Exercise Testing and Fitness Training in Juvenile Idiopathic Arthritis

Het testen en trainen van de inspanningscapaciteit bij kinderen met Juveniele Idiopathische Arthritis

(met een samenvatting in het Nederlands)

door

Davinder Singh-Grewal

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Proefschrift

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Contents

Chapter 1

Introduction

Davinder Singh-Grewal

Juvenile idiopathic arthritis, physical activity, fitness and chronic disease

Juvenile Idiopathic Arthritis (JIA) is an inflammatory arthritis of unknown aetiology that affects 1-4/1000 children below the age of 16 years (1). Children suffering from JIA experience pain (2, 3) and significant physical disability particularly after long durations of disease activity (4-12).

Children with JIA have significantly lower rates of participation in physical activity than their healthy peers (13,14) and it has been demonstrated that children with JIA also have reduced aerobic fitness when compared to their peers (15,16,17). This reduced activity and fitness are probably multi-factorial in causation - partly as a result of the effects of active disease or long term joint damage, but also undeniably as a result of the attitudes of the parents, teachers, physicians and patients themselves who feel that excessive activity may in some way may have caused the arthritis to have occurred in the first instance, may cause it to worsen, or increase the risk of further joint damage (18). Thus children may become "sidelined" and not encouraged to participate in physical activity. Such patterns of inactivity and de-conditioning are further compounded through a downward spiral of inactivity and de-conditioning (19). This cycle must be addressed to allow these children the short and long term benefits of physical activity and fitness.

By definition, JIA occurs in childhood, however, in excess of 40% of children with JIA graduate to become adults with chronic arthritis (4-12) meaning that the activity limitations experienced in childhood may be translated into issues of reduced activity and fitness in adulthood exposing these individuals to the long-term health consequences of increased cardiovascular risk, osteoporosis and obesity.

It has been demonstrated that physical de-conditioning as indicated by poor aerobic fitness is related to greater rates of death from cardiovascular causes in adults with and without rheumatic diseases (20-24). Additionally, significant physical and emotional benefits of physical fitness have been demonstrated in children and adolescents (25, 26). A systematic review of fitness training in adults with rheumatoid arthritis showed positive affects on aerobic capacity from both short term and long term land based exercise programs (27) and thus by extrapolation a reduction in cardiovascular risk. The included studies did not demonstrate any worsening of disease activity, function or pain due to any training programs (27).

It is known that maximal bone mineral densities are achieved in adolescence and that physical activity is a significant contributor to maximal bone density. Patients with JIA are at risk of osteoporosis due to chronic inflammation, delayed puberty, malnutrition, muscle weakness, physical inactivity and long term corticosteroid therapy (28-31). Thus children with JIA who are prone to inactivity are at risk of osteoporosis.

Physical inactivity is undoubtedly associated with obesity and it's long term detrimental health affects (32) and while there is no evidence currently to link JIA and obesity directly, one cross-sectional study has show an obesity prevalence of 16.7% in children with JIA (33). It is conceivable that the inactivity and de-conditioning that has been

observed in patients with JIA is likely to translate into a risk for obesity and it's metabolic complications.

Thus JIA is a chronic disease of childhood that has significant long term affects on a number of areas of a child or young person's health and function. Included in this are detrimental affects on physical activity, physical fitness and the subsequent long term health implications.

Current understanding of fitness in children with JIA

Physical fitness in a general sense is best thought of as being composed of a number of factors including physical speed, endurance, strength, flexibility and body composition. Fitness can be measured through a number of means including formal exercise testing in a dedicated laboratory setting or more informally in a field test situation.

There have been a number of studies looking at the aerobic fitness of children with JIA which have at times reported mixed results. These studies are summarised by Takken et al in a systematic review which showed that in 5 identified studies the peak oxygen uptake (VO_{2peak}) or aerobic fitness in children with JIA was more than 20% lower than that of their unaffected peers (16). The authors concluded that there was a moderate to large impairment of physical fitness as measured by VO_{2peak}. They also make the point that children with more severe disease are likely to have lower VO_{2peak} and that when considering the normal age related decline in VO_{2peak} seen in all individuals after the age of 18 years, patients with JIA entered adulthood at a significant disadvantage as their VO_{2peak} was estimated to equate to that of a person around 20 years older in fitness terms (16).

Furthermore it has been suggested that children with JIA have a reduced aerobic reserve as demonstrated by the fact that they show higher sub-maximal exercise heart rates and reduced VO_{2peak} during exercise (34) meaning that they may fatigue earlier than their peers when undertaking physical activities.

Even though anaerobic fitness in children with JIA has not been as extensively investigated as aerobic fitness it is known that children with JIA have impaired anaerobic fitness (15-17). Anaerobic measurements are based on the amount of power generated in a short, all out, maximal, dynamometer test such as that performed in the Wingate cycle protocol (35). Reduced anaerobic power in children with JIA may be related to the diminished muscle mass observed in patients with JIA (36-40). Studies in adults with rheumatoid arthritis have shown atrophy particularly of type II fibres (41) and it is these fibres which are responsible for anaerobic power but no similar studies are available in children. Reasons for this atrophy and weakness are most likely multi-factorial and may include disuse, pain and resultant reflex inhibition, and possible cytokine affects (42-44).

It has been shown that there is a correlation between anaerobic fitness and functional ability particularly in the spheres of dressing/grooming, hygiene and walking (17,45). This relationship is felt to be due to the fact that typical physical activity patterns of children require intermittent bursts of activity followed by periods of rest which is

fundamentally anaerobic in nature (45). Activity patterns are thought to become more aerobic in pattern with age. Considering the relationship between muscle strength and anaerobic capacity, it is not surprising that muscle strength itself has also been shown to have a correlation to function in children with JIA (46, 47).

Current understanding of exercise testing in JIA

As mentioned above, physical fitness is best considered as being composed of a number of different components. Methods have been developed to assess each of these components separately. Peak oxygen uptake as measured by the VO_{2peak} is accepted as the most reliable method of measuring aerobic fitness (48) and has become a pseudonym for fitness particularly in elite athletes. More recently in patients with chronic diseases measurement of VO_{2peak} has been found to be useful in assessing baseline fitness and response to training programs and fitness interventions.

Protocols used for the measurement of VO_{2peak} are rigorous and require the subject to complete a maximal test to volitional exhaustion. Testing may be performed on a treadmill, cycle ergometer or arm crank ergometer. While it has been show in small samples that graded exercise testing is safe and feasible in patients with JIA (49), such tests may prove difficult for those with chronic disease particularly children to complete and for this reason sub-maximal oxygen uptake ($VO_{2submax}$) has been suggested and shown to be a reliable predictor or independent measure of fitness in adults with rheumatoid arthritis (50, 51) and children with and without rheumatic disease (52-57).

Furthermore many centres may not have the technical capacity to measure VO_{2peak} or $VO_{2submax}$ as both require a considerable amount of equipment and specific expertise. Thus field tests of fitness including the 6-minute walk test may be used to assess fitness and have been thought to be a reasonable measure in normal children (58) and those with cerebral palsy (59). The 6-minute walk test has been used in JIA (60), however, it does not correlate well with VO_{2peak} which as previously mentioned is considered the gold standard in aerobic fitness measurement (61). Thus, where available formal laboratory measures should be preferred above field testing. For this reason other less intensive laboratory measures have been suggested including the measurement of peak work rate which does not require respiratory gas analysis equipment or high levels of expertise to perform and has been show to correlate well with VO_{2peak} in healthy children (62). These less intensive means of assessment may represent more feasible means of incorporating formal fitness measures into clinical applications.

Measurement of muscle strength may also be formally assessed and this may be done in two ways. Firstly by measuring isometric strength in which there is a sustained contraction at a fixed angle or isometric strength which involves measurement through an arc of movement at a constant angular velocity. Both isometric and isokinetic strength have been shown to be valid and reliable measures of muscle strength in normal children (63, 64). In JIA the reliability of isometric strength measurement of the lower limb muscles has been assessed using both hand held dynamometers (47, 65) and a dynamometer chair (66). Measurement using hand held dynamometers is reported to have

a high intra-rater and inter-rater reliability (47, 65). Measures of isokinetic strength have been reported but not formally validated.

Current evidence for fitness training in children with JIA

It has been demonstrated in healthy children that exercise training results in only modest improvements in VO_{2peak} (67, 68). However, it is postulated that those with pre-existing impairment in aerobic fitness such as is seen in JIA may show more significant improvements in fitness after training programs. This expectation has been the basis of a number of published studies of fitness training in children with JIA. A majority of these studies were either non-randomised or non-controlled with only one published randomised controlled trial prior to the work presented in this thesis. That trial of an aquatic fitness program of moderate intensity showed improvements which were not statistically significant in terms of fitness and quality of life but importantly showed no deterioration in arthritis over the duration of the trial (69). Other uncontrolled studies showed comparable results with some small improvements in muscle strength (70-73), joint range of motion (72, 73) and field tests of aerobic fitness (72, 73).

Aims and outline of this thesis

The material contained within this thesis examines fitness measures, fitness testing and training in children with JIA. Chapter 1 summarises the current understanding of fitness as it relates to children with JIA in the short and long terms. It also summarises the current understanding of measurement of fitness in JIA and the evidence for fitness training programs in children with JIA. Chapter 2 describes the findings of a pilot study of 9 children with JIA enrolled in a combined land and water based fitness program aimed at assessing the safety, feasibility and affect size of such a program for the development and completion of the large randomised, controlled, single-blinded trial of high intensity training protocol in children with JIA which is presented in Chapter 3. Chapter 4 examines the reliability of the measures used in the trial presented in Chapter 3 including measures of peak and sub-maximal oxygen uptake, anaerobic capacity and other measures of function and physical activity. Chapter 5 examines the relationship between peak work rate and VO_{2peak} in children with JIA and the utility of this measure as a proxy for VO_{2peak}. A pilot study of muscle strength changes after intra-articular steroid injections in children with knee arthritis is contained in Chapter 6. Chapter 7 contains a summary in English along with general discussion and Chapter 8 a summary in Dutch.

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Chapter 2

Pilot study of fitness training and exercise testing in polyarticular childhood arthritis.

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Arthritis & Rheumatism (Arthritis Care & Research) 2006; 55(3); 364–372

Abstract

Objectives

To 1) assess the safety and feasibility of laboratory-based exercise testing in juvenile idiopathic arthritis (JIA), 2) test the safety and feasibility of a 3-month exercise program in JIA, 3) assess pain during exercise in JIA, 4) compare ratings of perceived effort (RPE) with heart rate (HR) achieved, and 5) estimate the training effect on metabolic efficiency of gait as measured by submaximal exercise testing.

Methods

Nine children with JIA were enrolled in a 12-week circuit training program involving pool, stationary bicycle, treadmill, and Fitball. They underwent formal exercise testing before and after the program, underwent a full joint assessment, were administered the Childhood Health Assessment Questionnaire and Juvenile Arthritis Functional Status Index, and were assessed for overall quality of life and health-related quality of life. A visual analog scale was used to assess pain during testing and training, and the Borg scale was used to measure RPE.

Results

Children with JIA were able to participate in exercise testing without any significant problems. Children with severe hip disease dropped out of the exercise program due to pain during the exercise sessions and worsened arthritis symptoms. Target HR was achieved and correlated with RPE in the bicycle and treadmill sessions. Submaximal exercise testing showed an improvement with a small to moderate effect size.

Conclusion

This study suggests that it is safe, feasible, and acceptable for children with arthritis, in the absence of severe hip involvement, to participate in formal exercise testing and structured fitness programs.

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic illness that affects 1:1000 children (1,2). Patients with JIA may experience significant disability due to muscular weakness, joint pain, contracture and physical de-conditioning. Children with arthritis have been shown to participate in less physical activity and have a higher number of sleep hours than their peers (3). These factors may result in a spiral of de-conditioning and disability resulting in an inactive lifestyle (4).

Supporting this idea of impaired physical conditioning, a systematic review by Takken et al. (5) identified 9 studies addressing physical fitness in children with JIA. Five of these studies contained peak oxygen consumption (VO_{2peak}) measurements and were included in a meta-analysis that showed an overall 22% lower VO_{2peak} in children with JIA (5). Furthermore, Metin et al. (6) showed heterogeneity in VO_{2peak} measures within subgroups of JIA. Those with enthesitis related arthritis had a higher aerobic capacity but no difference was seen between patients with active and inactive disease (6).

Traditionally, physical therapy for JIA has been aimed at managing pain and inflammation, preserving range of motion and maintaining muscle strength through rest and limiting the strain on arthritic joints (7,8). More active forms of therapy have been instituted in recent times (9), and guidelines have included recommendations for fitness and strengthening exercise in children with JIA to improve function and promote lifetime physical activity (10). Nevertheless, the best therapeutic regimen for children with arthritis is as yet unknown.

Systematic reviews of trials examining the effects of aerobic training on adult patients with rheumatoid arthritis (11,12) have found that exercise interventions resulted in improved aerobic capacity, muscle strength and disease activity, with a possible beneficial effect on pain, function and quality of life. No detrimental effects in terms of disease activity, pain or function were identified.

Few studies of exercise training in children with arthritis are available. Most are small, not randomized and rely on field testing such as a timed walk rather than more precise, standardized laboratory measurements of oxygen consumption and power output to assess fitness outcomes. Oberg et al. (13) suggested that children with arthritis achieved improvements in muscular strength and endurance after a 3-month training program and that electro-myographic abnormalities observed at the beginning of the study improved with training. In an uncontrolled study of 25 children with polyarticular JIA, Klepper et al. (14) demonstrated improvements in aerobic capacity and flexibility after an 8-week low impact aerobics and resistance program performed 3 times a week. The program was well tolerated and all patients improved on all measures of arthritis severity (14). More recently a randomized controlled study of aerobic pool exercise involving 54 children, by Takken et al. (15), suggested an improvement in quality of life, joint status and sub-maximal endurance; these results were not statistically significant. No large-scale randomized studies of land based exercise programs are available.

The exact roles of aerobic and anaerobic fitness in the function of children with arthritis are not clear. Takken et al. (16) demonstrated an association between anaerobic physical fitness and function suggesting that in children, activities of daily living may depend on short intense bursts of anaerobic activity. Prolonged endurance types of activities may be more important in adult life. While precise roles are unknown, it seems reasonable that there would be long and short-term benefits to both aerobic and anaerobic conditioning in JIA.

Measurements of peak oxygen uptake (VO_{2max}) have been used in adult subjects to assess fitness. These tests are rigorous and require a plateau in VO_2 despite increasing workload. This has proven difficult to measure accurately in children and thus peak VO_2 (VO_{2peak}) has been used instead to assess exercise capacity (17). Maximal and peak VO_2 measurements may be inappropriate in those with limitation or disability and the use of sub-maximal VO_2 ($VO_{2submax}$) has been suggested as a predictor of VO_{2max} or to assess performance in standardized physical activities (18).

Disability in children with cerebral palsy is associated with a reduced VO_{2peak} along with reduced muscle power and endurance. These children are also known to have an exaggerated energy cost of locomotion as measured by sub-maximal treadmill exercise testing (15,19,20). Giannini and Protas (21) showed that children with juvenile arthritis had higher sub-maximal heart rates and tended towards higher $VO_{2submax}$ as compared to matched children without arthritis at the same workload during a bicycle task. Thus it may be that children with arthritis also have an exaggerated energy cost of locomotion that manifests as early fatigue during normal daily activity. Submaximal VO_2 may provide a means of measuring disability in JIA and provide an easier and more tolerable way to measure aerobic fitness and response to therapy than maximal exercise testing protocols. Sub-maximal exercise testing and specifically energy cost of locomotion have not been systematically examined in children with arthritis.

This study was undertaken as the pilot study for a randomized controlled study that will test the hypothesis that fitness exercise benefits the physical function and quality of life of children with JIA. This pilot study had 5 aims. First, to assess the safety and feasibility of laboratory based exercise testing in JIA. Second, to test the safety and feasibility of a 3-month aerobic and strength training program in JIA. Third, to examine the effect of arthritis pain during exercises in JIA. Fourth, to compare subject ratings of perceived effort (RPE) with actual HR achieved during exercise; indicating whether perceived effort can be used as a guide in exercise programs. Finally, to estimate the training effect of regular exercise on metabolic efficiency of gait as measured by VO_2sub-max.

Subjects & Methods

Nine subjects from the rheumatology program at the Bloorview MacMillan Children's Centre (BMCC), a regional pediatric rehabilitation center in Toronto, Canada were recruited. Prepubescent children (maximum Tanner stage 2), aged 8 to 11 years, with JIA and a polyarticular course were eligible. These criteria excluded pubescent children who might experience large increases in lean body mass within the study period and younger children who might not be able to cooperate with training and testing protocols. Co-

morbidity with cardiac, pulmonary or metabolic disease was grounds for exclusion. Children already engaged in three or more hours of structured physical activity per week (other than a physiotherapy pool program) were excluded, as they might not show additional gains from fitness training. No child with active features of systemic arthritis was enrolled. There were no restrictions on medication use in this pilot study.

Testing

Laboratory testing was undertaken at The Children's Exercise and Nutrition Centre, McMaster University. A habituation session was undertaken at BMCC to familiarize subjects with procedures.

Subjects underwent baseline (pre-) testing prior to and (post-) testing after the 12-week program. Standing height was measured in stocking feet on a Harpenden Stadiometer (London) with a precision of 0.1 cm and weight to the nearest 10 gm in a hospital gown or t-shirt and shorts, using an Ancaster electronic scale (Brantford, Ontario). Subjects were examined prior to and after each testing session by a physiotherapy (PT) assessor. A joint was considered active if it was effused or displayed 2 of the following features: heat, limited range of movement, tenderness or stress pain. Pain was measured using a 10 cm visual analogue scale (VAS).

The Childhood Health Assessment Questionnaire (CHAQ) was used to assess physical function. It is scored between 0 and 3 with 0 denoting no disability and 3 denoting severe disability; it is validated for use in JIA (22). The Juvenile Arthritis Functional Status Index (JASI) was used to give a more detailed assessment of functional ability and priority activities (23). It is scored between 0 and 100 with higher scores denoting better function. Overall quality of life (QOL) and health related quality of life (HRQL) were measured on a 10 cm. VAS, previously validated for children with JIA, with a higher score indicating better QOL or HRQL (24). A subject/parent satisfaction survey, designed by one of the authors (VW), was given to the subjects and their parents at the end of the final exercise session.

The exercise testing protocol consisted of three main components. Energy cost of locomotion was determined by $VO_{2submax}$ while treadmill walking at 1.5 and 3.0 km/hr for 5 minutes. These relatively slow speeds were chosen to ensure that even those subjects with severe active disease or disability due to chronic disease could complete the protocol. Expired gases were analyzed for O_2 uptake and CO_2 production (SensorMedics Vmax, Mississauga, Canada). Heart rate (HR) was measured every 5 seconds using a telemetric device (Polar Vantage XL, Polar Instuments, Kempele, Finland).

Peak VO_2 was measured through an incremental continuous cycling task on a Fleisch ergometer (Fleisch Metabo, Lausanne, Switzerland). Resistance was increased every 2 minutes with increments selected by the investigator based on the child's HR and overall appearance. The test duration was aimed at 6 to 10 minutes (4) with heart rate measured continuously and expired gases analyzed breath by breath for O_2 uptake and CO_2 production (SensorMedics Vmax, Mississauga, Canada). The test was continued until

volitional fatigue despite strong verbal encouragement (26,27); this method has been found reliable in previous studies (21,28).

Leg anaerobic capacity (peak and mean muscle power) was measured through a 30-second all-out cycling task on a cycle ergometer (Fleisch Metabo, Lausanne, Switzerland) following the protocol of the Wingate Anaerobic Test (26). This test has been shown to yield reliable results in normal children and those with neuromuscular disease including juvenile dermatomyositis (29,30). The resistance for this test was determined from each subject's force velocity curve derived from several 5 to 7 second sprints at different loads (31). The anaerobic performance of subjects' upper limbs was assessed in a similar way using a Fleisch ergometer modified for arm cranking.

Training Protocol

Sessions were held at BMCC twice weekly for 12-weeks. Groups were supervised by a physiotherapist with the assistance of a student PT.

Sessions began with a 15 minute pool warm up consisting of range of motion and light stretching designed to loosen stiff joints (32) preparing subjects for further exercise. This was followed by a structured pool program of jogging, jumping jacks, marching, running, hurdling and swimming with the assistance of flotation devices along with punching, swinging and rowing of the arms aimed at achieving the desired heart rate. In week 1, the program lasted 5 minutes, with duration increased by 1 minute each week until week 6. From weeks 6 to 12, the structured program lasted for 10 minutes with increasing complexity of the routine each week.

