fitness measures VO2peak and the 6-minute walking test.

	Assessment			Effect			
	T1 M (SD)	T2 M (SD)	T3 M (SD)	Time		Group x Time	
VO_{2peak}†				F	Sig.	F	Sig.
Exp-group	1.11 ± 0.32	1.21 ± 0.41	1.11 ± 0.41	7.746	.001	.736	.46
Con-group	1.07 ± .35	1.12 ± 0.34	1.00 ± 0.34				
6-mwt†				F	Sig.	F	Sig.
Exp-group	455.0 ± 71.8	471.1 ± 78.8	471.9 ± 67.58	1.281	.28	.395	.63
Con-group	458.1 ± 76.9	469.4 ± 86.6	457.1 ± 105.4				

(T1): Baseline = before the start of the training program, (T2) = 3 months after start, (T3) = immediately after the end of the training program, M = mean, SD = standard deviation, F = F-value, Sig = P-value, VO_{2peak} = maximum oxygen consumption ($L \cdot min^{-1}$), 6-mwt = 6-minute walking test, * $p < 0.05$, ** $p < 0.001$, † = adjusted using Greenhouse-Geisser Epsilon.

Discussion

The aim of this study was to determine the effects of an aquatic training program for JIA patients on functional ability, quality of life, joint status, and physical fitness.

We found no statistical significant effects of a 20-week aquatic training program for JIA patients on functional ability, quality of life, joint status, and physical fitness. However, there was a clear trend of an improved joint status during the training program. The small, non-significant effects could be explained by the chosen outcome measures. We hypothesised the aquatic exercises would improve physical fitness. This increased physical fitness could result in a better function ability, and increases in health-related quality of life. However this transfer of the training effects seems very difficult. Numerous exercise studies in adult RA patients found improvements in physical fitness, joint pain, morning stiffness and fatigue, but no clear improvements in functional ability[22,23]. In our study, the largest effects were found in the joint status domain.

The aquatic training did not improve the VO_{2peak} of leg exercise on the bicycle ergometer, maybe an arm exercise protocol would have shown improvements, since as lot of exercises in the program were performed using both legs and arms.

Moreover, the used outcome instruments might have lacked the sensitivity to detect the training effects. The majority of the instruments (CHAQ, CHQ, JAFAS, pEPMROM, JAQQ) are developed and validated as discriminative instruments for disability, and not yet as an outcome for effect studies. However, in clinical practice they are used frequently for evaluative purposes, and the Paediatric Rheumatology International Trials Organisation selected some of them for trial evaluation (CHAQ and CHQ). Van den Ende et al.[24] found a very limited sensitivity to change of the adult version of the CHAQ, the HAQ, in an exercise trial with adult RA patients. The value of the CHAQ for detecting changes due to an exercise-training program might be limited.

The lack of improvements in the current study could also be the result of a limited trainability of children with JIA. Even in healthy children, some investigators have found no or small effects in physical fitness of exercise training programs[25], out data more or less confirm this finding for JIA patients. A meta-analysis of all available exercise training programs showed on average an eight percent increase in physical fitness in healthy children[26]. Compared to adults, the degree of aerobic trainability is somewhat limited in children. Additionally, for detrained, chronically ill patients it might not be possible to adhere programs based on adult standards for intensity and duration. They might be compromised in their level of trainability.

For children with arthritis there are some guidelines available. However, they are based on preliminary-evidence[27]. Moderate intensity exercise, as in our program, will facilitate most of the disease prevention and health promoting effects of exercise[28], however these are long-term effects of exercise training.

Our program lasted approximately a half-year, however, healthy peers participate for years in certain sport activities like soccer, cycling, tennis, or athletics. A long-term exercise training study (> 2 years) would be of interest to perform in the current patient group.

Our results clearly indicated however, that our program, as measured by joint status does not negatively influence the disease process. As parents and JIA patients were highly interested to participate in adapted physical training programs, this study shows that an aquatic training program could be a valuable adjunct to the common medical care of children with JIA.

Limited information is available concerning changes in physical fitness and functional ability in JIA patients following an exercise-training program. Thus more research is needed in this area. From a practical point of view, it was not possible to increase the frequency of the training (i.e. two training sessions a week), busy family schedules and a limited pool access do not allow higher training frequencies. The inclusion of a home-based exercise part (land-based) should be considered in a future study. This might also support patients, and parents in achieving a more active life style.

The lack of significant improvements in the training group also shows the importance of an active life style for children with JIA. The current research project shows that it is very difficult to improve physical fitness. The sound bite "it is easier to maintain good health through proper exercise, diet and emotional balance than to regain it once it is lost" might be also true for JIA patients.