The 3 aerobic gym stations were initially five minutes each and were graded in duration as described above. Maximum heart rate (MHR) was estimated at 220 and heart rate was increased from 132 (approximately 60% of MHR) at week 6 to 165 (approximately 75% of MHR) at week 12. These relatively low target ranges with slow progression were selected for this pilot study as a safety precaution and to ensure that even children with significant impairment could meet the targets.

HR was measured every 60 seconds during the gymnasium sessions using a telemetric device (Polar Vantage XL, Polar Instuments, Kempele, Finland).

Ratings of perceived effort (RPE) were reported by the child at the end of each station in response to the question "How hard did you work in this exercise?". The child rated their RPE while looking at a printed copy of the Borg Scale. This self reported scale is graded from 6 to 20 and uses descriptive cues for each category of exertion within the scale ranging from "very, very light" to "very, very heavy". The RPE has been shown to be a reliable measure of physical strain (33-36) but has not previously been examined in children with arthritis. Subjects also were asked to rate their exercise related pain on a VAS at the same time as rating their RPE.

Details on the routines followed at the four stations are as follows. At the cycle station, the child cycled at speed of 60 to 100 revolutions per minute. The initial speed was

determined at the habituation session as the one that the child felt he/she could sustain for the entire ride. The speed and resistance were adjusted to achieve the targeted HR. Similarly, on the treadmill the initial speed was determined at the habituation session and the speed and slope adjusted to achieve the targeted HR.

The Fitball® station consisted of leg movements (marching, bouncing, rocking from heel to toe, foot tapping and leg kicking) and arm movements (clapping, reaching, swinging and raising). Once mastered, these were combined into more complex routines designed to achieve the target heart rate range (37).

Strength training consisted of progressive upper and lower limb static (isometric) and dynamic exercises using soft weights and Thera-Band® exercises concentrated on the biceps and triceps in the arms; hip abductors, adductors and quadriceps in the legs; along with the abdominal muscles. The intensity of exercise in the arms and legs was graded according to number of repetitions and maximal effort as a percent of repetition maximum (RM). The RMs for the weights and Thera-Band® were determined during habituation testing sessions (33). In weeks 5 and 6, the focus was on a 0.25 RM for 10 repetitions. From weeks 7 through 12, the number of repetitions was systematically increased to 20, and the RMs from 0.25 to 0.50.

Analysis

Data were analyzed descriptively with means, medians and standard deviations for pre- and post-test scores for the exercise and functional measures. Paired Student's t-tests were used to assess the significance of changes in fitness parameters between the pre- and post- testing sessions. Effect size (ES) and standardized response mean (SRM) were calculated to assess the magnitude of the observed differences (38-42). The ES and SRM are standardized measures that provide an estimate of the magnitude of the effect of the intervention in terms of standard deviations of the pre- test (ES) or standard deviations of the change between measures (SRM). An ES or SRM of 0.2 is thought to represent a small effect, 0.5 a moderate effect and 0.8 or greater a large effect (38-42).

Results

Patients (tables 1 and 2)

Nine children were enrolled (five female). Median age was 9.4 years (range 8.0 to 11.1).

Three subjects had oligoarticular onset JIA with mild disease. Three subjects had polyarticular onset JIA with some functional limitation. Subjects 5 and 6 had systemic arthritis with 10 and 40 active joints respectively at enrolment – both had active hip disease and a CHAQ score of 3 at enrollment.

All subjects received non-steroidal anti-inflammatory medications at recruitment, Subject 4 was on low dose prednisone, 6 subjects were on methotrexate and 2 were on tumor necrosis factor (TNF) blockers at the beginning of the study.

Testing

All patients completed pre-testing. Both subjects with systemic arthritis dropped out and did not have post-testing. Subject 8 completed the study but not post-testing due to the inconvenience of travelling to the testing facility.

Fifteen exercise testing sessions were completed and were well tolerated with only Subject 4 requiring modification of the protocol due to limited hip mobility. Subject 3 was noted to have an effusion after testing in a knee joint that was noted to be active but not effused at the commencement of testing. Both subjects with systemic JIA reported pain during the testing sessions – with scores on a 10-point scale of 2.8 and 2.1

Table 1 – Characteristics of patients at commencement of study.

Subject	Age (yr)	Sex	Disease onset	Program completed	Sessions attended (max 24)	Ht (cm)	Wt (kg)	NSAID	CS	MTX	Anti-TNF
1	9.42	F	oligo	yes	7	142.1	31.9	+			
2	9.63	F	oligo	yes	20	130.1	47.1	+		+	
3	8.96	F	poly	yes	16	135.9	32.4	+		+	
4	8.04	F	poly	yes	23	126.9	31.5	+	+	+	+
5	8.71	M	systemic	no	6	124.7	24.6	+		+	+
6	10.38	M	systemic	no	14	133.6	27.8	+		+	
7	10.85	M	oligo	yes	14	156.6	40.7	+			
8	9.17	M	oligo	yes	10	133.1	28.2	+			
9	11.09	F	poly	yes	16	141.2	34.2	+		+	

yrs =years; Ht=height; Wt=weight; NSAID = non-steroidal anti-inflammatory drug; CS = corticosteroids; MTX = methotrexate; Anti-TNF = Anti- Tissue Necrosis Factor therapy (infliximab or etanercept); M = male; F= female; poly = polyarticular; oligo = oligoarticular; n/a = not available

Table 2 - Disease activity, quality of life and functional measures at commencement (pre) and on completion of training program.

Subject	Total effused Joints (lower limb)		Total Active Joints (lower limb)		CHAQ		JASI		QoL		HRQL	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1 (1)	0 (0)	1 (1)	0 (0)	0.25	0	95.7	97	4.5	4.7	4.5	4.9
2	2 (2)	2 (2)	3 (2)	3 (2)	0	0	99.5	95.7	5.6	7.7	7.1	8.3
3	3 (1)	3 (2)	6 (2)	6 (2)	0.62	0.87	93	93	7.2	8.5	6.8	7.7
4	19 (3)	17 (2)	40 (14)	22 (2)	2	1.75	65	69	6.2	3.4	4	6.1
5	6 (3)	n/a	10 (5)	n/a	3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
6	30 (7)	n/a	40 (13)	n/a	3	n/a	n/a	n/a	7.1	n/a	5.8	n/a
7	0 (0)	0 (0)	2 (0)	0 (0)	0	0	100	100	9	9.4	8.8	7.7
8	2 (0)	2 (0)	2 (0)	2 (0)	0	n/a	100	100	7.8	n/a	8.6	n/a
9	3 (0)	2 (0)	5 (1)	3 (0)	0.37	0.37	100	100	n/a	9.9	n/a	4.5

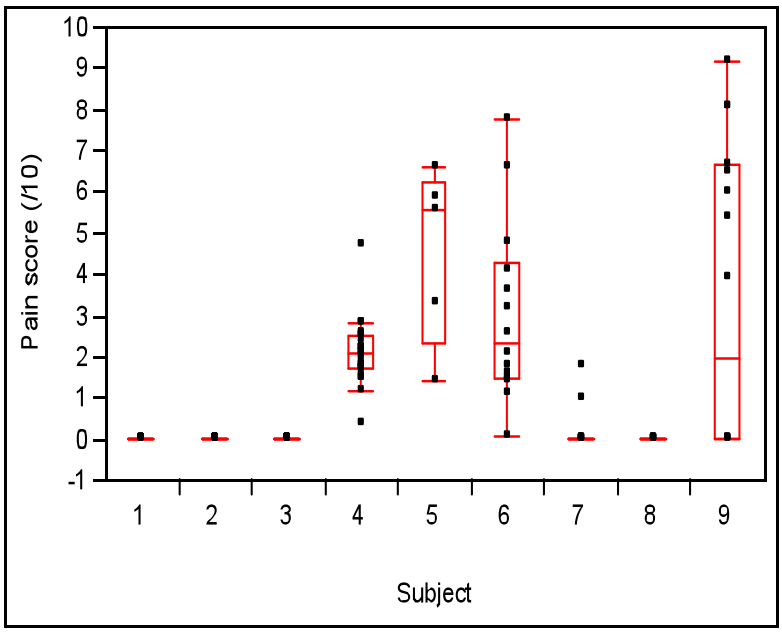
CHAQ = Child Health Assessment Questionnaire (score / 3); JASI = Juvenile Arthritis Status Index (score / 100) ; QoL =Quality of Life; HRQL = Health Related Quality of Life (score / 10); pre = prior to fitness training; post = after fitness training; n/a = not available

in one and 3.7 and 2.5 in the other. Subject 4 reported a score of 1.7 in the pre-testing session. Pain scores were generally mild and pain did not necessitate modification of the testing protocol.

Training Sessions

Subjects entered one of two exercise groups. The first group trained for the planned 12 weeks and the other for 16 weeks due to missed sessions over a holiday period. Of the seven subjects who completed the program, the median number of sessions attended was 15 of a maximum of 24 (range 7 to 23;mean=16.3;SD=5.4). Both subjects with systemic JIA had severe erosive hip disease and dropped out due to symptom exacerbation and prolonged fatigue after the exercise sessions.

Figure 1 – Box plot of pain scores on a visual analog scale during exercise sessions.



Box plot showing median 10th, 25th, 75th and 90th percentiles for pain experienced by the subjects as measured on visual analogue scale during the exercise sessions. Actual pain scores are shown by the superimposed dot plot.

Of the 123 exercise sessions, 62 (50.4%) were completed without any pain reported. Figure 1 shows the pain reported on VAS by each child. Four subjects reported no pain in any sessions; one reported pain in 2 sessions and 4 reported frequent pain. Subjects 5 and 6 with systemic arthritis reported significant pain with every session. Subject 4 with severe polyarticular JIA reported pain with every session requiring modification of the program. Subject 9 reported frequent pain with a severity of up to 9.2 out of 10, although this pain was not reported by instructors to hamper the child's participation.

As seen in table 3, the target HR was achieved on the stationary exercise bicycle and treadmill but not with the Fitball® station. Mean RPE also appeared higher in the stationary exercise bicycle and treadmill sessions than in the Fitball® sessions. Correlations between HR and RPE are shown in Table 3. Treadmill sessions showed the strongest correlation, followed by the stationary bicycle. Overall subjects with oligoarticular JIA appeared to have higher RPE during the gym exercises than those with polyarticular JIA (mean RPE 16.6/20 versus 10.1/20).

Table 3 – Heart Rate, Rating of Perceived Exertion (RPE) and their correlation during training exercise.

Activity	Mean Heart Rate (SD)	RPE /20 (SD)	Correlation Coefficient (95% CI)
Fitball	**131.9 (10.2)**	**10.6 (2.9)**	**0.46 (0.31-0.59)**
Exercise Bicycle	**146.2 (14.2)**	**13.1 (3.5)**	**0.55 (0.41-0.66)**
Treadmill	**141.1 (12.2)**	**12.9 (4.1)**	**0.79 (0.71-0.84)**
Pool	**n/a**	**11.2 (4.8)**	**n/a**

SD = standard deviation; CI = confidence interval; n/a = not available

Supervising therapists observed that during the Fitball® sessions children required a significant effort to stay balanced on the apparatus to avoid falling off. This concentration on balance and complexity of the routine distracted subjects from exerting maximal effort. These difficulties were not overcome through familiarity with the apparatus. Fitball® also aggravated hip arthritis in the two systemic arthritis subjects, and required modification for Subject 4 (who had polyarticular JIA with hip involvement).

No subject that completed the study experienced a definite worsening of arthritis. Three subjects had no change in active joint count and 4 improved. Subject 3's CHAQ deteriorated by 0.25, Subject 4 showed a decrease of 2.8 in QOL and Subject 7 a 1.1 deterioration in HRQL. For those that completed the study, the overall pattern was either an improvement or no change in functional and QOL parameters. Follow-up parameters were not available for those subjects that dropped out.

Effectiveness of training program

Complete results from exercise testing at both sessions were available for six subjects (tables 4 and 5).

Energy cost of locomotion was reduced in most subjects with a lower $VO_{2submax}$ percent ($VO_{2submax}$ %) at both 1.5km/hr and 3.0 km/hr walking speeds after training, although the P-values obtained from paired t-tests were non-significant. The ES and SRM for $VO_{2submax}$ % suggested moderate and small effect sizes at 1.5km/hr and 3.0km/hr respectively.

Absolute VO_2peak increased in four of six subjects – the changes were not significant. The ES and SRM suggested a possible small effect. However the relative VO_{2peak} measures did not support this finding.

Absolute and relative peak anaerobic leg power was improved in all subjects with a moderate ES and SRM. Leg muscular endurance did not show any overall change.

Table 4 – Results of exercise testing before and after (in brackets) training program.

	Relative Peak Power (Watts/Kg)		Relative Mean Power (Watts/Kg)		% Fatigue	
	Leg	Arm	Leg	Arm	Leg	Arm
Subject 1	6.1 (6.6)	1.7 (0.7)	4.9 (3.6)	0.6 (0.7)	32.0 (67.0)	100 (85.7)
Subject 2	7 (7.9)	3.5 (3.5)	3.6 (4.1)	1.8 (1.20)	86.0 (71.9)	75.0 (95.8)
Subject 3	5.6 (7.8)	1.7 (0.9)	4.2 (3.9)	0.7 (0.3)	38.1 (74.1)	100 (100)
Subject 4	2.6 (2.8)	0.6 (0.4)	1.3 (1.7)	0.3 (0.3)	84.2 (66.7)	81.8 (62.5)
Subject 5	3.9 (n/a)	1.0 (n/a)	1.8 (n/a)	0.9 (n/a)	56.1 (n/a)	62.4 (n/a)
Subject 6	3.6 (n/a)	1.5 (n/a)	2.3 (n/a)	0.8 (n/a)	51.1 (n/a)	82.4 (n/a)
Subject 7	10.6 (13.8)	4.8 (4.7)	7.6 (8.2)	2.3 (2.50)	48.5 (61.9)	79.2 (70.8)
Subject 8	10.4 (n/a)	4.8 (n/a)	7.9 (n/a)	2.9 (n/a)	55.8 (n/a)	77.8 (n/a)
Subject 9	7.3 (8.5)	3.5 (2.6)	5.3 (5.2)	2.0 (2.0)	43.3 (62.9)	52.6 (41.2)
Mean*	6.5 (7.9)	2.6 (2.1)	4.5 (4.4)	1.3 (1.2)	55.4 (67.4)	81.4 (76.0)
SD of mean*	2.6 (3.6)	1.6 (1.7)	2.1 (2.2)	0.8 (0.9)	23.7 (4.8)	17.7 (22.3)
Mean difference*	1.4	-0.5	-0.05	-0.12	12.1	-5.4
SD of difference*	1.1	0.45	0.7	0.3	23.3	14.4
P-value*	0.03	0.04	0.87	0.4	0.26	0.4
Effect size*	0.53	0.32	0.02	0.14	0.51	0.31
SRM*	1.21	1.12	0.07	0.37	0.52	0.38

n/a = not available; SD = standard deviation; SRM = standardized response mean.; * = Statistics only include those patients for which "pre" and "post" testing is available.

Absolute and relative peak anaerobic arm power was reduced in all subjects with a significant reduction in relative peak power and a small to moderate ES and SRM. Arm muscular endurance showed no real change.

Satisfaction questionnaires were completed by 8 subjects and 5 parents. Overall, families reported a positive experience with increased fitness and energy levels. The subjects

Table 5 – Results of exercise testing before and after (in brackets) training program.

	Relative VO_2 at 1.5km/hr (mL/kg/min)	VO2 % at 1.5km/hr	Relative VO_2 at 3km/hr (mL/kg/min)	VO_2 % at 3km/hr	Absolute VO_2peak (mL/min)	Relative VO_2peak (mL/kg/min)
Subject 1	**8.0 (9.6)**	**50 (38)**	**12.6 (14.1)**	**79 (56)**	**511 (845)**	**16.0 (25.2)**
Subject 2	**9.6 (10.8)**	**28 (32)**	**9.2 (14.6)**	**27 (46)**	**1613 (1478)**	**34.2 (31.8)**
Subject 3	**10.0 (9.6)**	**34 (30)**	**14.8 (10.3)**	**50 (32)**	**955 (1215)**	**29.5 (32.1)**
Subject 4	**19.4 (16.1)**	**67 (62)**	**21.1 (23.9)**	**73 (92)**	**911 (832)**	**28.9 (26.0)**
Subject 5	**14.1 (n/a)**	**56 (n/a)**	**17.2 (n/a)**	**68 (n/a)**	**620 (n/a)**	**25.2 (n/a)**
Subject 6	**18.3 (n/a)**	**62 (n/a)**	**20.5 (n/a)**	**70 (n/a)**	**809 (n/a)**	**29.4 (n/a)**
Subject 7	**12.6 (9.9)**	**25 (20)**	**15.1 (14.4)**	**30 (29)**	**2047 (2082)**	**50.3 (49.7)**
Subject 8	**13.1 (n/a)**	**39 (n/a)**	**15.4 (n/a)**	**46 (n/a)**	**1032 (n/a)**	**36.6 (n/a)**
Subject 9	**21.7 (11.7)**	**65 (31)**	**22.0 (18.2)**	**66 (36)**	**1141 (1337)**	**33.4 (37.1)**
Mean	**13.6 (11.3)**	**45 (36)**	**15.8 (15.9)**	**54 (49)**	**1196 (1298)**	**32.1 (33.7)**
SD*	**5.7 (2.5)**	**19 (14)**	**4.9 (4.6)**	**22 (24)**	**549 (464)**	**11.1 (9.0)**
Mean Difference *	**-2.3**	**-9**	**-0.1**	**-6**	**102**	**-1.6**
SD of difference*	**4.3**	**13**	**3.9**	**21**	**190**	**4.6**
P-value*	**0.3**	**0.14**	**0.89**	**0.54**	**0.25**	**0.79**
Effect size*	**0.40**	**0.47**	**0.02**	**0.27**	**0.19**	**0.14**
SRM*	**0.47**	**0.71**	**0.06**	**0.27**	**0.54**	**0.35**

VO_2 = oxygen consumption; VO_2peak = peak oxygen consumption; n/a = not available; SD = standard deviation; SRM = standardized response mean.; * = Statistics only include those patients fro which "pre" and "post" testing is available

reported that the most enjoyable experiences were related to time spent in the pool, interactions with instructors and the provision of small gifts as incentive for attendance. Parents reported that duration, frequency and scheduling of evening and weekend sessions was suitable. Long travel times were highlighted by many as a disincentive to participation. With the exception of two subjects who withdrew from the study, most others said they would consider participation in a similar program again.

Discussion

This study was undertaken as a pilot study for a large randomized controlled study to test the hypothesis that fitness exercise is beneficial in the physical function and quality of life of children with JIA. We have shown that children with JIA are able to participate safely in a 12–16 week exercise program, which is consistent with findings from other studies of aquatic (15,32) and land-based weight bearing fitness programs (14,42). These children can also undertake formal exercise testing protocols without experiencing severe pain or worsening of arthritis.

Some children with severe arthritis required modification of the exercise program and those with severe hip disease were able to complete exercise testing but not the exercise program. This suggests that intensive weight-bearing training programs may not be feasible in children with JIA and severe hip involvement.

The Fitball® program was included in the training schedule as it was hypothesized to cause less stress on the hip joints and provide an enjoyable form of aerobic training. However, subjects failed to achieve target HR ranges on the Fitball®, and it aggravated existing hip symptoms. Exercise bicycle and treadmill programs achieved the target HR, and did not worsen arthritis activity, suggesting that they would be acceptable forms of training for a larger study.

Published studies have generally used weekly or twice weekly protocols without clearly demonstrating improvements in fitness. It is believed that a minimum of twice weekly training is required for significant improvements in physical fitness (10). Only one uncontrolled study by Klepper et al. (14) has examined a three times per week aerobic program in children with arthritis over eight-weeks and showed improved fitness by field-testing. Based on the modest changes seen in our study it would seem that training more often than once or twice weekly is necessary.

While it is important to study programs with more frequent training sessions, geographical and logistic considerations, and family time constraints have an impact on attendance frequency. Training centers closer to subjects' homes were identified from parent surveys as a factor that may improve adherence. Incorporation of a home-based component to exercise programs, possibly with the aid of video taped or written instructions may also be a way of increasing exercise frequency. Future studies might best examine a combination of in class fitness exercise once weekly, with an additional twice-weekly exercise sessions at home guided by an exercise videotape.

During the exercise training sessions, RPE measured by the Borg Scale correlated well with measured HR during the treadmill and stationary bicycle sessions but not as well with the Fitball® sessions with correlation coefficients of 0.79, 0.55 and 0.46 respectively. These results suggest that RPE has potential as an indicator of physical strain in children with arthritis, and might be used to guide treadmill and stationary bicycle programs for these children.

A number of potentially beneficial outcomes were observed in this study. A reduced $VO_{2submax}$ % at both 1.5 and 3.0 km/hr was noted, suggesting a reduced energy cost of locomotion. The changes did not achieve statistical significance in this pilot study. The ES of 0.51 and 0.26 respectively were consistent with a small to moderate effect of the intervention. Waters et al. (43) estimated that in untrained children between the ages of 6 and 12 years, at an average customary walking speed of 4.2km/hr, O_2 consumption was approximately 28% of VO_{2peak} (20,43). At the slower speeds of 1.5 and 3.0 km/hr tested in this study O_2 consumption was higher (45% and 54% respectively for the pre-training measures) and may reflect differences in the testing protocol used or may suggest that children with arthritis have an elevated energy cost of locomotion. There is no previous literature on the energy cost of locomotion in JIA or on changes in energy cost of locomotion following training programs in children. Energy cost of locomotion may be an important and modifiable target for future studies of exercise in JIA.

Children without arthritis under the age of 14 years have been reported to experience an increase in VO_{2peak} of between 7 and 26% following training, with most studies reporting an improvement of less than 11% (44). Our study group showed a mean improvement of 7.1% in absolute VO_{2peak} (ml/min) but a reduction in relative VO_{2peak} (ml/kg/min) by 5.1%. These non-significant and inconsistent findings are likely a result of the small sample size of this pilot study.

Peak anaerobic power was significantly increased in the lower limbs but decreased slightly in the upper limbs of study subjects and may reflect the design of the training program which concentrated on lower limb exercise. Anaerobic capacity was not appreciably changed in this study and may reflect the format or frequency of the training protocol.

Measures of arthritis activity, functional status and quality of life were generally stable in those that completed the study, and overall satisfaction with the program was high.

While it is important to remember that this is a small pilot study without a control group and only fair compliance with the exercise program, our results suggest that it is safe, feasible and acceptable for children with arthritis who do not have severe hip involvement to participate in formal exercise testing and structured fitness programs. Furthermore it is possible that these programs will result in an improvement in physical fitness and quality of life of children with arthritis. These findings have been incorporated into the design of a randomized controlled trial examining the role of fitness exercise in improving physical function and quality of life for children with JIA.

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Chapter 3

Reliability of exercise testing and functional activity questionnaires in children with juvenile arthritis

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Abstract

Objective

To determine the reliability of formal exercise testing and the reliability of functional and activity questionnaires in children with juvenile idiopathic arthritis (JIA).

Methods

Children with JIA of any subtype ages 8-16 years who were recruited to a randomized trial comparing different exercise therapies participated in 2 pre-intervention sessions of exercise testing 2-6 weeks apart. Exercise testing included 1) submaximal oxygen uptake ($VO_{2submax}$) 2) peak VO_2 (VO_{2peak}), and 3) anaerobic power using modified Wingate tests (Want). Two physical function questionnaires (the Childhood Health Assessment Questionnaire [CHAQ] and Revised Activity Scale for Kids [ASK]) and 1 daily physical activity questionnaire (the Habitual Activity Estimation Scale [HAES]) were also completed at these times. Test-retest reliability was assessed using type 3, intra-rater intraclass correlation coefficient ($ICC_{3,1}$) and Bland and Altman plots were used to determine limits of agreement.

Results

Data were available for 74 patients (58 girls). $VO_{2submax}$, VO_{2peak}, and Want demonstrated high reliability ($ICC_{3,1}$ 0.82, 0.91, and 0.94, respectively). CHAQ and ASK questionnaires also had very high reliability ($ICC_{3,1}$ 0.82 and 0.91, respectively). The HAES demonstrated low reliability for total activity score ($ICC_{3,1}$ 0.15) and moderate reliability when the number of very active hours was analyzed separately ($ICC_{3,1}$ 0.59).

Conclusion

Results of this investigation suggest that exercise testing and functional questionnaires in children with JIA are consistent and reliable. Reliability of the HAES total score was poor, but moderate when the very active hours subscale score was used.

Introduction

Childhood arthritis is a relatively common and sometimes debilitating chronic disease afflicting approximately 1 in 1,000 children (1,2). It has been suggested that children with arthritis are deconditioned due to both inactivity and the disease process (3). Deconditioning may contribute to early fatigue and ongoing disability commonly described in juvenile idiopathic arthritis (JIA). Exercise has recently been shown to decrease disability and reduce arthritis activity in adults, leading to an increasing interest in exercise interventions in childhood arthritis (3,4).

To determine the efficacy of exercise interventions, reliable outcome measures must be used. Physiologic measures of aerobic and anaerobic function have been utilized as measures of fitness and deconditioning and as clinical outcomes when assessing interventions in children and adults. Self-reported questionnaires are also used as a subjective measure of function, and are important because they provide a quick and efficient method of evaluating an individual's health status. Changes in overall function may be evaluated through exercise testing or functional questionnaires and thus knowledge of the reliability (reproducibility) of these measures is vital in determining the efficacy of any treatment or rehabilitation program.

Submaximal and maximal treadmill testing have proven highly reproducible in healthy children and adults (5–7). Reliability studies using a walking protocol suggest a co-efficient of variation (CV) ranging from 2% to 7.5% and 12.4% for maximal oxygen uptake (VO_{2max}) and submaximal oxygen uptake ($VO_{2submax}$), respectively, on repeated testing in young healthy children (5–7).

Past research also suggests good reliability of physiologic tests in adults and children with certain chronic diseases. Submaximal walking at 3.2 km/hour and 7.2 km/hour was found to be highly reproducible in 30 women with rheumatic disease (8). A small study of 9 adults with cystic fibrosis found a CV of 6.9% in measures of maximal oxygen consumption (9). Almost perfect reliability of peak VO_2 (VO_{2peak}) was reported in 16 children with juvenile dermatomyositis (juvenile DM) (10). However, far fewer studies have evaluated the reliability of various exercise testing parameters in children with arthritis and none have looked at exercise testing using a treadmill. In a small feasibility study, 23 patients with childhood arthritis completed maximal cycle testing with a standard error of measurement (SEM) of 9.5% (11). Treadmill testing typically results in higher peak heart rates, oxygen consumption, and perceived exertion scores than cycle testing, making it difficult to compare the 2 testing modes (12,13). Peak oxygen consumption can differ by as much as 5–7%, with one study reporting interindividual differences ranging from 18.7% to -3.9% between treadmill and cycle ergometer testing (12,13). No other published studies have measured the reliability of exercise testing parameters in children diagnosed with childhood arthritis.

Anaerobic testing, specifically the Wingate anaerobic test (Want), which is used to measure local muscle strength and endurance in terms of peak power (watts), is a common exercise testing parameter used in children. It is frequently reported that participants in the Wingate test may benefit from a familiarization session (14,15). A trial

of 25 healthy men indicated a 14% improvement in peak power following a familiarization session (14); a learning effect was also noted in a study of 39 disease-free children and adolescents undergoing a single-leg Want test in which peak power improved significantly at the second test (14,15). Despite improvements in total peak power from test to test, high reliability coefficients were reported for peak power and mean power (intraclass correlation coefficients [ICC] 0.89 – 0.98) (15). Few data exist on the reliability of anaerobic testing in children with chronic musculoskeletal disorders; however, Takken et al (10) demonstrated a high reliability of the Want in children with juvenile DM. No studies have determined the reliability of anaerobic testing using the Want protocol in children with JIA.

Functional questionnaires are commonly used to evaluate children with chronic disease. The Childhood Health Assessment Questionnaire (CHAQ) disability index (DI) was developed to evaluate physical function and disability in children with arthritis and has demonstrated high internal reliability and test–retest reliability (16). The Activity Scale for Kids (ASK) questionnaire was developed to allow children with chronic musculoskeletal disorders to self-report disability and has been validated in children with musculoskeletal disorders (17). Eight additional questions related to the performance of physical activity tasks were added to the original ASK questionnaire to form the Revised ASK. Data about the validity of the Revised ASK have been presented in abstract form (18).

The Habitual Activity Estimation Scale (HAES) is a self report questionnaire that quantifies the amount of time spent in different intensities of physical activity over the preceding 2-week period (19). Reliability of the HAES questionnaire was evaluated in a study of 129 school children where the questionnaire was completed by parents as a proxy for the subjects; reports of generalizability coefficients indicated good reliability (0.75– 0.92) (20). The reliability of these functional and physical activity questionnaires has been confirmed in previous studies; however, the reliability of the Revised ASK and HAES questionnaires has not been studied in the JIA population, thus making this a valuable opportunity to determine the reliability of these scales. The purpose of the present study was to investigate the test–retest reliability of 1) submaximal treadmill walking at 3.0 km/hour, 2) maximal treadmill testing, 3) isokinetic Wingate testing, 4) the HAES, 5) the CHAQ, and 6) the Revised ASK questionnaire in children with JIA ages 8 –16 years.

Patients and Methods

Patients

The study group comprised 80 children ages 8 –16 years diagnosed with JIA using the International League of Associations for Rheumatology criteria (21) and enrolled in a randomized trial of fitness exercise. Patients were recruited from the rheumatology clinics at The Hospital for Sick Children and Bloorview Kids Rehab in Toronto, Ontario between 2003 and 2005. All patients with JIA eligible for the study were identified from a search of a rheumatology database and sent a letter informing them of the study (randomized controlled trial [RCT]). The letter was followed with a phone call from a

research coordinator to determine interest and eligibility. Children were excluded if they had unstable disease (defined as being likely to change medication regimen within the next 12 weeks); had any cardiac, metabolic, or pulmonary disease had moderate or severe hip pain while walking; had any active systemic symptoms (fever or rash); or engaged in ≥3 hours of structured physical activity per week outside of school.

Patients completed 3 exercise testing sessions: habituation (test 1), baseline (test 2), and post-testing (test 3) as part of a larger randomized blinded study of the effect of fitness exercise on physical function. We used the data collected at test 1 and test 2 (between which no intervention occurred) to determine the test-retest reliability of the various outcome measures. The period between test 1 and test 2 ranged from 2 to 6 weeks. Two patients from our sample were tested more than 6 weeks apart due to the closure of our laboratory during the Toronto severe acute respiratory syndrome (SARS) outbreak.

Exercise testing

Testing sessions were held on an evening or weekend in the cardiopulmonary exercise laboratory at The Hospital for Sick Children. Each test lasted 2.5 hours with a single patient tested on weeknights and up to 3 patients tested on weekends. A trained exercise physiologist and research coordinator were present for all tests. At test 1, patients were familiarized with the testing equipment, procedures, and staff. A description of each procedure was given to the children who were then led through each testing procedure and allowed time to familiarize and ask questions of the staff. Tests completed at the first session were repeated 2-6 weeks later during test 2 (scheduled according to the family's convenience).

Exercise testing procedures

Percent body fat was calculated from skin-fold measurements at the bicep, tricep, suprailiac, and subscapular sites and was performed by exercise physiologists trained in the technique. Measurements were taken on the right side of the body in rotating order, in accordance with the American College of Sports Medicine guidelines (22). The average of 3 trials was calculated and entered into the Slaughter equation (23). Spirometry including forced vital capacity (FVC), forced expired volume in 1 second (FEV), and maximal ventilatory volume (MVV) was performed using standard practices and techniques (Vmax Series, V6200 Autobox, and Vmax Series Software; SensorMedics, Yorba Linda, CA).

Walking economy ($VO_{2submax}$) was measured by a treadmill walking task at 3 km/hour for 5 minutes. Expired gases were collected continuously, with ventilatory equivalent, oxygen consumption (VO_2), carbon dioxide production, and the respiratory exchange ratio (RER) recorded at 20-second intervals (Physiodyne Max-II metabolic cart; Physiodyne Instruments, Quogue, NY). Heart rate was monitored continuously using a 4-lead electrocardiogram system (GE Case 8000, General Electric, Milwaukee, WI).

Steady state was recorded as the average of the last 3 minutes of VO_2 (ml/kg/minute) measurements. VO_{2peak} was assessed through a graduated treadmill test to volitional

fatigue. An individualized test format was used, with VO_{2peak} achieved through gradual increases in speed and/or grade. Criteria used to determine an acceptable VO_{2peak} performance included obtaining heart rate maximum values and an RER=1.1. Expired gases and heart rate were recorded as described above.

Anaerobic muscle endurance and strength (peak power) were assessed by a modified Want protocol using an isokinetic cycle ergometer (Biodex lower body cycle; Biodex Medical Systems, Shirley, NY). Patients were given a 2-minute warm-up and then instructed to pedal "as fast as you can" for 10- and 30-second periods. Patients pedalled at 90 revolutions per minute; the highest wattage obtained was recorded as peak power and the score at the completion of the task was recorded as end power.

Functional and activity questionnaires

During each testing session, patients completed the CHAQ DI, Revised ASK, and HAES questionnaires with the assistance of the research coordinator. The research coordinator provided a detailed explanation of how to fill in each questionnaire and was also available to read the questions to the participant. The CHAQ DI consists of questions from 8 functional domains comprising eating, dressing and grooming, walking, arising, hygiene, reach, activities, and grip. A summary score is given based on the 8 functional activity domains and is rated on a 3-point scale (where 0 indicates no limitations and 3 indicates severe limitations). The Revised ASK contains 38 items related to various daily living and physical activity-related tasks. Children use the 5-point scale of the Revised ASK to compare their ability to perform tasks with that of their healthy peers. Scores vary from -2 to 2, representing performing tasks "much worse" (score -2), "the same as" (score 0), and "much better" than their peers (score 2) (18). The total score is calculated by averaging the answered items (18).

The HAES questionnaire is a physical activity questionnaire in which children are asked to recall physical activity on a typical weekday and weekend day during the past 2 weeks. Activity is categorized into 1 of 4 intensity categories: inactive, somewhat inactive, somewhat active, and very active. Time spent in each of the 4 categories is reported by respondents and summary scores of total activity (TA) hours ("somewhat active" plus "active") and total very active hours scores (VA) are calculated separately for weekends and weekdays (19).

Statistical analysis

Test-retest reliability was assessed by comparing means using $\overline{\text{type 3}}$, intrarater intraclass correlation coefficient ($ICC_{3,1}$) considered to indicate substantial agreement while an ICC>0.8 indicated excellent agreement (24). Paired differences between test 1 and test 2 were plotted against the average of the 2 tests in accordance with the Bland and Altman method (25). Limits of agreement (LOA) were calculated as twice the standard deviation of the mean paired difference (25). The standard error of measurement was calculated as the SD of the square root of (1-ICC), with the 95% confidence interval (95% CI) calculated (26). The data were analysed using JMP 5.1.2 (SAS Institute, Cary, NC) and SPSS 12.0 (SPSS, Chicago, IL) statistical software.

Table 1. Reliability analysis of exercise testing in juvenile idiopathic arthritis*

Exercise test	Test 1	Test 2	Paired difference	$ICC_{3,1}$	LOA	SEM	95% CI of SEM
$VO_{2submax}$ (liters/minute) at 3.0 km/hr	0.50±0.14	0.48±0.12	0.02±0.08	0.82	±0.16	0.03	±0.06
$VO_{2submax}$ (ml/kg/minute) at 3.0 km/hr	11.6±1.9	11.1±1.9	0.47±1.7	0.60	±3.4	1.1	±2.1
VO_{2peak} (liters/minute)	1.5±0.5	1.5±0.5	0.02±0.22	0.91	±0.44	0.07	±0.13
VO_{2peak} (ml/kg/min)	34.0±7.0	34.2±8.5	0.62 ±5.5	0.72	±11.0	2.9	±5.70
Power at 10 sec (watts)	198.0±122.0	241.0 ±132.0	48.0 ±61.0	0.92	±122.0	17.3	±33.9
Power at 10 sec (watts kg^{-1})	4.1±1.8	5.1 ±2.0	1.10±1.3	0.78	±2.6	0.61	±1.20
Power at 30 sec (watts)	214±119	235 ±119	24.0 ±49.0	0.94	±98.0	12.0	±23.5
Power at 30 sec (watts kg^{-1})	4.5±1.8	5.0±1.8	0.55±1.1	0.85	±2.2	0.43	±0.84

Values are the mean ± SD unless otherwise indicated. ICC = intraclass correlation coefficient; LOA = limits of agreement; SEM = standard error of measurement; 95% CI = 95% confidence interval; $VO_{2submax}$ (liters/minute) = absolute submaximal oxygen uptake; $VO_{2submax}$ (ml/kg/minute) = relative submaximal oxygen uptake; VO_{2peak}= maximal oxygen uptake to volitional fatigue; Min =minutes; sec=seconds

The protocol was approved, and all children and their parents gave written consent in accordance with the Research Ethics Boards at The Hospital for Sick Children and Bloorview Kids Rehab.

Results

A total of 80 patients were enrolled; 5 dropped out after test 1 and 1 patient was ineligible due to a change in diagnosis. Complete data were available for 74 patients (58 girls). Mean ± SD age was 11.4 ± 2.3 years (range 8 -16). The JIA subtypes included

polyarticular (n = 37), oligoarticular (n = 20), systemic (n = 5), psoriatic (n = 5), and enthesitis related (n = 7). Active joint counts varied from 0 to 28 at test 1 with a group average of 2.84 ± 5.8 joints. The mean ± SD age at onset was 8.1 ± 3.6 years with an average disease duration of 3.74 ± 3.21 years. An average of 0.76 ± 1.8 joints had limited range of motion in our population (range 0 —9) according to a score of 0.1 on the Pediatric Escola Paulista de Medicina Range of Motion Scale (27). The mean ± SD patient-rated pain, scored from the CHAQ, was 1.7 ± 2.1 (range 0 -7.3) and overall mean ± SD quality of life scored on a 10-cm visual analog scale was 8.3 ± 1.7 (range 0 -10). The mean ± SD time between test 1 and test 2 was 21 ± 11 days. Mean ± SD height was 148 ± 13.5 cm (range 121-176), weight was 45 ± 15.8 kg (range 22-94), body mass index was 20.4 ± 4.6 kg/m2 (range 12.5-37.5), and body fat was 23.7% ± 8.2% (range 8.5-43%) at baseline. The change in weight between test 1 and test 2 was determined using the average absolute paired difference (mean ± SD change 0.84 ± 0.9 kg). Pulmonary function was normal in our sample, with a mean FEV_1 percent predicted of 89% ± 10.6% (range 61-110%), mean FVC percent predicted of 87% ± 10.1% (range 68 -111%), and mean MVV percent predicted of 79% ± 17% (range 30 -148%) (28).

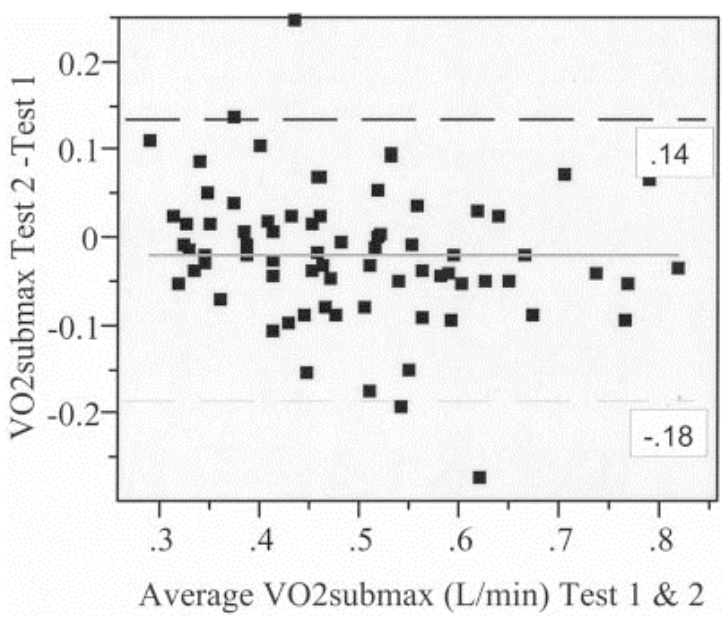

Figure 1. Bland and Altman plot of submaximal oxygen uptake ($VO_{2submax}$; liters/minute). The paired difference between tests **1** and 2 is represented on the vertical axis, while the paired average is represented on the horizontal axis. The solid line is the overall paired average. The broken lines represent 2 SDs above and below the overall average and are therefore the limits of agreement. Under a normal distribution we would expect ~95% of the data to fall between these lines

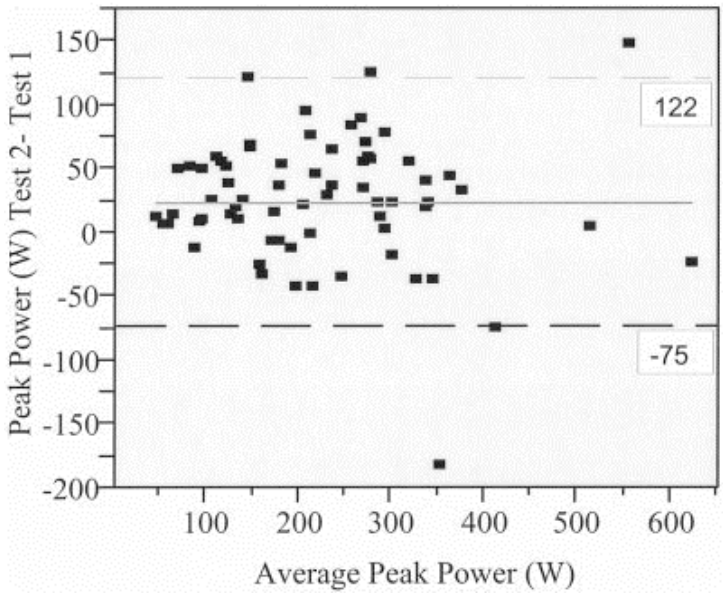

Figure 2. Bland and Altman plot of peak power (watts). The paired difference between tests 1 and 2 is represented on the vertical axis, while the paired average is represented on the horizontal axis. The solid line is the overall paired average. The broken lines represent 2 SDs above and below the overall average and are therefore the limits of agreement. Under a normal distribution we would expect ~95% of the data to fall between these lines.