Conclusion

With the advances in the medical treatment of JIA patients using new and successful treatments the interest in adapted physical training programs is increasing. The effects of adapted training programs are not well investigated. The current research found small, non-significant effects of an aquatic fitness-training program in children with JIA. Since there were no signs for worsening in health status, one can conclude that this was a save exercise program. As there are lot of different exercise modalities, effort should be invested to create and investigate the safety and effectiveness of exercise training programs for children with JIA.

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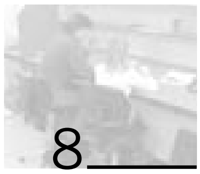
Summary & General Discussion

Tim Takken



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Summary

In Chapter 1 a brief introduction on physical fitness and physical training is provided. This literature review showed the diminished physical fitness of JIA patients on different outcome measures such as muscle strength, muscle bulk, pulmonary function, anaerobic capacity, and aerobic performance. In Chapter 2, the findings of a pilot study with 10 JIA patients were described. We found effects on health-related quality of life but not on sub maximal endurance (as measured using the 6-minute walking test) and on functional ability (as measured using the CHAQ). Using the experiences of this pilot study, we developed our aquatic fitness-training program. We also found that parents and JIA patients were highly interested to participate in adapted physical training programs. In Chapter 3 we describe the reliability of the assessment of the maximum oxygen consumption (the gold standard for physical fitness; VO_{2peak}). Our data indicated that the variability of VO_{2peak} measurements were slightly higher compared to reported values in the literature. This might be due to the small day to day differences in disease activity and well being in JIA patients. We also noticed that our JIA patients had significantly lower VO_{2peak} values compared to reference values from healthy peers. Additionally, we performed a systematic literature review and conducted a metaanalysis on the available physical fitness studies that measured VO_{2peak} in JIA patients. These results are described in Chapter 4. The VO_{2peak} of JIA patients was on average 21.8 % lower compared to healthy peers.
The relationship between functional ability (as measured using the CHAQ) and anaerobic physical fitness (as measured on the Wingate anaerobic test) was much stronger compared to the relationship between functional ability and aerobic physical fitness (as measured during a maximal exercise test), as described .
In Chapter 6 the association between physical activity and physical fitness was investigated. We determined small to moderate significant correlations between VO_{2peak} and physical activity measurements.
Chapter 7 describes the effects of our physical training study on physical fitness, functional ability and quality of life in JIA patients. Although we found favorable effects of exercise training for JIA patients in all domains, these effects were too small to reach statistical significance.

The significance of the current study related to the existing evidence

The current research contributed significantly to the existing literature. Only a few reports are published on this topic. However, it can not be regarded as the definite research in this area, as there are many different exercise modalities and outcome measures. The current project answered our questions; however, it raised even more new questions. We hope this thesis will encourage other researchers to try to answer some of these questions.

General Discussion

In the following paragraphs some issues that not have been addressed, or discussed in detail in the previous chapters will be highlighted.

The threshold hypothesis: linking physical fitness to functional ability

Considerable evidence from geriatric studies suggests that the ability to perform physical tasks is determined by a threshold level of physical fitness[1-4]. Patients lacking the requisite physical fitness may not be able to perform various activities of daily living that are important determinants of independence. For instance, Shephard[3] suggested that older subjects need a maximal oxygen uptake of at least 15 $ml \cdot kg^{-1} \cdot min^{-1}$ to perform certain activities of daily living. In Figure 1, the relationship between the CHAQ score and the power output on the Wingate anaerobic test (WaNT) is displayed (Figure from Chapter 4). In these results from 18 JIA patients, there seems to be a non-linear relationship between anaerobic physical fitness and functional ability. At around 200 Watt mean power a "threshold" could be observed in this relationship. Patients who performed over the 200 Watts at the WaNT had a low functional disability, the patients who performed lower than 200 Watts, perceived a higher level of disability.