Table 2. Reliability analysis of functional and activity questionnaires in juvenile idiopathic arthritis*

Scores	Test 1	Test 2	Paired difference	ICC	LOA	SEM	95% CI SEM
CHAQ DI	0.33±0.48	0.29±0.44	—0.05±0.27	0.82	±0.5	0.1	±0.2
Revised ASK	0.07±0.52	0.03±0.47	—0.04±0.30	0.91	±0.6	0.1	±0.2
HAES WD TA	6.1 ±2.1	6.8±2.5	0.66±3.0	0.15	±6.0	2.8	±5.4
HAES WE TA	6.9 ±2.8	6.9±3.0	0.03±2.7	0.34	±5.4	2.2	±4.3
HAES WD VA	2.2 ±2.0	2.1 ±1.9	0.05±1.8	0.59	±3.6	1.2	±2.3
HAES WE VA	2.3 ±2.3	2.3±2.3	0.03±2.7	0.34	±5.4	2.2	±4.3

* Values are the mean ± SD unless otherwise indicated. CHAQ DI = Childhood Health Assessment Questionnaire disability index; Revised ASK = Revised Activity Scale for Kids; HAES = Habitual Activity Estimation Scale; TA = total activity; VA = very active; WD = weekday; WE = weekend; see Table 1 for additional definitions.

Functional and activity questionnaires

The CHAQ DI and Revised ASK both demonstrated high test-retest reliability and little change from test 1 to test 2 (Table 2). The HAES physical activity questionnaire had low reliability for both the weekday and weekend day as measured by total activity hours. In a sub-analysis of the HAES data, 3 outliers were excluded from the data (2 patients who had been tested more than 6 weeks apart and 1 patient who was ultimately found ineligible from the RCT). The ICCs for all of the HAES measures remained the same except for VA hours during the weekend (ICC3,1 0.43) and TA weekday hours (ICC3,1 0.20). In another separate analysis of the HAES, VA hours showed less variability in the weekday measurements.

Discussion

The findings of this study indicate that maximal and submaximal treadmill testing as well as anaerobic testing using a modified Want protocol are highly reliable in children with arthritis. The Revised ASK and CHAQ DI were also found to be reliable measures of functional status. The HAES questionnaire had low reliability in determining activity levels of children with arthritis when the total active hours score was used; however, when the very active hours score was used the score was reliable, especially for weekday activity.

The population of patients in this study is representative of what has been reported in other urban academic centers. Disease severity, assessed by active joint counts, was 2.84 joints in our population and is in keeping with active joint counts reported in other recent studies (29, 30).

Walking economy, the amount of energy required to ambulate, is determined by monitoring oxygen consumption during submaximal (below maximal effort) walking tasks ($VO_{2submax}$). Submaximal walking economy correlates well with the energy required to perform tasks of daily living and may be used as an assessment of physical function. A lower requirement for oxygen by the working muscle during submaximal tasks indicates good walking economy. The reliability of submaximal treadmill walking tasks in our population is similar to the reproducibility findings of submaximal tasks in healthy children (6, 7, 31). Little change was found in our study between tests however, when the data were plotted according to the Bland and Altman method (Figure 1), a small improvement in economy was noted, suggesting that a brief familiarization period might be beneficial to reduce measurement error. Tseh et al (6) found that $VO_{2submax}$ improved only slightly over 3 separate walking trials in able-bodied children after a familiarization session. Although our testing indicates excellent reliability, it appears slightly lower than that seen in healthy children (6,31). This could be explained by the longer period between tests in our study (2- 6 weeks) as compared with other studies (1 day to 1 week). This finding agrees with the work by Figueroa-Colon et al (7) who reported a larger CV (12.4%) in prepubertal girls who underwent submaximal walking tests 6 weeks apart. Variability of maximal oxygen consumption has also been shown to increase when the duration between testing sessions is lengthened (7,32).

There may also be greater variation in $VO_{2submax}$ due to the disease state in our children. Children with arthritis may have greater variability in $VO_{2submax}$ dependent on their level of deconditioning, resulting in a greater variation in oxygen transport and availability (33). Katch et al (34) found a 5.6% variation in VO_{2max} testing in 5 highly trained subjects participating in 80 total maximal tests repeated every 2 days for 2-4 weeks. Biologic variation accounted for 90% of the within-subject variation while 10% of the variation was determined to be technical error (34).

Findings of highly reliable VO_{2peak} measurements from treadmill testing in this study are consistent with those of Takken et al (11) (SEM of 9.5% or 0.16 liters/minute) in children with JIA using a cycle ergometer. Similar findings were also reported in a study of 16 children with juvenile DM using repeated cycle testing (10). Maximal treadmill testing in healthy children found a CV between 5% and 7.5% in prepubertal and adolescent girls (7,35) and 5.8% in healthy boys when tested 4 weeks apart (5). However, we found a lower degree of agreement in relative VO_2 measurements (ml/kg/minute) than in absolute VO_2 (liters/ minute). This can be accounted for by a fluctuation in weight observed in the children between test 1 and test 2 rather than change in exercise response.

Differences in the findings from previous studies and the present study may stem from the length of time between testing sessions, or could also be related to the conditioning status of the children involved in the trial. Unnithan et al (5) reported that the subjects they studied were active to very active, which may have reduced the between-subject and between-testing session variability. Frost et al (33) suggest that potential confounders including diet, walking and running mechanics, circadian variation, ambient temperature, footwear, and length of treadmill habituation may influence the results of reliability studies of exercise tests. In our study, the laboratory environment was controlled; however, other possible confounders such as walking and running mechanics were not controlled in our patients.

Peak power in our sample, as measured by a modified Want, agreed with other studies examining anaerobic power in healthy and chronically ill children and adolescents. Reliability of peak power during a single-leg Want test was high in healthy children, adolescents, and young adults (15). Takken et al (10) reported high reproducibility of the Want in children with juvenile DM (ICC 0.87). Despite the high reliability reported in all the previous studies, an increase in peak power (watts) from the first to second test was noted. Results from the Want tests performed in our study also demonstrated an average increase in peak power varying from 21 to 43 watts (SEM 12.0-17.0) from the first to second test (Figure 2). A learning effect may occur with this test, indicating the potential need for familiarization prior to data collection.

Reliability results from our study parallel those of Singh et al, who reported a Spearman's correlation coefficient of 0.79 for the CHAQ DI in children with juvenile rheumatoid arthritis (16). Results for the Revised ASK in the current study (ICC 0.91) also correspond well with reliability findings from the original ASK questionnaire, which had an ICC of 0.97 in patients with musculoskeletal disorders (17). The reliability of both functional questionnaires is similar and very high, suggesting that either could be used to assess the response to exercise testing; however, the Revised ASK has not been tested for

sensitivity to change over time and it is likely premature to use this questionnaire as a major outcome measure in a clinical trial.

Analysis of the TA hours from the HAES questionnaire demonstrated poor reliability on both weekdays and weekends. However, in a separate analysis of weekday VA hours, reliability was moderate (ICC 0.59). There are several possible explanations for these findings. Seasonal variations in physical activity patterns have been well documented (36). Because some of our patients were tested up to 6 weeks apart, significant changes in season/weather may have resulted in changed activity patterns, resulting in greater variability. A shorter period between tests may have captured a more consistent period of physical activity pattern. In addition, previous reliability studies involving the HAES have used a parent proxy rather than child self-report when completing the questionnaire. In this study, children were asked to complete the questionnaire on their own assisted only by a research coordinator; it is also possible that children and youth may not be reliable at recalling their day-to-day activity without parental input. Based on the findings that vigorous activity reporting (VA hours) is moderately reliable, it may also be suggested that children find it more difficult to recall activities of lower intensities.

In our study, exercise testing in children with JIA was found to be highly reliable over a 2 to 6-week retest interval. Although submaximal and maximal treadmill testing along with the modified Want are highly reproducible, children may benefit from a brief familiarization session to decrease variation associated with a learning effect. Physical function, as characterized by the Revised ASK and CHAQ DI, showed high reproducibility in children with JIA as previously reported in children with musculoskeletal disease. Physical activity participation as determined by the HAES questionnaire demonstrated slight reliability when using the total active hours score, but moderate reliability when very active hours were used.

The findings of this study indicate that exercise testing procedures and measures of function are highly reproducible in children with JIA. More research is required to determine how best to measure and characterize the level of usual physical activity in children with arthritis.

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Chapter 4

The effects of vigorous exercise training on physical function in children with arthritis: a randomized, controlled, single-blinded trial.

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Abstract

Objective

To examine the effectiveness of high-intensity aerobic training compared with low-intensity training in terms of energy cost of locomotion, peak oxygen uptake, peak power, and self-reported physical function in children with juvenile idiopathic arthritis (JIA).

Methods

Eighty children with JIA, ages 8-16 years, were enrolled in a randomized, single-blind controlled trial. Both groups participated in a 12-week, 3-times-weekly training program consisting of high-intensity aerobics in the experimental group and qigong in the control group. Subjects underwent exercise testing measuring submaximal oxygen uptake at 3 km/hour ($VO_{2submax}$) as the primary outcome, maximal oxygen uptake, and peak power at the beginning and end of the program. Physical function was measured using the Child Health Assessment Questionnaire (CHAQ).

Results

The exercise program was well tolerated in both groups. There was no difference in $VO_{2submax}$ or any other exercise testing measures between the groups through the study period and no indication of improvement. Both groups showed significant improvements in CHAQ with no difference between the groups. Adherence was higher in the control group than the experimental group.

Conclusion

Our findings suggest that activity programs with or without an aerobic training component are safe and may result in an important improvement in physical function. The intensity of aerobic training did not seem to provide any additional benefits, but higher adherence in the qigong program may suggest that less intensive regimens are easier for children with JIA to comply with, and provide a degree of benefit equivalent to more intensive programs.

Introduction

Juvenile idiopathic arthritis (JIA) affects 1 in 1,000 children (1). These children participate in less physical activity and have more sleep hours than their peers (2). A meta-analysis of studies examining peak oxygen consumption (VO_{2peak}) showed a 22% reduction in children with arthritis compared with their peers (3). Other studies have shown a reduction in muscular endurance in children with JIA (4,5). These factors may lead to a spiral of deconditioning and inactivity resulting in further deconditioning and limited participation, culminating in prolonged disability (6).

Traditionally, physical therapy for JIA has aimed to manage pain, preserve range of motion, and limit the strain on arthritic joints (7,8). More active forms of therapy have been recently instituted (9), and guidelines have included recommendations for fitness and strengthening exercise to improve function and promote lifetime physical activity (10).

Systematic reviews examining aerobic training in adults with rheumatoid arthritis (RA) found improvements in aerobic capacity, muscle strength, and disease activity, with possible beneficial effects on pain, function, and quality of life (11,12). Early studies in children suggested that exercise was well tolerated and might improve function (13–15). However, these studies were small, uncontrolled, and relied on field testing rather than laboratory measurements. Subsequently, Oberg et al (16) reported that children with arthritis achieved improvements in muscular strength and endurance after a 3-month training program and that electromyographic abnormalities improved with training. An uncontrolled study of 25 children with polyarticular JIA demonstrated improvements in aerobic capacity and flexibility after an 8-week, low impact aerobic and resistance program (17). A recent randomized controlled study of aerobic pool exercise involving 54 children suggested (nonsignificant) improvements in quality of life, joint status, and submaximal endurance (18).

Maximal oxygen uptake (VO_{2max}) protocols used to assess fitness in adults are rigorous and have proven difficult to apply in pediatrics. Less intensive peak VO_2 (VO_{2peak}) protocols have been used in children (19). However, VO_{2peak} may be an inappropriate outcome measure in groups with significant limitations. Instead, submaximal VO_2 ($VO_{2submax}$) may be used as a predictor of VO_{2max} or as an independent measure of performance in standardized activities (18,20 -23). Giannini and Protas (24) reported that children with JIA had higher submaximal heart rate (HR) and tended towards higher $VO_{2submax}$ (higher oxygen requirement) as compared with matched controls during a bicycle task. Children with JIA may also have an exaggerated energy cost of locomotion (higher $VO_{2submax}$) that manifests as early fatigue during normal activity. Thus $VO_{2submax}$ may provide a means of measuring disability in JIA and provide a well-tolerated measure of aerobic fitness and response to therapy.

The goals of this study were to examine the effectiveness of a high-intensity 12-week program in terms of $VO_{2submax}$ in children with inflammatory arthritis and to determine the effectiveness of this program in terms of self-reported physical function, VO_{2peak}, and peak power.

Patients and Methods

Patients

Eighty patients with JIA, ages 8–16 years, who were considered stable by their rheumatologist and unlikely to require modification of therapy during the study were recruited from The Hospital for Sick Children. No restrictions were placed on medication use, but every effort was made to maintain stable dosage through the study. Patients were excluded if they had significant cardiac, pulmonary, or metabolic comorbidity; if they had moderate or severe hip pain while walking (judged by the patient as ≥3 on a 4-point scale) because hip pain was identified as a major limitation to participation in our pilot study (25); if they were engaged in ≥3 hours per week of extracurricular physical activity, excluding physiotherapy pool programs because these children might not show additional gains from fitness training; or if they were unable to cooperate with training or testing.

Block randomization balanced for pubertal stage (less than or equal to Tanner stage 2 versus greater than or equal to Tanner stage 3) and degree of disability as measured by the Childhood Health Assessment Questionnaire (CHAQ) (26) (score ≥0.125 versus score <0.125) was undertaken, as these factors might independently influence fitness measures. The concealed allocation scheme involved sequential opaque envelopes in blocks of 2-4. Although it was impossible to blind the subjects because the programs were obviously different, study personnel responsible for administering the fitness testing, statistical analysis, and manuscript preparation were blinded to patient allocation.

Interventions

Groups undertook a 12-week exercise program consisting of 1 supervised session and 2 unsupervised sessions per week. The supervised sessions, held in 6 locations, were led by an exercise therapist with a 1:4 instructor to subject ratio. Experimental sessions commenced with a 10-minute warm-up mimicking the exercise routine, followed by light stretching. The aerobic training program, drawn from dance and martial arts (cardio-karate), was designed to avoid activities that might be unsafe (details of the exercise programs are available from the authors). The 30-minute sessions increased progressively in intensity from low to moderate/high as tolerated. Sessions concluded with 5–10 minutes of passive stretching. HR was measured either as a manual 15-second count at the carotid artery or by HR monitor (Polar 650i, Polar Instruments, Kempele, Finland). Target HR range was >75% of the maximal HR (MHR) determined from VO_{2peak} testing conducted at enrolment. Instructors encouraged subjects to exercise in this range. Rating of perceived exertion (RPE) using the children's OMNI scale (27) was used to determine exercise intensity.

Control sessions were held at the same locations as the experimental group session, but at different times. The program was based on qigong (28), a gentle relaxation program similar to tai chi. Tai chi has been reported as a safe and feasible activity for adults with RA (29). Sessions were based on an 18-posture program designed to avoid aerobic training or elevating HR. Each posture was repeated 8 times. A cool down of gentle

stretching concluded the session. Subjects recorded HR and RPE to ensure that it was below 75% of MHR. Unsupervised sessions for both groups followed the same program as in-class sessions, but used videotaped instruction. Subjects were asked to complete 2 at home video sessions per week, and if a class session was missed, the subject was instructed to make up that session at home.

Outcomes

Subjects underwent 3 testing sessions: the first at enrolment, during which subjects were familiarized with the testing equipment and the data collected was used in balancing the randomization process; the second planned 2 weeks later at the time of group allocation and just prior to commencement of the program; and the third within 2 weeks of completion of the training program. At each session, height (Harpenden Stadiometer, London, UK) and weight (SR555 Stand-on Scale System, SR Instruments, Tonawanda, NY) measurements were obtained to the nearest 0.1 cm and 0.1 kg, respectively, with the subjects wearing light clothes, but not shoes. Percent body fat was calculated from skin-fold measurements of the bicep, tricep, subscapular, and suprailiac crest regions using the average of 3 trials and entered into the Slaughter equation (30).

The $VO_{2submax}$ was measured while treadmill walking at 1.5 km/hour and 3.0 km/hour for 5 minutes (8,31). Absolute $VO_{2submax}$ at 3 km/hour was the primary outcome measure. During all treadmill testing expired gases were collected continuously, with ventilatory equivalent ratio for oxygen (VE/VO_2), ventilatory equivalent ratio for carbon dioxide (VE/VCO_2), respiratory exchange ratio (RER), and HR recorded at 20-second intervals (Physiodyne Max-II metabolic cart, Quogue, NY) using a 4-lead electrocardiogram system (GE Case 8000, General Electric Medical Systems, Milwaukee, WI) and RPE was assessed using the Children's OMNI scale (27). Steady state for each stage was recorded as the average of the last minute of VO_2 measurements.

The VO_{2peak} was measured through an incremental, continuous walking task on a treadmill with speed or incline increased every minute until volitional fatigue. No preselected increments were used due to low and heterogeneous fitness common in children with chronic disease (8). Increments were selected by an experienced exercise tester according to the child's HR, RER, RPE, and overall appearance. Test duration was targeted at 6–10 minutes. Criteria for VO_{2peak} were attaining RER $\geq$1.0 and reaching age-predicted MHR. After 10–15 minutes of rest, subjects performed a modified Wingate test via 10-second and 30-second all-out cycling tasks on an isokinetic cycle ergometer (Biodex lower body cycle, Biodex Medical Systems, Shirley, NY). The isokinetic cycle fixes the speed of pedalling to measure the force output and is a highly reproducible and safe method of assessing anaerobic power (32,33). Peak power was measured over 10 seconds at 90 revolutions per minute, and then over 30 seconds (after a 2-minute recovery period) to estimate total work output in watts.

The CHAQ was used to assess physical function. Items are scored on a 4-point scale with scores of 0 denoting no disability and 3 denoting severe disability. It is validated for use in JIA (26). We chose to use the CHAQ in preference to the modified CHAQ38 as the latter instrument has not yet been validated for longitudinal studies (34). Physical activity levels outside the study were measured using the Habitual Activity Estimation Scale

(HAES), a validated tool for measuring activity levels in both healthy and chronically ill children (35,36). It asks children to recall an average weekday and a weekend day with regard to the proportion of time spent inactive (e.g., sleeping), somewhat inactive (e.g., sitting), somewhat active (e.g., walking), and active (e.g., running), and provides a summary score of these activity levels. Overall quality of life (QOL) and health-related quality of life (HRQOL) were measured on 10-cm visual analog scales (VAS) previously validated for children with JIA, with higher scores indicating better QOL or HRQOL (37).

Adherence and safety

The study coordinator and fitness instructors maintained frequent contact with the subjects to maintain adherence, and the instructors met together on a monthly basis to review each individual's progress. Subjects measured and recorded RPE, HR (pulse point or monitor), and pain on a 10-cm VAS in a diary for each session they completed. HR monitors were loaned intermittently to check adherence. Children were rewarded with stickers for completed sessions and were able to trade these for small gifts to further encourage adherence. These strategies had enhanced adherence in our pilot study (25).