Thus, just as older people, children seem to need a certain level of physical fitness for performing all kinds of activities of childhood daily living. Impaired physical fitness means that certain activities cannot be performed at the same pace as healthy children, or cannot be performed at all. The resulting deconditioning would accelerate this process of inactivity and deconditioning (See also Chapter 1, Figure 1)

In the current thesis different functional outcome tools have been used. In 2001 two functional outcome tools (Childhood Health Assessment Questionnaire [CHAQ], and Child Health Questionnaire [CHQ]) have become available in 32

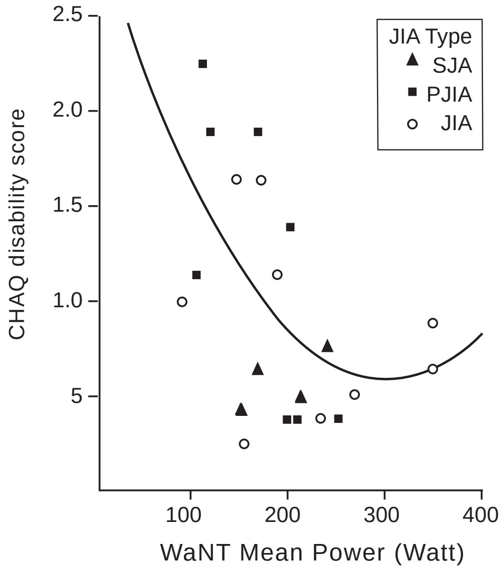

Figure 1.

Relationship between Functional Ability as measured on the Childhood Health Assessment Questionnaire and mean power as measured on the Wingate anaerobic test.

countries[5]. With the more and more widespread use of these instruments the advantages and shortcomings of these instruments also become apparent. One of the shortcomings of these instruments is their design. The CHAQ for instance, was adapted from a general health questionnaire for adults, the Stanford Health Assessment Questionnaire[6]. The questionnaire is not specially designed for children with JIA, but was adapted more than a decade ago for children with JIA. However, in the last decade the treatment of children with JIA has improved considerably. The introduction of new potent medications like Methotrexate, and Tumor Necrosis Factor alpha blocking agents has improved the "functional prognosis" of JIA patients considerably. The levels of disability in JIA patients might currently be lower compared to their peers ten years ago[7]. Therefore, it is possible that the CHAQ is not able tot detect levels of disability in the current JIA population as it used to do due to floor effects. Moreover, the CHAQ has been adapted to measure differences in functional ability between JIA patients, different onset types, and healthy peers, but not for measuring changes in functional ability in JIA patients over time, for example in a intervention. In a trial studying the effects of Etanercept (TNF alpha blocking agent) in a group of patients with a persistent JIA, the CHAQ was able to detect changes in the intervention group, while it did not in the group who received a placebo. This shows that the CHAQ is able to detect changes in severely diseased patients during a very rigorous intervention. Its psychometric properties in mild to moderate diseased patients during less rigorous interventions should be determined. As discussed in Chapter 2, the sensitivity of change of the CHAQ, and its relevance in the evaluation of physical therapeutic interventions may be insufficient but it needs to be determined in future studies.

This was, to our knowledge, the first intervention study in JIA patients reporting results on the CHQ[8]. CHQ is a generic health questionnaire for measuring physical and psychosocial health in the pediatric population and is based on the theoretical framework of the Short-Form 36, a wide spread used quality of life questionnaire for adults[9].
Since the Pediatric Rheumatology International Trials Organization (PRINTO) included the CHQ in a trial studying the effects of Methotrexate for JIA patients, its properties to detect changes in physical and psychosocial health will be published soon. Because of its generic use, the CHQ might not be able to detect all clinical relevant changes in a patients' health status. The addendum of an recently developed arthritis specific supplement to the CHQ (The Childhood Arthritis Health Profile, CAHP) might improve its psychometric properties[10]. However, the CAHP has not been released in the public domain.

The Juvenile Arthritis Functional Assessment Scale (JAFAS) was the first functional outcome tool especially developed for children with juvenile arthritis[11]. The JAFAS is an observer based scale requiring standardized simple equipment and is administered by a trained health professional in less than 10 minutes. The patient's performance of 10 physical tasks is timed. The JAFAS was developed in de United States and published in 1989, but is not very often used since then, at least not for research purposes. It seems reasonable that the JAFAS need some cross-cultural adaptation. Currently the instrument has only been translated. Maybe performing a new item-reduction process in the Netherlands will result in a more valid instrument. However, this approach generates a new problem of comparing scores between different countries.

Another issue that should be addressed is the need for age and gender specific norm times. In the current instrument, all children are judged against the same reference time, however there are age and gender differences in performing these kind of tasks. Moreover, floor effects as often seen (a score of 0), could be prevented by spreading out the score interval. In the current instrument only three score options are available, faster or the same time, slower, or not able to perform the task. Adding additional score options for the children who are able to perform a task, might reduce the chance of a "0" score.

Recently Duffy et al published a JIA specific quality of life instrument, the Juvenile Arthritis Quality of Life Questionnaire (JAQQ)[12]. This questionnaire consists of 74 items, in five domains (See also METHODS in Chapter 2). The JAQQ is already available in different languages; English, Canadian French, Swedish and Dutch. After completing the full questionnaire at the first assessment, the JAQQ is only scored on 5 particular items of interest per domain on the follow-up assessments. Additionally, children may add own items of interest to each domain. This approach results in a different questionnaire on each occasion for each patient and makes group statistics difficult to interpret. One of the weaknesses of this approach of the JAQQ is that lots of patients (especially the young patients) find it very difficult to add questions and to mark questions that they would like to improve. Another shortcoming of this instrument is that the items were derived from certain existing functional ability instruments that were known in JIA research. Thus the JAQQ is based on assessment tools which were developed and validated more than a decade ago. Maybe the importance of certain items is different nowadays, or maybe is no longer applicable. Maybe an other approach, such as the one used for developing the Activity Scales for Kids (ASK)[13], would result in a questionnaire with more "practical valid" items. In the development process of the ASK patients were asked what kind of activities they would like to do the most, and in what kind of activities they encountered most of their "functional" problems in daily life.
Thus, although there are numerous functional ability and quality of life instruments available for the JIA population, there is still lot of work to do to improve these instruments.

Prevention of the reduction in physical fitness

A lower quality and quantity of muscle mass probably cause the reduced physical fitness of JIA patients (See Chapter 1 and 4 for review). As discussed in Chapter 4

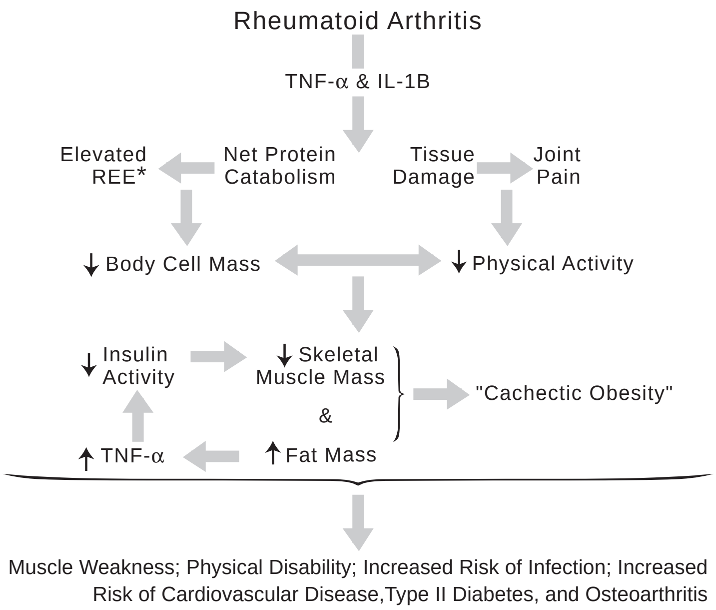

Figure 2.

Summary of the metabolic consequences of rheumatoid arthritis. The increased levels of inflammatory parameters leads to a loss of body cell mass, predominantly skeletal muscle mass, and reduced physical activity, which reinforce each other and lead to further losses of skeletal muscle mass and predispose to fat gain. *Resting energy expenditure (REE) is elevated in active rheumatoid arthritis. From Walsmith and Roubenoff (14).

and 5, the reduction might be caused by e.g. high levels of inflammatory parameters, and particularly tumor necrosis factor alpha (TNF alpha; See for review Walsmith and Roubenoff[14]). This muscular atrophy has been called "*Rheumatoid Cachexia*"[15]. A study in adult RA patients[16] showed a significant relationship between plasma TNF alpha levels and protein breakdown. Early treatment of JIA patients with TNF alpha blocking agents, such as Infliximab or Etanercept, might reduce the TNF alpha induced muscular atrophy. A recent study found also very promising effects of a TNF alpha blocking agent on disease activity and functional ability in patients with a persistent JIA[17]. There are also indications that

Methotrexate treatment could prevent this protein breakdown, at least in adult RA patients[16]. Early treatment of all JIA patients with Methotrexate or TNF alpha blocking agents might give a better outcome for physical performance and functional ability in JIA patients. The long-term risks and benefits of these agents are still not well documented in patients with JIA. Also the efficacy and required dose of these therapies for the treatment of the cachexia are unknown. These kinds of therapies can only be initiated in JIA patients, when additional studies have been performed.
Exercise training has been shown its value in adult RA patients[18], also during episodes of active disease[19]. In children, there are no well-controlled studies researching rheumatoid cachexia. However exercise studies in adults with RA using resistance training, are promising in preventing the loss in muscle mass[16].