Safety was monitored in diary records of pain and through joint examination at testing sessions. A joint was considered active if it was swollen or had 2 of the following features: limited range of movement, pain on movement/ tenderness, and/or warmth. Range of motion was assessed at testing sessions using the Pediatric Escola Paulista de Medicina Range of Motion scale (38).

Statistical analysis

A sample size of 35 subjects per group was calculated to detect a meaningful difference between the groups in absolute $VO_{2submax}$ at 3 km/hour, with an α (false-positive) error of 0.05, β (false-negative) error of 0.20, and δ (the size of a clinically important difference) of 10% (39). Based on an anticipated 10% dropout rate, the intended recruitment number was 80 subjects.

The change in $VO_{2submax}$ between the 2 groups was compared using a linear mixed-effects model with compound symmetry covariance structure. Potential confounders (sex, pubertal stage, CHAQ score, and HAES activity level outside the study) were entered into the model. Differences between the groups for secondary outcomes were tested similarly. Analyses were completed using SAS software version 9.1 (SAS Institute, Cary, NC) and SPSS version 12.0 (SPSS, Chicago, IL). The primary analysis was intent-to-treat, with the subjects analyzed per their original group assignment regardless of adherence. The exercise dosage used in this study was considered a minimum to improve aerobic capacity. However, exercising less often has been shown to have benefit for adults with arthritis (11,12). In an attempt to see whether adherence significantly influenced the results, we analyzed data from experimental subjects and controls who participated in >70% of sessions and also those experimental group subjects who attended >70% of sessions and also achieved >75% of MHR in >50% of sessions attended compared with controls. Missing primary outcome data was analyzed through a sensitivity analysis using imputation with the mean and median of nearby points

replacing missing values. Post hoc subgroup analyses of Tanner stage (Tanner stage ≤2 versus Tanner stage ≥3), sex (boys versus girls), and baseline activity (HAES <2 active weekday hours versus ≥2 active weekday hours) were also completed.

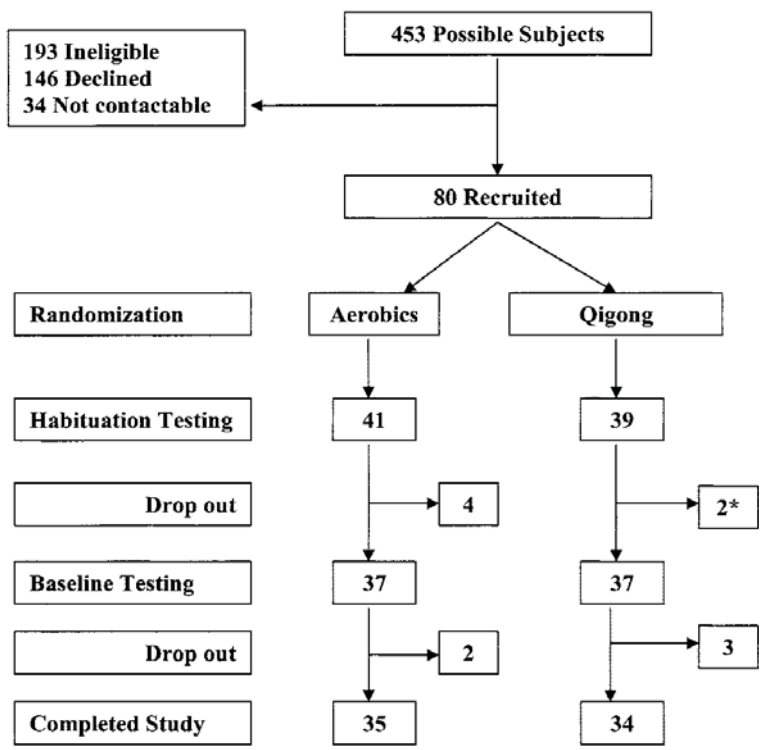
This study was approved by the Research Ethics Boards at The Hospital for Sick Children and Bloorview Kids Rehab. All subjects were enrolled only after fully-informed written consent was obtained from the parent and the child**.**

Results

Patients and adverse events

Of 453 potential subjects, 80 were recruited (Figure 1). Ten patients dropped out after randomization and 1 patient was ineligible (6 from the experimental group and 5 from the control group). All dropouts reported lack of time as the reason. Patient characteristics at enrolment are shown in Table 1. Differences are evident in the distribution of JIA subgroups between the groups. The blocking factors, Tanner stage, and CHAQ used in randomization were equally distributed.

Figure 1. Flowchart of recruitment and completion of the trial.



*** = includes 1 ineligible subject.**

Table 1. Patient characteristics at enrolment

Characteristic	Control group (n = 39)	Experimental group (n = 41)
Female, n (%)	29 (74.4)	35 (85.4)
Age, mean ± SD (range) years	11.5 ± 2.4 (8—16)	11.7 ± 2.5 (8—16)
Postpubertal, n (%)	22 (56.4)	23 (56.1)
CHAQ score, mean ± SD (range)	0.34 ± 0.43 (0—2.0)	0.31 ± 0.48 (0—2.13)
JIA subtype, n		
Polyarticular	15†	19
Persistent oligoarticular	2	5
Extended oligoarticular	5	6
Systemic	6	1
Enthesitis-related	4	7
Psoriatic	6	2
Other	1	1

* CHAQ = Childhood Health Assessment Questionnaire; JIA = juvenile idiopathic arthritis.
† Including 2 patients with rheumatoid factor-positive polyarticular disease.

No adverse events were reported during testing or training sessions. There was no worsening of active joint count, Pediatric Escola Paulista de Medicina Range of Motion scale, CHAQ, QOL, or HRQOL in either group during the study (Table 2). Low levels of pain were recorded on a 10-cm VAS during training sessions. These were not different between the 2 groups (median 0; range 0–10 in both groups; P =0.09 Mann-Whitney U test).

Adherence

Patient adherence is outlined in Table 3. Completion of training sessions was 78% in the control arm and 56% in the experimental arm. An average of 2 sessions per week were completed by the experimental subjects and 1.7 sessions per week by the control subjects. The difference was most apparent in the number of home based sessions. As expected, RPE was significantly different between interventions with a median (range) of 5.0 (0.0 – 10.0) and 1.0 (0.0 –9.0), respectively, for the experimental and control groups (P < 0.0001). Only 51% of the completed experimental sessions succeeded in achieving the

Table 2. Exercise testing and questionnaire results at enrolment and completion of the trial for patients that completed the trial*

Outcome variable	Control group (n = 34)		Experimental group (n = 35)		Estimate† (*P*†)
	Commencement	Completion	Commencement	Completion	
$VO_{2submax}$ 1.5 km/hour					
Absolute, liter/minute	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.03 (0.07)
Relative, ml/kg/minute	9.4 ± 1.6	9.3 ± 1.8	9.5 ± 1.7	8.7 ± 1.4	0.7 (0.051)
$VO_{2submax}$ 3.0 km/hour					
Absolute, liter/minute	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.02 (0.31)
Relative, ml/kg/minute	11.5 ± 1.9	11.6 ± 1.8	11.4 ± 1.9	11.0 ± 1.5	0.53(0.23)
VO_{2peak}					
Absolute, liter/minute	1.5 ± 0.5	1.6 ± 0.5	1.4 ± 0.4	1.5 ± 0.5	—0.04
Relative, ml/kg/minute	35.7 ± 7.8	36.2 ± 8.0	33.3 ± 6.8	34.8 ± 8.8	—0.01
Peak power, watts					
10 seconds	211 ± 136	216 ± 137	204 ± 120	233 ± 125	—12.6
30 seconds	218 ± 133	225 ± 134	209 ± 103	236 ± 114	—9.7
Active joints, mean ± SD (range)	2.5 ± 5.1 (0—21)	2.1 ± 5.1 (0—21)	3.5 ± 6.8 (0—28)	2.2 ± 6.5 (0—15)	0.93
EPM score	0 ± 0.1	0.1 ± 0.4	0.1 ± 0.1	0.1 ± 0.2	0.03
Body fat percentage	23.1 ± 7.5	23.3 ± 8.1	24.0 ± 8.8	22.9 ± 7.3	0.58
CHAQ score	0.32 ± 0.45	0.21± 0.35	0.34 ± 0.49	0.22 ± 0.37	—0.01
QOL	8.5 ± 1.6	8.7 ± 1.4	7.9 ± 1.8	8.4 ± 2.0	—0.3
HRQOL	8.3 ± 1.9	8.5 ± 1.7	7.7 ± 1.8	7.8 ± 1.9	0.2

Values are the mean ± SD unless otherwise indicated. $VO_{2submax}$ = submaximal oxygen consumption; VO_{2peak} = peak oxygen uptake; EPM = Pediatric Escola Paulista de Medicina Range of Motion scale; CHAQ = Childhood Health Assessment Questionnaire; QOL = quality of life; HRQOL = health-related quality of life. † Estimates and *P* values are presented for the 3-term for the interaction of (group allocation X testing session) in the repeated measures, auto-regressive model, and represent the difference of the paired differences in response seen in each of the 2 groups.

target HR. The RPE correlated moderately with HR in the experimental group (r = 0.41; $P < 0.0001$) and less so in the control group (r = 0.32; $P < 0.0001$).

Exercise testing outcomes

Subjects' baseline fitness measured by VO_{2peak} and compared with published age and body surface area matched norms (40) demonstrated a significantly lower VO_{2peak} in our patients (Table 4). Results of exercise testing and questionnaires are also shown in Table 2. No difference was found in the change in the absolute $VO_{2submax}$ at 3 km/hour between the groups from baseline to completion of the study (Figure 2). Nor were any significant differences seen in the change in other fitness parameters between the groups. When missing data was accounted for through imputation analysis, there was still no difference in the primary outcome between the groups.

Table 3. Adherence measures in both groups*

Adherence measure	Control group	Experimental group
Training sessions completed		
Supervised in class, 12 possible sessions	**7.8 ± 2.8**	**7.3 ± 2.9**
Home-based sessions, 24 possible sessions	**20.4 ± 7.1**	**14.9 ± 7.1**
Total sessions completed of 36 possible session, n (%)	**28.6 (79.4)**	**20.5 (56.9)**
HR during sessions	**95 ± 26**	**136 ± 33**
Sessions in which HR >75% MHR, %	**7.4**	**51.0**
Total minutes of training per session	**32.2 ± 8.2**	**34.3 ± 10.0**

* Values are the mean ± SD unless otherwise indicated. HR = heart rate; MHR = maximal heart rate.

Analysis of those with >70% completion of training sessions showed no significant difference in any of the fitness parameters between the 2 groups over time. We examined subjects in the experimental arm who attended >70% of training sessions and achieved HR >75% of MHR in >50% of sessions. This subgroup contained only 8 patients and, when compared with the control group, showed no significant benefit in $VO_{2submax}$. Subgroup analyses for sex, pubertal stage, and baseline activity did not show any difference between the subgroups in $VO_{2submax}$ in response to training. The amount of improvement in self-reported physical function as measured by the CHAQ was similar between groups (Figure 2), although the within-group change was statistically significant (mean difference -0.12, $P < 0.0001$) and clinically meaningful in magnitude (41).

Table 4. Comparison of maximum oxygen consumption values according to body surface area, between subjects at study start and published values for healthy untrained children*

Body surface area	Washington Study (Ref 40)	Current Study
<1.0 m^2		
Boys	**47 ± 6**	**49.6†**
Girls	**42 ± 5**	**35.8 ± 5.3**
1.0 m^2 and <1.2 m^2		
Boys	**46 ±5**	**39.6, 42.8, 38.1†**
Girls	**43 ± 7**	**35.8 ± 6.7**
≥1.2 m^2		
Boys	**47 ± 10**	**39.3 ± 9.4**
Girls	**41 ± 6**	**31.9 ± 7.3**

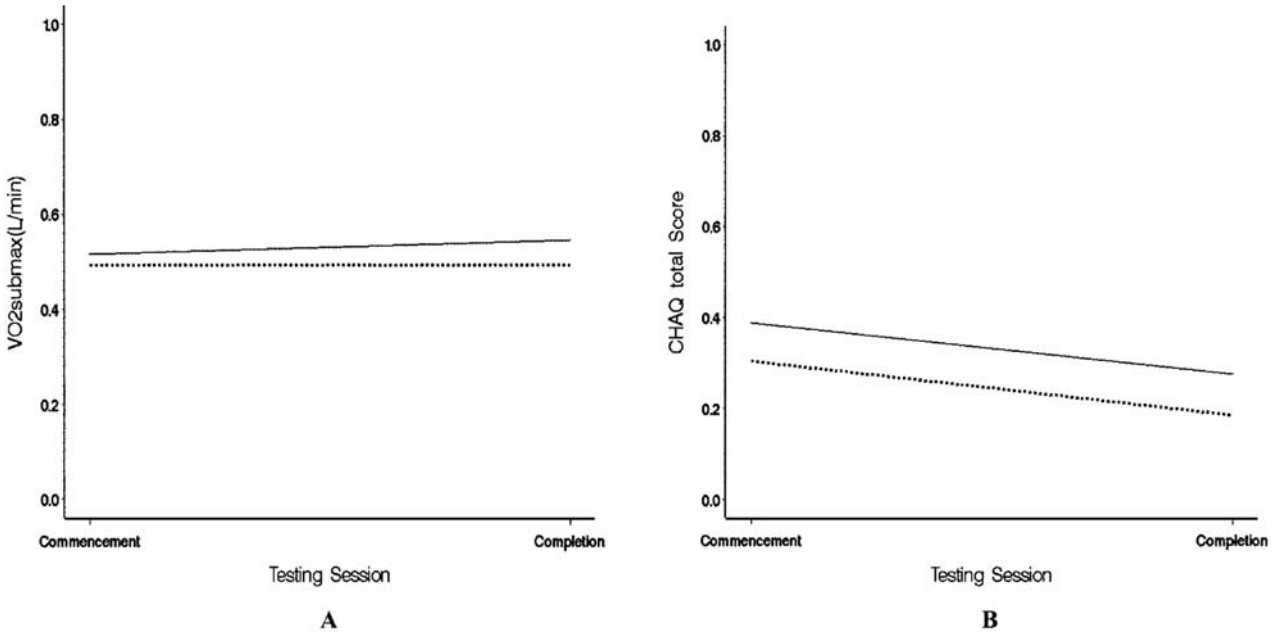
* Values are the mean ± SD in ml/minutes/m^2. † Subgroup had <7 patients, therefore all results are listed.

Discussion

This study is the first well-powered, randomized controlled trial of land-based aerobic training in children with JIA. We found that participating in a 12-week exercise program did result in improved physical function as measured by the CHAQ, but did not result in improved economy of locomotion, and that there was no extra improvement conferred by high-intensity aerobic training. The benefits observed in the CHAQ might be a result of being involved in a trial and the added attention received from trainers and study personnel (Hawthorne effect), or it may reflect a true benefit of training.

When considering the role of vigorous physical training in childhood arthritis, we must consider that the failure to demonstrate improvements in this study may have been a result of patient selection, the training program instituted, adherence with the program, or a general poor response of fitness training in young children. It is possible that subjects were too mildly affected as measured by their CHAQ scores to have benefited from the training program. Previous studies have shown that children with arthritis have reduced fitness when compared with their healthy peers (3), and while many of our subjects had mild disease, they were deconditioned when compared with available normal values for healthy untrained children (40). In adults, treadmill protocols attain 6–10% higher VO_{2max} than bicycle protocols (42,43). Thus, as the comparison data from Washington et al (40)

Figure 2. A, Plot of predicted absolute submaximal oxygen uptake ($VO_{2submax}$) at 3 km/hour, and B, Childhood Health Assessment Questionnaire (CHAQ) by treatment group using a mixed model procedure.



Solid line =control group; dotted line = experimental group;.L = liter; min= minute.

were obtained using a cycle ergometer and ours were obtained from treadmill testing, it is likely that subjects in this study were even more deconditioned than these data suggest. Nonetheless, even though it might be expected that the deconditioned subjects included in this study would be more likely to benefit from an exercise program, no benefit in fitness parameters was seen.

Submaximal exercise testing has been reported as a safe, simple, and well-tolerated estimate of VO_{2max} and functional ability in children with chronic disease (20,22–25). Giannini and Protas (24) showed that children with arthritis had higher submaximal HR and trended towards higher $VO_{2submax}$ than healthy peers, suggesting significantly lower submaximal efficiency. The failure of our study to show significant changes after training may be because disease activity of patients in the Giannini and Protas study (24) was significantly greater than in our study, with a mean joint count of 13 compared with <3 in our study. However, we feel that the subjects included represent a realistic cross section of JIA patients in our clinic and that the results are generalizable to clinic populations in most developed countries.

Training programs should involve an exercise prescription of adequate frequency, intensity, and duration to achieve the desired results. A minimum of twice-weekly training is required to achieve significant improvements in physical fitness (12,44). An 8-week study by Klepper (17) involved training twice weekly in class format and once weekly at home. Studies of aquatic training (18,45) and the pilot study undertaken prior to this trial (25) used once weekly class-based training for 15, 20, and 12 weeks, respectively. Feedback from our pilot study highlighted difficulties in attending frequent formal training sessions and suggested that a partially home-based program would help adherence (25). The program used in our present study was designed to provide adequate frequency (3 sessions per week), intensity (≥75% MHR), and duration (30 minutes) of aerobic training based on existing recommendations and the findings of earlier studies. Failure to achieve target HR may have been due to the training program not being strenuous enough to achieve the desired range. While RPE measured in training sessions was significantly higher in the experimental group than in the control group, which suggests at least moderate exertion in the experimental group, HR and RPE were only moderately correlated. It is possible that the more complicated exercise maneuvers in the experimental program, compared with treadmill walking or running, added complexity which translated as a higher RPE without concurrent increase in HR. Also, the novelty of the vigorous program may have resulted in earlier exertion in the subjects with a tailing off towards the end of the session when RPE was measured. Furthermore, the OMNI scale was validated using treadmill or cycling protocols that were continuous in nature, but our program was intermittent, possibly resulting in a lower correlation (27).

Differences in the modality of training and testing may have affected our results. Patients were trained in floor based programs but tested on treadmill and cycle ergometers. In the pilot study, subjects were trained in a circuit format incorporating treadmill and stationary cycle and then tested on these 2 apparatus (25). Thus there may be an issue with the specificity of the testing method to detect changes resulting from the training modality. Adherence in this study was higher in the control group than in the experimental group. Takken et al (18) showed good adherence with once-weekly aquatic training, whereas our own pilot study achieved only fair adherence with a once-weekly

program (25). A home exercise intervention in cystic fibrosis from Schneiderman-Walker et al (46) reported good long-term adherence with a 3-times–weekly program out to 3 years, while Greenan-Fowler et al (47) were unable to maintain adherence in children with hemophilia in home exercises. Munneke et al (48) found that adult patients with RA maintained good adherence in a 2-year, twice-weekly training program. Our results highlight the difficulties in obtaining adequate and sustained adherence with intensive exercise programs from children with arthritis.

The training HR was only achieved in half of all sessions in the experimental arm, reducing the effective training frequency to once a week when adherence with sessions was taken into account. This may have significantly reduced the training effect, and may explain the lack of efficacy. Post hoc analyses of compliant subjects showed no differences, but these sub-analyses may not have been adequately powered to show a difference if one did exist. Our results are not consistent with studies of fitness training in adults with RA that have shown significant benefits in fitness and functional outcomes (11,12). They are, however, consistent with existing studies of exercise interventions in children with arthritis that have shown slight or no significant improvement in fitness or functional outcomes (15,18,25,45).

Studies of exercise training in healthy children suggest that prepubertal children experience only modest improvements (11%) in VO_{2max} after training (49). Pubertal children are capable of achieving 20–25% increases in VO_{2max} with training, which is similar to adults (49). Furthermore, it has been suggested that aerobic training of healthy prepubescent children may require training intensities of up to 90% MHR (50), which are significantly higher than those used in this study. Half of the subjects in this study were postpubertal, and post hoc analysis failed to show a response in VO_{2max} or $VO_{2submax}$ in either the prepubertal or postpubertal groups, which does not support the idea that a differential training effect in these 2 groups could explain our results.

Our findings suggest that activity programs with or without aerobic training are safe and may result in improved physical function. This is supported by other studies of exercise programs in childhood arthritis (17,18,25,45). A higher intensity of aerobic training did not provide any additional benefits in this study to functional outcome. This may be a result of the experimental program not being intensive enough to show a response; however, it would require additional studies of different training protocols to determine whether measurable benefits are achievable in this population. A high adherence rate of 80% in the qigong program may suggest that less intensive regimens are easier for children with JIA to comply with and seem to produce an equivalent degree of benefit as more intensive programs.