Directions for future research

Future studies should try to reveal the acute and long-term effects of exercise, both risks and benefits, on immunological status of JIA patients. The exercise immunology of fitness training programs for arthritis patients should become one of the main targets for new research. For children with a rheumatic condition, the effects of long-term interventions should be investigated. Current studies ranged from 6 weeks to almost 6 months. However, healthy peers participate for years in certain sport activities like soccer, cycling, tennis, or speed skating. A long-term exercise program (> 2 years) could be performed as a group training program as in the current study in the water, but also on land (fitness or resistance training). Other possibilities are home-based exercise programs, a cyber-training program using internet, or a combination of all options. However one must bear in mind that an individualized approach is very important. Exercise intensity and exercise duration should be monitored by an educated specialist because of the risk of over training. A long-term training program during childhood and adolescence increases adult values for physical fitness. In this respect, the prevention of age-related decline in physical fitness using angiotensin-converting enzyme inhibitors is promising for patients with a chronic disease[20]. However, medication can never replace exercise, a long-lasting exercise adherence might improve not only physical fitness, but also quality of life, psychosocial well-being and life expectancy[21]. These are very important “side effects” of physical training.
Because of the costs of a specialist supervised training program, patients who will be most at risk for a very low exercise capacity and who will benefit the most

from the exercise program should be identified in the JIA patient population and should have priority in entering such a training program. Thus far, no studies are undertaken to investigate the differences in training-response in arthritis patients.
Tracking physical fitness, physical activity, immunological status, and functional ability of JIA patients into adulthood, will increase our understanding of functional ability in JIA patients as well as in the underlying immunological, physical and physiological determinants in JIA patients. This data might also reveal patient subgroups that are at risk for a low physical fitness when entering adulthood.

Main conclusions

Exercise scientists and physiologists are more and more involved in the clinical treatment of rheumatic conditions. Their research techniques and clinical interventions are becoming an important part of today's medical care and research of pediatric patients with a rheumatic condition such as juvenile idiopathic arthritis or juvenile dermatomyositis. The current research project shows the importance of including a pediatric exercise physiologist in the treatment team for pediatric rheumatic conditions.

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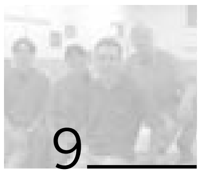
Dutch Summary
(Nederlandse Samenvatting)

Tim Takken



In Hoofdstuk 1 wordt een inleiding gegeven over algemene fitheid en algehele gezondheid. Uit diverse studies blijkt dat er een relatie bestaat tussen de hoeveelheid beweging van een persoon en zijn of haar gezondheidstoestand. Gezondheid wordt hier vaak uitgedrukt als mortaliteit, en/of kans op diverse ernstige ziekten. Overigens is gezondheid niet alleen gekoppeld aan de hoeveelheid beweging maar ook aan de lichamelijke fitheid. In het tweede deel van dit hoofdstuk wordt er ingegaan op de diverse onderzoeken naar de lichamelijke fitheid bij patiënten met Juveniele Idiopathische Artritis (JIA). Op diverse uitkomstmaten (o.a. spierkracht, anaëroob prestatievermogen, long functie, spiermassa, submaximaal uithoudingsvermogen en maximale zuurstofopname) blijken JIA patiënten minder te scoren dan gezonde leeftijdsgenoten. Verder wordt er ingegaan op de trainbaarheid van de kinderen met JIA. Alhoewel kinderen met JIA minder actief zijn dan hun leeftijdsgenoten en (dus) over een lagere lichamelijke fitheid beschikken, kunnen ziekte activiteit (ontsteking parameters) en medicatie de trainbaarheid verminderen. Echter, er is nog geen onderzoek gedaan naar de effecten van deze factoren op de trainbaarheid van JIA patiënten. In het laatste deel van dit hoofdstuk wordt er een overzicht gegeven van de beschikbare (pilot) studies die de effecten van een trainingsprogramma hebben onderzocht bij kinderen met JIA. Er zijn in de literatuur 9 trainingsstudies verschenen, die in totaal 108 patiënten met JIA hebben laten trainen. In deze studies kunnen er die verschillende trainingsmodaliteiten worden onderscheden; training op het land, training in het water en trainen op een fietsergometer. Alle drie deze modaliteiten lieten positieve effecten zien, hoewel veel verschillende uitkomstmaten werden gebruikt in deze studies. In de toekomst zouden trainingsstudies bepaalde kern instrumenten moeten gebruikten, zoals gebruikelijk in de Pediatric Rheumatology International Trials Organisation (PRINTO), waardoor de studies onderling beter met elkaar vergelijkbaar zijn.

In Hoofdstuk 2 van dit proefschrift worden de resultaten beschreven van een pilot studie naar de effecten van een trainingsprogramma in het water voor patiënten met JIA. Tijdens deze pilot werd er gekeken naar zowel de praktische realiseerbaarheid van zo'n onderzoek als naar de bruikbaarheid van diverse instrumenten bij deze patiënten groep, met name naar de Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Quality of Life Questionnaire (JAQQ) en de 6 minuten wandel test.

Er werden 25 ouders van patiënten met JIA in de regio Utrecht benadert om mee te doen in een trainingsstudie. Tien van deze ouders stemde toe mee te doen in deze studie. De training bestond uit een 15 weken durend programma waarbij de patiënten 1 maal per week een uur trainde in een verwarmd zwembad (Locatie WKZ). Voor deze studie werden er 4 metingen uitgevoerd, 1 voor de start van de studie, 1 na 7 weken training, 1 gelijk na afloop van het trainingsprogramma en 1 na een drie maanden uitwas periode. De resultaten waren als volgt; de CHAQ en de 6-minuten wandel test lieten geen statistisch significante veranderingen zien. De JAQQ daarentegen liet wel een verbetering zien, met name op het domein van de "algemene symptomen".

In Hoofdstuk 3 is de bruikbaarheid en de betrouwbaarheid van de maximale inspanningstest onderzocht. Bovendien werd het inspanningsvermogen van patiënten met JIA vergeleken met geslacht en leeftijd specifieke referentie waarden. Drieëntwintig patiënten met JIA (leeftijd tussen 6 en 14 jaar) namen deel aan deze studie. De patiënten voerden elk twee maximale inspanningstests uit op een fiets ergometer tot uitputting. De maximale zuurstofopname werd bepaald door middel van oxycon-metrie. In totaal waren er 46 inspanningstest van drieëntwintig kinderen beschikbaar voor analyse. Tijdens deze tests traden er geen complicaties op. De meetfout tussen de twee tests was 9.5%. Het merendeel van de patiënten had een verminderde maximale zuurstofopname (in $L{\cdot}min^{-1}$). Gemiddeld gezien was deze vermindering 24 % lager dan voorspeld (spreiding van 8 % boven voorspeld tot 61 % lager dan voorspeld). Wanneer de waarden werden gecorrigeerd voor lichaamsgewicht, was de vermindering in maximale zuurstofopname 22 %, (spreiding van 65 % boven voorspeld tot 69 % lager dan voorspeld.)
Uit deze studie kan geconcludeerd worden dat maximale inspanningstests mogelijk zijn bij JIA patiënten en er een grote variatie is in aëroob vermogen bij kinderen met JIA. Dit laatste maakt een generalistische uitspraak over het aërobe uithoudingsvermogen bij patiënten met JIA moeilijk. Wel kunnen patiënten met een laag inspanningsvermogen met behulp van een maximale inspanningstest worden geïdentificeerd voor een mogelijk trainingsprogramma.

In Hoofdstuk 4 is een systematische literatuur onderzoek beschreven over het maximale inspanningsvermogen bij kinderen met JIA. Voor dit literatuur onderzoek werden de volgende databases geraadpleegd; Medline, Cinahl, Embase en Sportdiscus. De bruikbare artikelen werden uitgezocht en opgevraagd. Uit deze artikelen werden de gegevens gehaald en in de Review Manager software ingevoerd. De maximale zuurstofopname (VO_{2peak}; in $ml{\cdot}kg^{-1}\,{\cdot}min^{-1}$) behaald tijdens een maximale inspanningstest tot uitputting werd als de primaire uitkomstmaat voor dit onderzoek beschouwd. Er werden 9 studies gevonden in de literatuur. Gegevens van 5 studies (144 patiënten) konden worden samengevoegd en worden geanalyseerd. De VO_{2peak} van de JIA patiënten was 21.8 % lager (95 % betrouwbaarheidsinterval: 13.7 %, 29.9 %) dan die van gezonde proefpersonen en/of referentie waarden ($p < 0.0001$). De resultaten van deze zogenaamde meta-analyse suggereert dat kinderen met JIA een gematigde tot grote vermindering hebben in hun maximale zuurstofopname capaciteit in vergelijking met gezonde leeftijdsgenoten.