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Chapter 5

Can peak work rate predict peak oxygen uptake in children with juvenile idiopathic arthritis?

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Abstract

Objectives

To examine whether peak work rate (W_{peak}) can predict peak oxygen uptake (VO_{2peak}) in children with juvenile idiopathic arthritis (JIA).

Methods

Ninety-one patients with JIA with mean age of 11.4 ± 2.9 years underwent a cardiopulmonary exercise test in which VO_{2peak} and W_{peak} were determined. A multivariate regression model was used to formulate a regression equation to predict VO_{2peak}, using W_{peak}, anthropometric and demographic details. This regression equation was subsequently cross-validated using an unrelated data set from children with JIA (n = 17).

Results

The following linear regression equation to predict VO_{2peak} was established: VO_{2peak} (L/min) = 0.308 + 0.146 × gender [0=female, 1=male] + 0.005 × weight [kg] + 0.008 × W_{peak} [Watts]. (R^2=0.91; SEE= 0.18). Using this equation the predicted VO_{2peak} was strongly related with the measured VO_{2peak} (r = 0.96, p<0.001). Bland-Altman analysis revealed a mean difference of 0.01 L/min and limits of agreement between -0.35 to 0.35 L/min.

Conclusion

This study suggest that W_{peak} is a strong predictor of VO_{2peak} in children with JIA and may be used as a surrogate measure of VO_{2peak} in situations where it is not possible to formally assess $VO_{2peak.}$

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in children and encompasses a clinically heterogeneous group of arthritides. Children with JIA may have joint swelling, pain, limited mobility and muscle weakness and atrophy around inflamed joints which can result in decreased physical fitness (1). Exercise programmes are becoming increasingly important in the therapeutic approach to patients with JIA (2), and many patients now require a tailored pharmacological approach to therapy in conjunction with a tailored exercise programme as part of their comprehensive management plan.

The peak oxygen uptake (VO_{2peak}) attained during a graded maximal exercise test to volitional exhaustion is considered as the single best indicator of aerobic fitness by the WHO (3).

There is a large body of evidence showing that the VO_{2peak} of children and adolescents with JIA is lower than their healthy peers. In the most recent studies in children with JIA between 6.7 to 18 years of age, showed VO_{2peak} (L/min) and VO_{2peak} corrected for body mass (VO_{2peak}/kg in ml/min/kg) were respectively 69.8% and 74.8% of predicted in children and 83% and 80% in adolescents respectively (4,5). These observations support the results of a previous meta-analysis showing that VO_{2peak}/kg was on average 21.8% lower in children with JIA compared to healthy controls or reference values (6).

Since a decreased VO_{2peak} is related with increased morbidity and mortality (7-9), measurement of VO_{2peak} is important to assess health status and to determine the most appropriate aerobic exercise prescription (exercise intensity). Subsequently, the progression of exercise training in an individual patient can be monitored by repeating the exercise test. Several studies have shown that VO_{2peak} can be reliably assessed during graded exercise (both cycle ergometer and treadmill) in children and adolescents with JIA (10). Although VO_{2peak} is considered as the best indicator of aerobic fitness, in clinical practice, direct measurements of VO_{2peak} during a graded exercise test are not always feasible due to limitations of the expense and availability of the respiratory gas analysis equipment and staff required. Maximal exercise tests, with only a determination of the peak work rate (W_{peak}), are less resource intense. Dencker et al. have demonstrated that W_{peak} is a good surrogate measure of VO_{2peak} in healthy children aged between 8 and 11 years (11). Thus W_{peak} could also serve as a surrogate for VO_{2peak} in children and adolescents with JIA. It is, however, not known if the W_{peak} is a valid measure of VO_{2peak} in children and adolescents with JIA. Thus, the aim of this study is twofold. Firstly, to determine whether W_{peak} can predict VO_{2peak} in children with JIA and develop a disease-specific prediction model for VO_{2peak} in JIA. Secondly, to compare our prediction equation in chronic diseased children with JIA to the equation published by Dencker et al. in healthy children.

Patients and Methods

Patients

Ninety-one patients, aged between 6.1 and 17.4 years old, with JIA were recruited in the Child Development & Exercise Center of the Wilhelmina Children's Hospital, Utrecht, the Netherlands. All were diagnosed with JIA according to International League of Associations for Rheumatology (ILAR) criteria (12). Patient characteristics at enrolment (between 2001 and 2004) are shown in table 1.

Inclusion and exclusion criteria

All children with JIA who were referred for exercise testing were included in this study. This sample is an unselected cohort. Exclusion criteria were active systemic disease, lower extremity complaints (pain/swelling/limited range of motion) that interfered significantly with exercise testing, fever, and influenza in the week before exercise testing. Further, we used generally accepted cardiopulmonary contraindications for exercise testing (13).

Anthropometry

Body weight and height were measured using an electronic scale and stadiometer, respectively. Body mass index (BMI) was calculated as body mass/height^2 (kg/m^2). Standard deviation (SD) scores ware calculated for weight for height, height for age and BMI for age using Dutch normative values (14,15). Subcutaneous fat mass was measured by skin fold measurements using Harpenden skin fold callipers. Measurements were performed at 7 locations: triceps, biceps, sub scapular, suprailiac, mid-abdominal, medial calf, and thigh following the criteria of the American College of Sports Medicine (16).

Cardiopulmonary exercise testing

VO_{2peak} was determined through a graded exercise test until exhaustion. This test was performed on an electronically braked cycle ergometer (Lode Examiner, Lode, Groningen, the Netherlands).

A bicycle protocol was chosen as exercise testing modality in this population since it was thought to give less stress on the joints of the lower extremity in children with JIA especially in children with an active disease in the lower extremities. However, recently Stephens et al (10) reported a good feasibility and reliability of exercise testing using a treadmill protocol in children with JIA.

Cycling started at a workload of 0 Watts and work rate was increased by 20 Watts every minute. Patients were instructed and encouraged to cycle until exhaustion. Patients breathed through a mouthpiece that was connected to a calibrated metabolic cart. An oximeter was used to collect expired gas that was sampled and analyzed breath-by-breath for oxygen (VO_2), carbon dioxide (VCO_2), and volume (Jaeger Oxycon, Care Fusion, Houten, the Netherlands). Heart rate (HR) and electrocardiographic activity were

continuously monitored using a 3-lead electrocardiograph. The oximeter was coupled to a computer, which plotted workload against VO_2, VCO_2, and HR and the VO_2 used for sampling and statistical calculations were taken from the means of every 30 seconds. Patients were instructed to cycle with a pedal frequency of 70 (range: 60 and 80) rpm until exhaustion. The pedal frequency was displayed for the patient on a pedal rate indicator so that the rate could be easily maintained. The test was ended when the pedal frequency rate declined below 50 rpm and the patient was unable to continue the test. The highest achieved work rate at the end of the test that was completed for at least 30 seconds was taken as the W_{peak}. The mean VO_2 completed in the last 30 seconds was considered VO_{2peak}.

Statistical analyses

Univariate regression analyses were performed with VO_{2peak} (L/min) as the dependent variable and gender, height, weight, body mass index, age, W_{peak} and sum of skin folds as the independent variable. The independent variables that revealed significant correlation were then entered into a multivariate regression model (backward procedure) to obtain a regression equation for predicted VO_{2peak}. Statistical significance was set at $p < 0.1$. The multivariate regression model was also used to calculate the standard error of estimate. Bland-Altman analysis was used to calculate the limits of agreement between directly measured VO_{2peak} and predicted VO_{2peak} calculated from the regression equation. A paired t-test was performed to analyse differences between predicted and measured VO_{2peak}. Cross-validation was performed with data from 17 JIA patients described in a previously published study (17). In this sample a paired t-test was performed to analyse differences between the VO_{2peak} calculated using the prediction equation and the directly measured VO_{2peak}. Pearson correlations were determined between predicted and measured $VO_{2peak.}$

Finally, our prediction equation was compared to that of Dencker et al. equation by entering the individual test results from the children with JIA recruited in this study into the mixed-gender equation of Dencker et al (11). All statistical analyses were performed in SPSS version 15.0. Significance level was set at 0.05.

Results

The patient characteristics and aerobic fitness results of the 91 patients with a mean age of 11.4 ± 2.9 years who underwent a cardiopulmonary exercise test are presented in table 1. The patients had a normal weight for height, height for age and BMI for age.

The mean HR_{peak} achieved during the maximal testing performed in our study was 181 bpm for both boys and girls. The peak respiratory exchange ratio (RER) was 1.09 for the boys and 1.10 for the girls indicating that they performed the exercise test until exhaustion hence providing an accurate measure of VO_{2peak}.

The association between W_{peak} and VO_{2peak} is shown in figure 1. Univariate regression analysis revealed that W_{peak}, gender and weight were the best predictors of $VO_{2peak.}$ When

Table 1: Patient characteristics and fitness results in the sample used to formulate the prediction equation.

	Male (n = 25)	Female (n = 66)
Age and Anthropometry		
Age (y)	**11.5 ± 3.2**	**11.3 ± 2.8**
Weight (kg)	**42.5 ± 16.2**	**42.1 ± 15.0**
Weight for height SD-score	**0.10 ± 0.93**	**0.21 ± 1.26**
Height (m)	**1.52 ± 0.21**	**1.48 ± 0.15**
Height for age SD-score	**-0.05 ± 1.22**	**-0.14 ± 1.82**
Body mass index (BMI; kg/m^2)	**17.7 ± 2.5**	**18.8 ± 4.4**
BMI for age, SD-score	**0.04 ± 0.91**	**0.04 ± 0,91**
Sum of 7 skin folds (mm)	**69 ± 30**	**104 ± 48**
Juvenile Idiopathic Arthritis classification, n (%)		
Systemic arthritis	**1 (4)**	**9 (14)**
Oligoarthritis persistent	**8 (32)**	**21 (32)**
Extended oligoarthritis	**2 (8)**	**4 (6)**
Polyarticular rheumatoid-factor positive	**8 (32)**	**14 (21)**
Polyarticular rheumatoid-factor negative	**6 (24)**	**18 (26)**
Physical fitness		
VO_{2peak} (L/min)	**1.763 ± 0.842**	**1.343 ± 0.449**
Relative VO_{2peak} (ml/min/kg)	**41 ± 7**	**33 ± 7**
Peak work rate (Watt)	**137 ± 88**	**102 ± 48**
Relative peak work rate (Watt/kg)	**2.96 ± 1.08**	**2.39 ± 0.82**

Where y=years; kg=kilograms; m=metres; BMI = Body Mass Index; SD = standard deviation; mm=millimetres; min=minutes; ml=millilitres.

entering these variables in a multivariate model, the following prediction equation was formulated from the data:

Predicted VO_{2peak} (L/min) = 0.308+0.146×gender+0.005×weight+0.008×W_{peak}

Where SEE = 0.18 L/min, gender: 0 = female, 1 = male, weight in kg and W_{peak} in Watts

W_{peak} was closest related with $VO_{2peak.}$ The greatest contributor to this regression equation was W_{peak} with an R^2 of 0.90, followed by weight (R^2 = 0.574) and gender (R^2 = 0.096). The association between W_{peak} and VO_{2peak} is presented in figure 1.

Figure 1: Relationship between measured peak work rate (Watts) and measured VO_{2peak} (L/min).

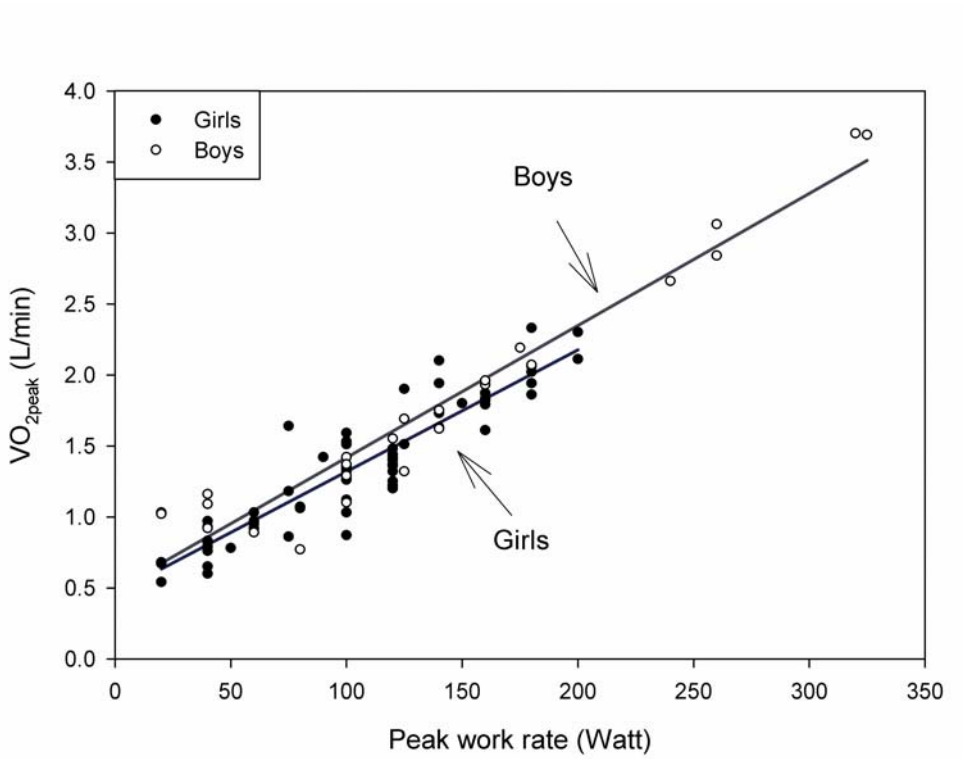
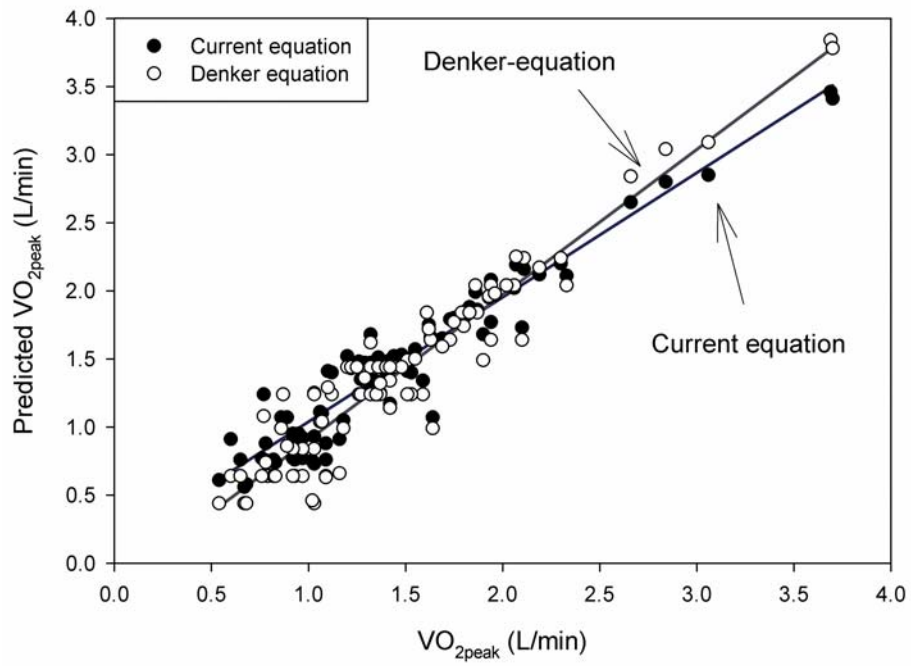


Figure 2: Plot of agreement between data from this current cohort used to estimate VO_{2peak} (L/min) using the prediction equation formulated in this study as well as from the prediction equation of Dencker et al (11) for healthy children.



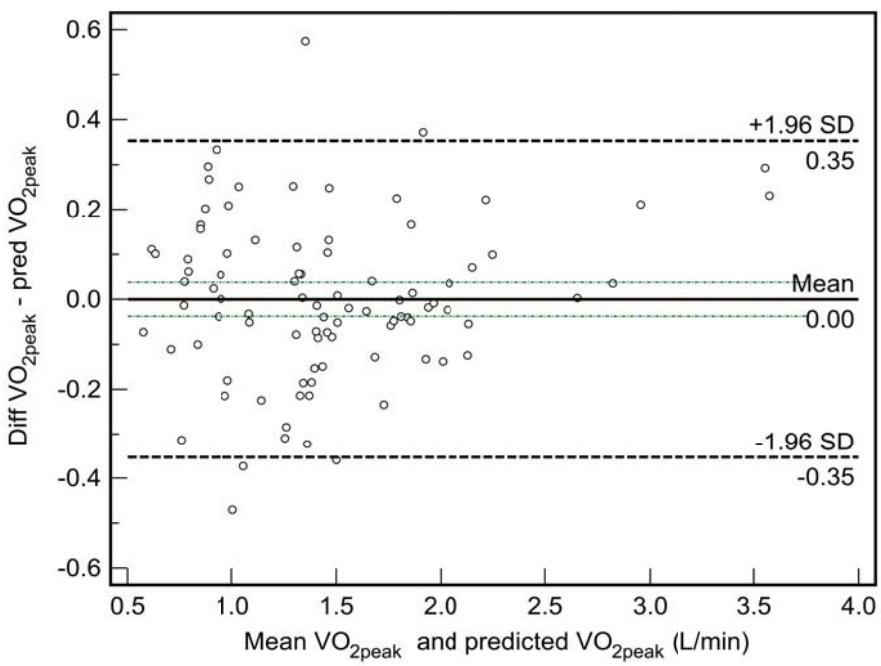
The mean measured VO_{2peak} was 1.46 l/min, while the mean predicted VO_{2peak} was 1.46 l/min ($p = 0.99$). Figure 2 shows the relationship between VO_{2peak} predicted using the equation and that which was directly measured. There was a strong linear relationship (Pearson correlation $r = 0.96$; $p<0.0001$) between predicted VO_{2peak} and measured VO_{2peak}. The Bland-Altman plot of this data seen in figure 3 shows limits of agreement of ± 0.35 L/min for directly measured VO_{2peak} versus predicted VO_{2peak}.

Cross validation was performed in a group of 17 children (6 boys and 11 girls) with JIA with a mean age of 13.3 ± 3.1 years. When entering gender, weight and W_{peak} of these 17 children into our regression equation the predicted VO_{2peak} was 97.23 ± 10 percent of measured VO_{2peak} ($p = 0.279$). Pearson correlation indicated a strong association between measured and predicted VO_{2peak} ($r = 0.97$, $p<0.001$).

Although our children were older by one year on average than the healthy children of Dencker et al. (mean age of 9.8 ± 0.6 years vs. 11.35 ± 2.87 the measured VO_{2peak} in our children with JIA was lower (42 ±7 vs. 41±7 and 36±6 vs. 33±7 ml/min/kg for boys and girls respectively). Data from our prediction equation in children with JIA is plotted

against VO_{2peak} predicted using data obtained in our subjects but using the Denker equation in figure 2. Although there was a strong association (Pearson r = 0.995, p < 0.001) between our prediction and the Dencker prediction, the mean VO_{2peak} was significantly higher in our predication equation (1.46 ± 0.58 L/min) as compared to the equation of Dencker (1.39 ± 0.68 L/min; p < 0.05), especially in the children with lower values of VO_{2peak}. While this difference was small (0.06 L/min), the limits of agreement using the Denker equation where somewhat larger (-0.36 to 0.47 L/min), indicating that there was a higher prediction error using the Denker equation. A secondary analysis on only the children with JIA between 8 and 11 years of age, gave comparable results (a small but significant under prediction of VO_{2peak} with 0.099 L/min <0.0001).

Figure 3: Bland-Altman plot showing the limits of agreement between predicted VO_{2peak} and directly measured VO_{2peak} in the sample used to formulate the prediction equation.



Discussion

The aim of our study was to determine whether W_{peak} could be used to predict VO_{2peak} in children with JIA and to develop, if possible, a disease-specific prediction model for VO_{2peak}. Our study found that the combination of W_{peak}, gender, and weight was a strong

predictor of VO_{2peak} in children with JIA. To our knowledge this is one of the first studies reporting a disease-specific prediction for children with a chronic disease and the first study reporting a disease specific prediction equation for VO_{2peak} for children with JIA. A recent study by Houghton et al. developed a regression equation in 15 children with systemic lupus erythematosus (SLE) to predict VO_{2peak} from the distance walked in 6 minutes (6MW) and the peak heart rate during this test ($R^2 = 0.45$, SEE = 6.1 ml/min/kg). The researchers concluded that 6MW may be used as a marker of aerobic fitness but it is preferable to determine VO_{2peak} with a graded exercise test (18).