In Hoofdstuk 5 is er gekeken naar het aërobe en anaërobe vermogen in relatie tot de functionele mogelijkheden van kinderen met JIA. Hiertoe werden achttien kinderen met JIA (leeftijd tussen de 7 en 14 jaar) getest op zowel hun aërobe als anaërobe inspanningsvermogen. Het aërobe inspanningsvermogen werd gemeten door middel van de eerder beschreven maximale inspanningstest, het anaërobe inspanningsvermogen werd getest door middel van de Wingate anaërobe test. Dit is een 30 sec *all-out* sprint test op een fietsergometer. Gelijktijdig werden de functionele mogelijkheden bepaald met behulp van de door de ouders in te vullen Childhood Health Assessment Questionnaire (CHAQ). De relatie tussen het aërobe inspanningvermogen en CHAQ was laag (r = tussen -0.289 en 0.132). De correlaties tussen het anaërobe inspanningsvermogen en functionele mogelijkheden waren groter (r tussen piek vermogen en CHAQ = -0.528; tussen gemiddeld vermogen en CHAQ r= -0.527). Dit laat zien dat er een goed relatie is tussen anaërobe inspanningsvermogen en functionele mogelijkheden. Bovendien laat deze studie het belang zien van het anaërobe inspanningsvermogen voor de functionele mogelijkheden van kinderen met JIA.

In Hoofdstuk 6 is de interactie tussen dagelijkse lichaamsbeweging en componenten van fysieke fitness bij patiënten met JIA onderzocht. Voor deze studie werden er negenenveertig kinderen met JIA (10 jongens en 39 meisjes) met een gemiddelde leeftijd van 8.8 (± 2.2) jaar onderzocht. Lichaamsgewicht, lengte, huidplooi dikte, aantal gezwollen gewrichten en bewegingsuitslag van de gewrichten werden bepaald. De maximale zuurstofopname (VO_{2peak}) werd gemeten door middel van een maximale inspanningstest op een fietsergometer. De hoeveelheid lichaamsbeweging werd gemeten door middel van een Caltrac™ activiteiten monitor en een inschatting van het activiteiten patroon door de ouders op een 5 punts Likert-schaal.

De resultaten laten zien dat de partiële correlatie coëfficiënten (om zo voor leeftijd te corrigeren) tussen lichamelijke activiteiten en indicatoren van fysieke fitness significant waren tussen Caltrac™ tikken en absolute VO_{2peak} (r = 0.31) and relatieve VO_{2peak} (r = 0.34). Er waren geen significante correlaties met de indicatoren voor de lichaamssamenstelling. Bovendien was er een significante correlatie tussen de inschatting van het activiteiten patroon door de ouders en relatieve VO_{2peak} (r = 0.33).
Uit dit onderzoek kan geconcludeerd worden dat er een significante relatie was tussen de hoeveelheid lichamelijke activiteiten en aëroob inspanningsvermogen, maar niet met lichaamssamenstelling bij kinderen met JIA. Een longitudinale follow-up van deze patiënten zal moeten uitwijzen of een actieve levensstijl beschermt tegen de afgenomen aërobe fitheid bij deze patiënten.

In Hoofdstuk 7 zijn de effecten van een aquatraining programma voor kinderen met JIA beschreven. Vierenvijftig kinderen met JIA in de leeftijd tussen 5 en 13 jaar namen deel aan deze studie. De patiënten werden gerandomiseerd in een experimentele groep (n=27) een controle groep (N = 27). De patiënten in de experimentele groep kregen een trainingsprogramma in een lokaal zwembad van 1 uur per week gesuperviseerd door een geïnstrueerde trainer. Het programma bestond uit ongeveer 20 trainingssessies.
De functionele mogelijkheden (CHAQ score) van de kinderen in de trainingsgroep verbeterde 22% meer ten opzichte van de controlegroep en 3.5 % meer op de JAFAS schaal. De gezondheidsgerelateerde kwaliteit van leven (JAQQ), veranderde niet in de trainingsgroep, terwijl de score 15% daalde bij de controlegroep. Op de CHQ verbeterde de Fysieke score 8% in de trainingsgroep en nam 4% af in the controle groep. In de trainingsgroep, de psychosociale score verbeterde 7% in the trainingsgroep maar bleef gelijk in de controlegroep. Het aantal gezwollen en pijnlijke gewrichten nam met 55% af in de trainingsgroep, terwijl er een 21% verslechtering te zien was in de controlegroep.
De flexibiliteit nam 18% af in de trainingsgroep (in absolute waarde was de verandering slechts minimaal) maar nam maarliefst 30% af inde controle groep.
De fysieke fitness (de maximale zuurstofopname) bleef onveranderd in de trainingsgroep, terwijl deze 3% af nam in de controlegroep. Het submaximale prestatie vermogen verbeterde 3% in de trainingsgroep, terwijl deze gelijk bleef in de controle groep. Al deze veranderingen waren echter niet statistisch significant verschillend.