Our developed prediction equation for aerobic fitness compared well with the prediction equation obtained in healthy 8-11 year old children (11), our disease specific prediction equation resulted in small but significant higher values for VO_{2peak}, but still within the margin of the standard error of the estimate (SEE).

The small difference in prediction equation may be caused by a difference in exercise test protocol (initial workload at 30 W and increments of 15 W) between Dencker et al. and our study (start with unloaded cycling and 20 W/min increments). However, since the difference is small and within the margin of the SEE, the similarity suggests that the efficiency of the aerobic energy pathways to generate ATP and muscle contraction is not impaired in children with JIA.

In the prediction equation of Dencker et al. and in our prediction equation W_{peak} is the most important predictor of VO_{2peak}. However, it is important to mention that there is a distinction between these two variables. VO_{2peak} is a measure of aerobic fitness, whereas W_{peak} is a combined measure of both aerobic and anaerobic fitness (11). Since children have an under developed anaerobic energy system (19), the anaerobic energy contribution to the total work performed might be small.

For performing all kinds of activities of childhood daily living a certain level of physical fitness seems to be indicated (20,21). In addition, patients with JIA with a higher fitness level perform more physical activities compare to less fit patients (21). Although cardiovascular diseases manifest in older age, there is increasing evidence that starting from childhood there is a relation between aerobic fitness and cardiovascular risk factors. A large multicentre study in 2845 children aged 9 or 15 years from different European countries demonstrated that lower aerobic fitness is strongly associated with cardiovascular disease risk factors in children independent of country, age and sex (8). Assessing aerobic fitness in children with JIA is imperative to understand the functional ability of children. In this manner, physiotherapy programmes can be adjusted according to the individual levels of physical fitness of children.

Practical Implications

Many centres do not have the equipment to perform respiratory gas analysis to measure VO_{2peak}. However, W_{peak} during a graded bicycle test can be used a surrogate measure for VO_{2peak}, the current prediction equation can be used by clinicians to predict VO_{2peak} in children and adolescents with JIA with a wide age range (between 6 and 18 years old) and wide range in JIA onset types.

Limitations

This prediction equation might not be valid for use in other paediatric rheumatic disease such as Juvenile Dermatomyositis, in which the inflamed muscle becomes hypoxic during exercise or in which the excitation-contraction coupling might be impaired (22). In this study VO_{2peak} was assessed in children between 6 and 17 years old, therefore, care should be taken when using this equation in patients with JIA outside this age range or young adults with rheumatoid arthritis.

Conclusion

This study suggests that W_{peak} is a strong predictor of VO_{2peak} in children with JIA and may be used as a surrogate measure of $VO_{2peak\ in}$ situations where it is not possible to formally assess $VO_{2peak.}$

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Chapter 6

A pilot study of the effect of intra-articular steroid injection on isokinetic muscle strength in children with juvenile idiopathic arthritis.

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Abstract

Objectives

To determine the magnitude of changes in isokinetic muscle strength in children with juvenile idiopathic arthritis (JIA) after intra-articular (IA) corticosteroid injection of inflamed knee joints and to assess the feasibility of a larger study of the same effect.

Methods

Eight children with unilateral knee arthritis were treated with intra-articular steroid injection. Isokinetic dynamometry was used to measure knee extensor and flexor strength, prior to treatment and then 2, 6, and 12 weeks. Thigh circumference, joint range of motion active joint count, physical function, and physical activity were assessed at each visit.

Results

Isokinetic knee extensor strength was significantly reduced on the affected side ($p=0.03$). A clinically but not statistically significant increase in knee extensor strength (measured as ratio of peak torque of the injected over the non-injected limb) was observed at two weeks post injection ($p=0.07$) but not sustained over time. No improvement in knee flexor strength was observed. Improvements in joint range of motion were seen in the affected limb at 2 weeks ($p=.04$). Pain was reported in some subjects during testing but there was no increase in pain scores post testing. There were no adverse events of testing.

Conclusions

Knee extensor strength appears to be reduced in children with JIA with active synovitis and may be improved by IA injection. Isokinetic dynamometry was well tolerated and safe in our study sample. Investigation with a larger sample size to ensure adequate power is warranted to confirm these results.

Juvenile Idiopathic arthritis (JIA) is a relatively common and potentially debilitating disease and affects 1 in 1,000 children aged below 16 years (1).

Intra-articular steroid injection is established as an integral part of the management of acute joint inflammation in JIA (2,3,4). The benefits of intra-articular steroid injection in the setting of acute joint inflammation are well documented and include reduced pain, reduced local inflammation and improved range of motion, as well as decreased long-term sequelae of JIA such as leg length discrepancy (5). While a variety of corticosteroid compounds have been used including hydrocortisone, betamethasone, triamcinolone acetonide and triamcinolone hexacetonide, it has been demonstrated that triamcinolone hexacetonide is the most effective in reducing pain and joint inflammation (6,7,8).

Regardless of the specific steroid preparation used, the effect of IA injections on muscle strength remains unclear. Both muscle cross-sectional area and strength have been shown to be decreased in JIA (9-11), with the greatest loss understandably seen in muscles adjacent to and acting on inflamed joints (12). Loss of muscle strength in JIA is thought to be due to a combination of local and systemic factors including pain, muscle atrophy due to inactivity, inactivation of muscle due to reflex inhibition, and the effect of cytokines (13,14,15).

The general clinical impression is that both muscle strength and bulk seem to improve following IA steroid therapy and corresponding increases in thigh circumference (an indirect measure of muscle cross sectional area) have been reported following IA steroid injections in JIA (5). While muscle circumference and cross-sectional area show some correlation with muscle strength it is not possible to attribute all force changes to these parameters (16). As such a quantifiable assessment of muscle strength is warranted to determine if there are increases in strength following IA steroid joint injection

Muscle strength may be measured in two ways. Isokinetic strength is measured with the joint moving through a range at a constant angular velocity while isometric strength is measured at a fixed angle with sustained contraction against resistance (17). Both isokinetic and isometric strength have been shown to be reliable and valid assessments of muscle strength in children (18,19), and have both been shown to be reduced in patients with JIA (10-12).

Isokinetic strength may be the most clinically valid measure as the information it provides on the dynamic capacity of the muscle may be more closely related to functional activities such as walking, hopping or jumping (20,21). Studies in able bodied and disabled athletes have shown a direct correlation between isokinetic strength and performance in specific movement patterns (22). In the only study examining the relationship between isometric strength and self-reported function in JIA no statistically significant correlation between the two was found (23) however, correlation between isokinetic muscle strength and function in children with JIA has been reported (24).

The purpose of this pilot study is to test the hypotheses that patients with JIA and active arthritis affecting their knee joint: 1) have reduced muscle strength on the affected side compared to the unaffected side, 2) that IA steroid injection will result in improvements

in isokinetic strength, and 3) that testing will be safe and feasible in a larger trial setting.

Patients and Methods

Study design and patient population

This is a single centre, prospective, longitudinal cohort study conducted at The Children's Hospital at Westmead, Sydney, Australia and approved by the Research Ethics Board of this institution. Each patient/parent gave written informed consent to participate in the trial.

Children aged between 6 and 16 years with a diagnosis if JIA based on the International League against Rheumatism (ILAR) Criteria (25) and requiring an IA steroid injection of the knee as part of standard therapy were invited to participate in the study. The lower age limit of 6 years was chosen as isokinetic dynamometry has not been validated in children below this age and children younger than 6 years have previously been unable to comply with isokinetic dynamometry, and may be physically too small for the dynamometer (26,27).

The following exclusion criteria were applied: active arthritis or enthesitis affecting other joints of the ipsilateral limb; active arthritis or enthesitis in any joint of the contralateral limb; previous IA steroid injections into any joint in either limb in the preceding 6 months; evidence of significant degenerative changes in the ipsilateral or contralateral limb (based on rheumatologist knowledge of patient and previous x-ray results); previous surgery to ipsilateral or contralateral limb and any other abnormality or disease affecting the ipsilateral or contralateral limb; active sacroiliac disease; subjects using a wheelchair; systemic onset juvenile idiopathic arthritis if there were active systemic features in the preceding 6 months; significant cardiac or respiratory disease or an inability to comply with isokinetic dynamometry.

Intra-articular corticosteroid injections

All patients had IA injection performed under close supervision by a paediatric rheumatologist. They received sedation with a combination of oral midazolam and inhaled nitrous oxide where required and all patients had topical anaesthetic cream applied at the injection site before treatment. Triamcinolone hexacetonide (Sandoz Pharmaceuticals; Australia) was injected into the synovial space under aseptic conditions at a dose of 1 mg/kg body weight up to a maximum of 40 mg (5,7).

Clinical assessments

Patients were assessed prior to their IA steroid injection (baseline) and again at 2, 6 and 12 weeks. The baseline assessment was performed up to one week prior to the IA injection. Further assessments were all made within one week either side of the allocated time point.

Age, gender, height (using a stadiometer), weight (Tanita Body Composition Analyser TBF-410), self-reported Tanner stage, ILAR subgroup classification of JIA, date of diagnosis, duration of current active knee symptoms, previous and current medication use were recorded in all subjects at baseline. Documentation of current medication use and active joint count were determined at each visit to monitor disease activity.

Primary outcome

Isokinetic strength in knee extension and flexion was assessed using a computerized isokinetic dynamometer (Cybex Norm with UMAC Software, CSMi Medical Solutions, Stoughton, Minnesota, USA). Isokinetic dynamometry has been shown to be safe to use with children (18) with good inter−session and intra−session reliability (21, 22). Measurements of isokinetic knee extension and flexion were made on both the affected and unaffected sides. Measurements of isokinetic strength were made at a velocity of 60 degrees per second. This speed is used in pediatric isokinetic strength testing as children are better able to understand movement patterns at this speed (17) and the lower speed reduces the risk of injury (28). Participants performed five sub maximal trials to familiarize prior to maximal testing (29). Participants then performed 5 maximal attempts on the affected side and the single best effort was recorded. This process was then repeated on the unaffected side. A rest period of 1 min between sub-maximal and maximal trials was given in order to elicit maximal torque values (30).

Absolute peak torque was adjusted for weight and expressed in Newton metres per kilogram (Nm/kg). The primary outcome measure of was then expressed as a ratio of peak knee extensor or flexor torque of the affected limb over the peak torque of the unaffected limb (Figure 1). Expressing the primary outcome measure as a ratio of peak extensor torque and peak flexor torque allowed the unaffected limb to be used as a comparator.

Figure 1: Calculation of extensor and flexor torque ratios

$$\text{Peak Knee Extensor Torque} = \frac{\text{Peak knee extensor torque affected limb (Nm/kg)}}{\text{Peak knee extensor torque unaffected limb (Nm/kg)}}$$

$$\text{Peak Knee Flexor Torque} = \frac{\text{Peak knee flexor torque affected limb (Nm/kg)}}{\text{Peak knee flexor torque unaffected limb (Nm/kg)}}$$

Nm = Newton metres

Secondary outcomes

Thigh circumference was measured at a point 2/3 of distance from the greater trochanter of the femur to the lateral joint line of the knee. Measurement of thigh circumference has been validated as proxy detecting change in muscle cross-sectional area (31).

Joint range of motion at the knee was measured with a goniometer using standardised landmarks. Proximally the greater trochanter, the lateral knee joint line and the lateral

malleolus of the ankle distally.

Pain experienced by subjects before, during and after strength testing was assessed to determine the safety and comfort of testing and also to determine if pain influenced effort and thus measurements. A verbally administered numerical rating scale of acute pain was used with subjects scoring pain levels between zero and ten. This method of assessment of acute pain has been validated and shows good correlation with visual analog scales of pain. (32,33)

Physical function was assessed using the Child Health Assessment Questionnaire (CHAQ), the most widely validated measurement of function for children with JIA (34-36). The CHAQ consists of questions from 8 functional domains comprising eating, dressing and grooming, walking, arising, hygiene, reach, activities, and grip. A summary score based on the 8 functional activity domains is formulated between 0 and 3 (where 0 indicates no limitations and 3 severe limitations).

Level of physical activity was assessed using the Habitual Activity Estimation Scale (HAES). The HAES is a physical activity questionnaire in which children are asked to recall physical activity on a typical weekday and weekend day during the past 2 weeks. Activity is categorized into 1 of 4 intensity categories: inactive, somewhat inactive, somewhat active, and very active. Time spent in each of the 4 categories is reported by respondents and summary scores of total activity (TA) hours ("somewhat active" plus "active"), and total very active hours scores (VA) are calculated separately for weekends and weekdays (36). The HAES has been validated and shown to be reliable assessment of physical activity in both healthy children and children with chronic illness (37-39).

Statistical analysis

Due to the small sample size most data is presented descriptively and a nonparametric test of statistical significance for dependent variables (the Wilcoxon rank sum test) was used for data analysis where relevant. Analyses were completed using SPSS software version 18.0 (SPSS Inc, Chicago, IL).

Results

Nine patients fulfilled the inclusion criteria between July 2008 and January 2009 and were invited to participate. One patient declined to enroll due to inability to attend regularly for assessments. One patient was unable to attend for the 3 month post-injection visit due to an unrelated illness. The median age of the 8 included patients was 12.1 years (range = 8.5-16.8 years). Two subjects were male and six were female. Median duration from initial diagnosis with JIA was 11.75 months (range 1.5-77.0 months). The median duration of current knee symptoms before baseline was 5.2 months (range 0.5-12 months). Five of the eight patients had involvement of their non-dominant leg. Table 1 summarizes patient characteristics at study inclusion.

months). Five of the eight patients had involvement of their non-dominant leg. Table 1 summarizes patient characteristics at study inclusion.

Primary outcome measure

The data for peak knee extensor and peak knee flexor strength are displayed in Table 2 and Table 3. Baseline strength testing results are summarized in Figure 2.

The median peak knee extensor torque at baseline was reduced by 38.9% (range = -8.77% – 150%) on the side affected by active arthritis when compared to the unaffected side. This difference reached statistical significance (median difference=0.35Nm/kg, range -0.09-0.86 Nm/k, p=0.03). The median peak knee flexor torque was reduced by 7.7% (range = -20.6% - 74.3%) on the affected side compared to the unaffected side. This difference approached but did not reach statistical significance. (median difference =0.05 Nm/kg, range -0.13-0.75 Nm/kg, p=0.21).

Changes in knee extensor and flexor strength ratios over time for each subject are displayed in Figure 3 and 4.

Figure 2 - Median Changes in Knee Extensor Peak Torque at Baseline

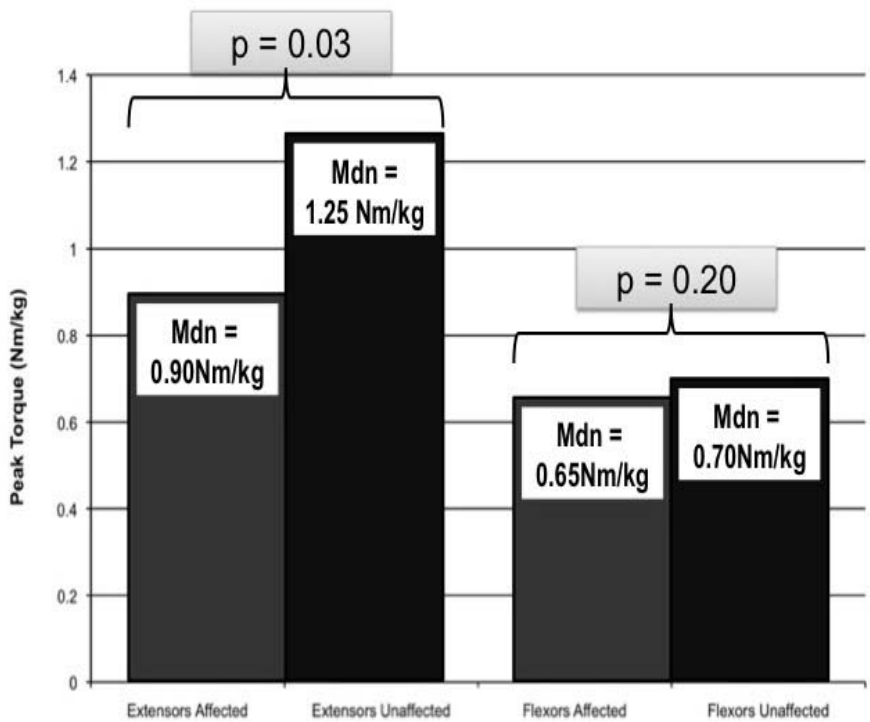


Table 1: Individual patient characteristics at commencement of study

Subject	Age (yrs)	Sex	Ht (cm)	Wt (kg)	Tanner Stage	Disease Duration (months)	Pre-Injection Symptom Duration (months)	JIA Subtype	Medications			
									NSD	SLZ	OCS	MTX
1	16.8	M	181	61.1	5	65	1	ERA	Yes	Yes	No	No
2	12..3	F	156	44.0	2	15	6	Oligo	Yes	No	No	No
3	11.9	F	146	34.8	1	2	2	Oligo	Yes	No	No	No
4	13.7	M	158	53.9	3	41	3	ERA	Yes	Yes	No	No
5	11.9	M	140	40.9	1	4	4	Oligo	No	No	No	No
6	8.5	F	123	17.0	1	77	6	Oligo	No	No	No	No
7	10.9	F	131	40.7	1	12	12	Oligo	No	No	No	No
8	12.8	F	154	42.5	2	25	1	Oligo	No	No	No	No

yrs=years; Ht=height; cm=centimetres; Wt=weight; kg=kilograms; JIA = Juvenile Idiopathic Arthritis, ERA = Enthesitis Related Arthritis, Oligo= Oligoarticular, NSD= Non-steroidal Anti-inflammatory, SLZ = Salazopyrin,, OCS =Oral Corticosteroids, MTX=Methotrexate

Table 2: Isokinetic knee extensor strength by subject

Subject	Baseline			Two weeks			Six Weeks			Twelve Weeks		
	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio
1*	1.54	1.7	0.90	1.77	1.64	1.08	1.51	1.77	0.85	1.39	1.82	0.77
2	1.36	1.57	0.87	1.27	1.48	0.86	1.23	1.61	0.76	1.32	1.93	0.68
3*	0.57	1.44	0.40	1.18	1.29	0.91	1.01	0.92	1.09	1.64	1.72	0.95
4	1.15	1.06	1.09	1.00	1.21	0.83	0.96	1.26	0.76	0.98	0.91	1.08
5	0.29	0.34	0.86	0.39	0.22	1.78	0.29	0.39	0.75	0.34	0.39	0.88
6	0.65	0.94	0.69	0.59	0.53	1.11	1.12	1.12	1.00	Not tested	Not tested	N/A
7	0.57	1.01	0.56	1.15	1.38	0.84	1.01	1.28	0.79	0.96	1.28	0.75
8	1.45	1.96	0.74	1.84	1.93	0.95	1.86	2.27	0.82	1.81	1.93	0.94

Nm=Newton metres, kg=kilogram; *denotes dominant leg affected, Ratio = peak torque affected knee/peak torque unaffected limb (see figure 2)

Table 3: Isokinetic knee flexor strength by subject

Subject	Baseline			Two weeks			Six Weeks			Twelve Weeks		
	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio	Affected (Nm/kg)	Unaffected (Nm/kg)	Ratio
1*	1.11	1.31	0.85	1.36	1.44	0.94	1.23	1.31	0.94	1.06	1.23	0.87
2	0.70	0.75	0.94	0.64	0.80	0.80	0.59	0.93	0.63	0.93	1.11	0.84
3*	0.26	1.01	0.26	1.09	0.86	1.27	0.69	0.69	1.00	1.24	1.49	0.83
4	0.76	0.63	1.21	0.96	0.87	1.11	0.69	0.78	0.88	1.08	0.91	1.18
5	0.44	0.54	0.82	0.46	0.44	1.06	0.56	0.54	1.05	0.49	0.49	1.00
6	0.47	0.65	0.73	0.53	0.59	0.90	0.82	0.82	1.00	Not tested	Not tested	N/A
7	0.59	0.64	0.92	0.81	1.01	0.80	0.69	0.91	0.76	0.81	0.93	0.87
8	1.28	1.14	1.12	1.35	1.28	1.06	1.37	1.28	1.08	1.26	1.11	1.13

Nm=Newton metres, kg=kilogram; *denotes dominant leg affected, Ratio = peak torque affected knee/peak torque unaffected limb (see figure 2)

Mean and Median knee extensor and flexor strength ratios are presented in Table 5 and Table 6.