De conclusie van deze trainingsinterventie is dat er geen statistisch significante effecten optraden bij een aquatraining programma voor kinderen met JIA. Echter, er waren ook geen verslechteringen zichtbaar, dus er kan gesteld worden dat dit programma een veilige trainingsvorm is voor kinderen met JIA. Omdat er veel verschillende bewegingsmogelijkheden bestaan, zal er verder onderzoek moeten komen naar de effectiviteit en veiligheid van de diverse mogelijkheden.

Dankwoord

Dit proefschrift is het eindresultaat van de onderzoeksinspanningen van de afgelopen vier jaar als promovendus bij de afdeling Kinderfysiotherapie van het Wilhelmina Kinderziekenhuis/ Universitair Medisch Centrum Utrecht. Bij een promotietraject is het altijd zo dat een onderzoeker de kar moet trekken, waarbij anderen zo nu en dan assisteren en helpen. Ik wil dan ook alle personen bedanken die mij hebben aangemoedigd en/of hebben geholpen deze kar naar de eindstreep te krijgen.

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Curriculum Vitae

Tim Takken werd op 25 april 1975 geboren te Schellingwoude (Gemeente Amsterdam). Na de lagere school in Schellingwoude, Zunderdorp en Ransdorp te hebben doorlopen, ging hij in 1988 naar de Scholengemeenschap Noord (Amsterdam), waar hij in 1993 zijn VWO-diploma in ontvangst mocht nemen. Vanaf 1993 studeerde hij aan de Faculteit Bewegingswetenschappen van de Vrije Universiteit Amsterdam, alwaar hij zich specialiseerde in de inspanningsfysiologie. In 1997 verbleef hij 7 maanden in Australië, waar hij stage liep bij een onderzoeksproject naar de bruikbaarheid van "geïsoleerde huidtemperaturen als maat voor de kerntemperatuur" in het thermofysiologie laboratorium van de University of Wollongong onder leiding van Dr Nigel Taylor en Brad Wilsmore. In 1998 studeerde hij af aan de Vrije Universiteit met als specialisatie inspanningsfysiologie en met de sub-specialisaties psychologie met betrekking tot het menselijk bewegen en de docentenopleiding. Drie maanden later begon hij aan het promotieproject "aquatraining voor kinderen met jeugdreuma" bij de afdeling Kinderfysiotherapie van het Universitair Medisch Centrum Utrecht, Locatie Wilhelmina Kinderziekenhuis onder leiding van Prof Dr P.J.M. Helders.
Naast zijn promotietraject is Tim altijd een zeer actief (bestuurs)lid geweest van de vif (Vereniging voor Inspanningsfysiologie, thans Vereniging voor Bewegingswetenschappen Nederland). Zo is hij initiator en moderator van de inspanningsfysiologie emaillijst, (mede)organisator van diverse thema avonden en minisymposia en zit hij in de redactiecommissie voor de mededelingenpagina in Geneeskunde & Sport. Daarnaast is hij altijd een actief wielrenner geweest bij de amateurs. Tim woont op dit moment, samen met Editha Bergkotte, in Alphen aan den Rijn.

List of Publications

Peer-reviewed papers

* Takken T, Van der Net J, Helders PJ. Do juvenile idiopathic arthritis patients benefit from an exercise program? A pilot study. Arthritis Rheum 2001; 45:81-5.
* Takken T, Van der Net J, Helders, PJM. Methotrexate for treating juvenile idiopathic arthritis (Cochrane Review). Cochrane Database Syst Rev 2001; 4:CD003129.
* Takken T, Van der Net J, Helders PJM. Maximum exercise testing in juvenile rheumatoid arthritis (JRA) patients. Clinical Exercise Physiology 2002; 4:38-43.
* Takken T, Hemel A, Van der Net J, Helders PJM Aerobic fitness in children with juvenile idiopathic arthritis: a systematic review. The Journal of Rheumatology. In press
* Takken T, Spermon N, Prakken AB, Helders PJM, Van der Net J. Aerobic exercise capacity in juvenile dermatomyositis patients. The Journal of Rheumatology. Accepted

In review

* Takken T, Van der Net J, Helders PJM Relationship between functional ability and physical fitness in juvenile idiopathic arthritis (jia) patients. Submitted
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