The mean isokinetic knee extensor ratio two weeks following intra-articular steroid joint injection improved and this approached but did not reach statistical significance (0.77 vs. 1.06, Z=1.59 p=0.09). Improvements in mean knee extensor strength ratio were seen at 6 and 12 weeks but these improvements were not statistically significant compared to baseline.

Table 5 - Ratio Peak Torque Knee Extensors Affected/Unaffected Knee

	N	Median	Range	Change from Baseline	Statistical Comparison to Baseline
Baseline (Pre-injection)	**8**	**0.80**	**0.40-1.09**	**-**	**-**
2 wks post-injection	**8**	**0.93**	**0.83-1.78**	**0.13 (16.3%)**	**Z=-1.82, p=0.07***
6 wks post-injection	**8**	**0.80**	**0.75-1.09**	**0.00 (0.0%)**	**Z-0.42 p=<0.67***
12 wks post injection	**7**	**0.88**	**0.68-1.08**	**0.13 (16.3%)**	**Z=-1.01 p<0.31***

* p value represents comparison to baseline using Wilcoxon Signed Ranks Test

Table 6 - Ratio Peak Torque Knee Flexors Affected/Unaffected Knee

	N	Mean	Range	Change from Baseline	Statistical Comparison to Baseline
Baseline (Pre-injection)	**8**	**0.89**	**0.26-1.21**	**-**	**-**
2 wks post-injection	**8**	**1.00**	**0.80-1.27**	**0.11 (12.4%)**	**Z=-0.70 p=0.48**
6 wks post-injection	**8**	**0.97**	**0.63-1.05**	**0.08 (9.0%)**	**Z=-0.14 p=0.89**
12 wks post injection	**7**	**0.87**	**0.83-1.18**	**-0.02 (-2.3%)**	**Z=0.34 p=0.74**

* p value represents comparison to baseline using Wilcoxon Signed Ranks Test

Some improvements in mean knee flexor strength ratio following intra-articular steroid joint injection occurred at 2, 6 and 12 weeks but these improvements were not statistically significant.

Secondary outcome measures

At baseline there were no differences in thigh circumference between the affected (median = 38.0 cm, range 25.7-39.0) and unaffected sides (median= 37.0cm, range - 25.5-39.0 Z = -0.94, p=0.35. There were no changes in thigh circumference seen in the affected limb at 2 weeks post injection (median = 36.5 cm vs 38.0cm, Z= 1.24 p=0.22), 6 weeks (median = 37.0cm vs 38.0cm, Z= -0.74, p=0.46), or 12 weeks (mean = 38.0 cm vs 38.0cm, Z= -0.41 p=0.68) compared to baseline.

There was a statistically significant difference in total joint range of motion between the affected and unaffected sides (median 121.4 vs 145.2 degrees at baseline, Z = -1.99 p=0.05) Improvements in total joint range of motion from baseline measurements were seen in the affected limb at 2 weeks (median 139.1 degrees, Z = -2.03, p=0.04) and 6 weeks (median = 138.1 degrees, Z = -2.03, p=0.04) and 12 weeks (median = 132.5 degrees, Z = -2.03, p=0.04).

Although reported pain scores increased during testing for some patients, on every occasion the subject was able to complete strength testing without limitation and subjects reported that their pain returned to pre testing levels at the cessation of testing.

No statistically significant differences were identified in CHAQ scores at 2 weeks (median= 0.125; range = 0.00-1.88, Z=-1.46 p=0.14), 6 weeks (median= 0.13, range = 0.0-2.25, Z=-0.94 p=0.35), or 12 weeks (median= 0.0, range = 0.000-1.63, Z=-0.54 p=0.59, compared to baseline CHAQ scores (median= 0.63, range = 0.00-2.25).

A statistically significant improvement in weekday total activity hours (median= 6.65 vs. 9.50 hours; Z=-1.99 p=0.05) but not weekend total activity hours (median = 5.91 vs 7.19 hours: Z=-1.15, p=0.25) was identified between baseline and 2 weeks using the HAES Questionnaire. Although levels of physical activity were increased compared to baseline at 6 and 12 weeks these improvements were not statistically significant.

All eight patients in this study had a single active joint at baseline. None of the subjects developed a new active joint during the study period, although one had a recurrence synovitis in the affected knee three months after the conclusion of the study period.

None of the patients on regular medications had an increase in their medications during the study period. Three of the patients on NSAID ceased these medications by six weeks.

Figure 3: Changes in knee extensor strength ratio over time by subject

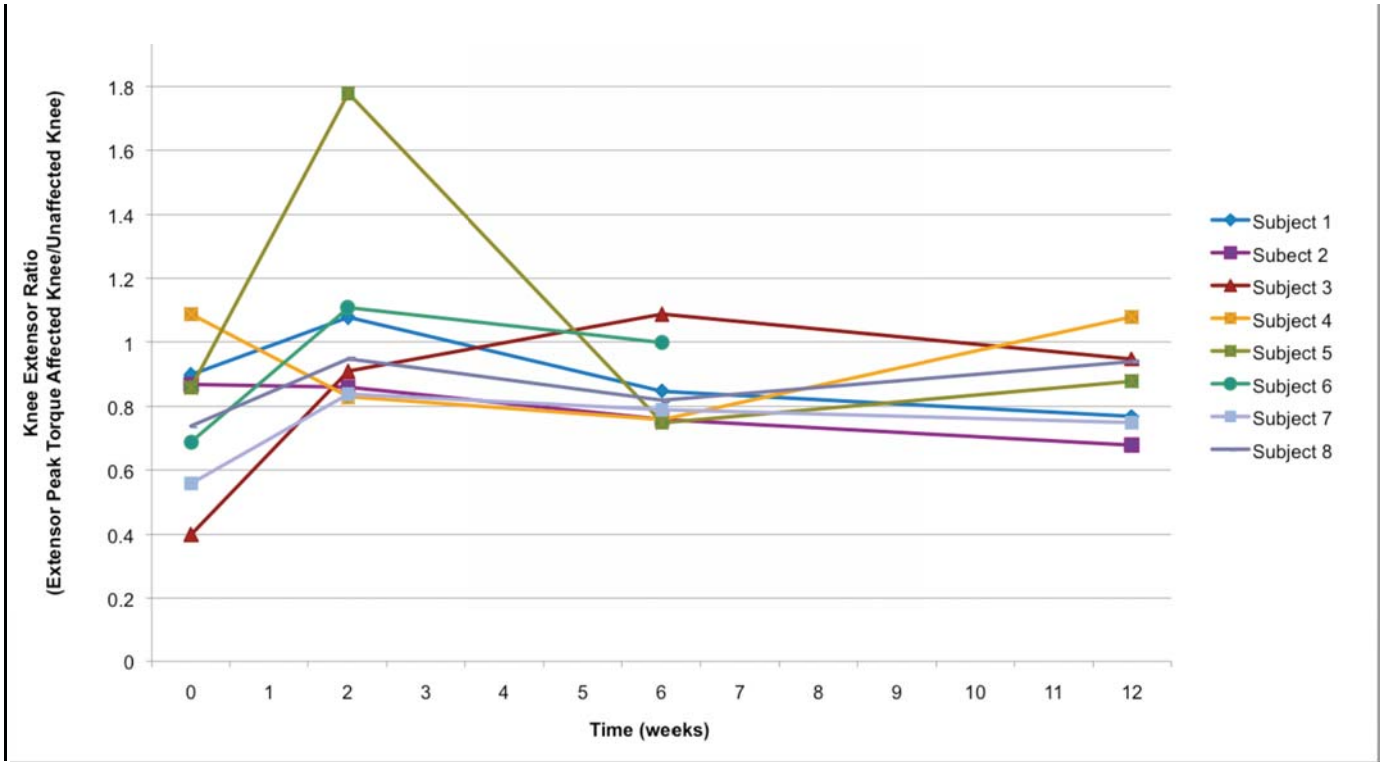
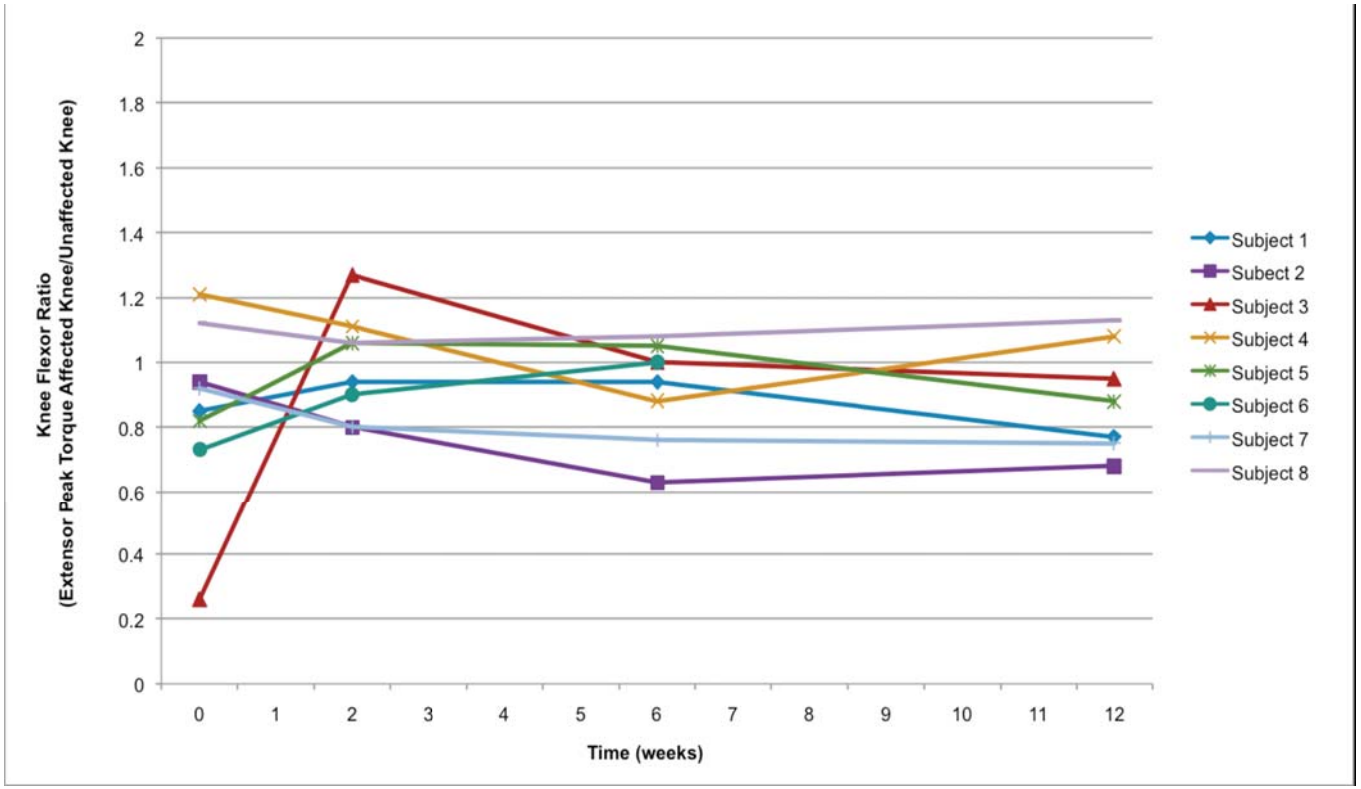


Figure 4: Changes in knee flexor strength ratio over time by subject



Discussion

This study was undertaken as a pilot study for a larger study to test the hypothesis that strength is reduced in muscles surrounding knee joints affected by JIA and that improvements would be seen following injection of IA corticosteroid injection.

The result of strength assessments at baseline in this study concur with previous studies indicating that the strength of movements are reduced in active knee arthritis (40). In this study median isokinetic knee extensor strength on the affected side was reduced by 38.9% and median knee flexion strength by 7.7%. While only small numbers of patients were included in this pilot study, the magnitude of the changes observed in extensor strength are of the order which previous studies have considered clinically significant due to injury or disuse at around 15-20% (41,42).

Although it is possible that the non-significant reduction in isokinetic knee flexion strength observed is due to type 2 error due to the small sample size, other authors have also noted greater reductions in knee extensor than flexor strength in conditions such as ligamentous injury of the knee (42). Computerized tomography studies of thigh muscle cross-sectional area after ligamentous knee injury have demonstrated greater muscle loss in quadriceps femoris than in the hamstrings muscle group (42). In this study it is possible that the effusion associated with active synovitis of the knee had a greater effect on knee extensor strength than knee flexor strength as it is well known that even small volumes of effusion result in dysfunction of vastus medialis oblique (43).

Six of eight patients in our study had involvement of their non-dominant leg. While it is not possible to perform a sub-group analysis to determine the possible influence of limb dominance, it is a generally accepted that the dominant side is the stronger in adults (44) but in children no significant effect of dominance on isokinetic knee extension or flexion strength has been identified (26). Nonetheless even allowing for the potential influence of dominance in our study, the median baseline ratio of isokinetic extensor strength of affected /unaffected leg was 0.80 (range 0.40 to 1.09) and is substantially lower than the non-dominant leg/dominant leg ratio of 0.90-0.95 seen in published normative data (27) for children meaning that the influence of active knee synovitis is likely to be greater than that of limb dominance.

Height, weight and limb length are known to influence isokinetic dynamometry measurements of muscle strength with age and height alone accounted for more than 50% of the variance observed in isokinetic strength in normal children aged 7-15 years of age (45). Hormone levels, in particular testosterone have also been shown to have a significant impact on strength. Puberty also exerts a significant influence on strength and the sex difference in peak torque between boys and girls (46).

In this study isokinetic strength was assessed over time and compared as a ratio of isokinetic strength of the affected side over isokinetic strength of the unaffected side in an attempt to correct for many of the potential confounding influences that may influence

peak torque other than the intra-articular steroid joint injection.

Improvements in knee extensor strength ratio were identified at 2 weeks but only partially sustained. Inspection of the individual subjects reveals improvement in the knee extension strength ratio in 6 of 8 subjects at 2 weeks, in only 4 of 8 subjects at six weeks, and in only 4 of 7 patients tested at 12 weeks. Of the two patients that initially improved and then became weaker, Subject 5 had markedly reduced isokinetic strength in the unaffected knee extensor at two weeks with a corresponding report of marked pain during testing resulting in the knee extensor ratio being falsely increased due to a decrease in the denominator of the equation. Patient 1 had a gradual reduction in absolute isokinetic knee extension strength at 6 and 12 weeks after an initial increase. No other factors for this reversal of improvement in strength were identified.

The absence of improvement in muscle mass as measured by thigh circumference is not surprising as muscle hypertrophy from increased use would not be expected in such a short period of time (47).

Levels of physical activity improved following IA steroid injection highlighting the potential clinical benefits of intra-articular steroid injection. Although time spent in physical activity increased, physical functioning measured using the CHAQ did not. This may be explained by the fact that the CHAQ is a relatively insensitive tool for assessing small or short-term changes, especially for children with the high levels of function seen in the subjects recruited to this study (58). All eight patients had a single active joint at commencement and no new active joints occurred during the study period. One patient had a CHAQ score greater than 1.0 at commencement and most patients scored 0 on all visits suggesting that our study group had little impairment of function.

Although pain scores did increase during testing in 3 of 8 patients, all subjects could complete strength testing and self reported pain did not appear to impair performance during testing other than in subject 4. This subject reported high levels of pain during testing for both the affected and unaffected limbs and investigators conducting the testing felt that the pain negatively influenced the degree of effort the subject was able to exert in maximal testing. This is reflected in that subject's results as there was no consistent pattern of affected or unaffected limb being stronger with testing and no identifiable pattern of improvement. Pain levels returned to baseline upon completion of the testing for all participants and no injuries occurred during testing and there were no flares of arthritis in any of the subjects during the study period based on changes in either joint count or increases in medication.

As study visits were timed with the patients' routine post injection reviews, all patients were able to attend all four assessment sessions within the desired time frame except one who was unable to be assessed at 12 weeks due to an unrelated illness. The high compliance seen in this pilot study suggest that the testing and follow-up schedule is agreeable to subjects and their families. Importantly the youngest patient aged only 8 years was able to complete the testing without difficulty.

Of the previous reported studies using isokinetic dynamometry to assess strength in children with JIA (11,24,49) the presence of active arthritis in the joint being tested is only reported in one study (11). In that study 12 of 16 subjects had active arthritis and although pain was not formally assessed no adverse outcomes were specifically reported. Thus from the data presented in our study together with past data, isokinetic dynamometry appears to be a safe method with which to quantify isokinetic muscle strength around the knee in children with JIA even when there is active arthritis present.

Not withstanding the limitations of a small sample size, this pilot study has demonstrated that the study procedures are safe and feasible and that a statistically significant improvement in knee extensor strength after IA injection of actively inflamed knee joints is evident. The effect size was significant and equal to that expected in patients with clinically significant knee injury or chronic knee disease as described above. The improvements following intra-articular steroid injection were not universal nor were they sustained.

Based on the results of this pilot study, a larger appropriately powered study would be feasible. Such a study would be of clinical importance as persisting deficits in knee extensor strength may indicate the need for specific strengthening exercises or a physiotherapy program following IA steroid injection in order to address strength deficits.

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Chapter 7

Summary & General Discussion

Davinder Singh-Grewal

In this present thesis the measurement of physical fitness as estimated by both aerobic and anaerobic testing is considered along with the effects of exercise training in children with Juvenile Idiopathic Arthritis (JIA). In addition to this the reliability of activity and functional questionnaires is examined along with the muscular strength benefits of intra-articular steroid injections to the knee joints in patients with acute inflammatory arthritis.

Identifying the problem

Traditionally the therapy of children with JIA has concentrated on the control of inflammation, management of pain, maintenance of joint range of motion and overall function. As such fairly gentle means of physical therapy such as rest and passive range of motion activities were utilized (1,2). While these aims remain paramount in the management of JIA, recent advances in the management of inflammation including the widespread use of methotrexate, intra-articular steroid injections and biologic therapies for patients with disease recalcitrant to other therapies means that the effective control of inflammation is more achievable. In this new treatment paradigm clinicians have come to appreciate the importance of more active forms of therapy for children with JIA (3).

Furthermore, the past decade has also lead to an appreciation of the association between inactive youth, poor fitness and obesity in children and adolescents with elevated risks for cardiovascular disease including blood pressure and hypercholesterolaemia. Children with JIA have been shown to have lower participation in physical activity (4,5) and a lower rate of physical fitness (6-8) compared to their unaffected peers making them a risk for these cardiovascular risks.

The randomised trial presented in chapter 4 of this thesis demonstrates a significant reduction in baseline fitness of children with JIA as measured by VO_{2peak} and compared to data available for children without JIA (9). This difference in fitness was demonstrated in our sample of patients despite the fact that a majority had relatively mild disease with an overall mean CHAQ score of 0.32 ± 0.45 (range of 0 to 2.13).

Habitual activity was also measured in Chapter 4 using the Habitual Activity Estimation Scale (HAES), a questionnaire which has been widely used in patients with Cystic Fibrosis (CF) and found to be a reliable and valid instrument in that patient group when compared to accelerometry (10). There are no published or available “normal” HAES scores for activity in a non-chronic disease cohort but what can be said is that physical activity levels in our relatively well cohort of JIA patients was comparable to that of Canadian patients with CF reported by Wells et al (10). This is concerning as CF is considered to be a potentially life-threatening disease with progressive cardiorespiratory decline and one would expect that activity would be more limited in these patients than patients with JIA. We found that the HAES was not a particularly reliable measure of activity in patients with JIA and this data is presented in Chapter 3. Other authors have found that using a combination of single axis accelerometry and activity diaries that children with JIA have reduced activity levels when compared to those without JIA (11).

What are the solutions?

The United States Centres for Disease Control and Prevention recommends daily exercise in youth aged 6-18 years to reduce body fat and improve aerobic fitness in children without any chronic illness (12). Other studies have advocated the functional benefits of exercise in children with cerebral palsy (13,14), there is some limited evidence that exercise may benefit patients with CF in terms of their exercise capacity, muscular strength and lung function (15) and also adult rheumatoid arthritis (16).

Prior to the papers published in this thesis there is only a very limited amount of data examining the benefits of exercise in JIA. Most of these papers were small or uncontrolled and many used inaccurate field testing techniques to measure outcomes. Of the properly randomised trials available, Epps et al (17) completed a randomised controlled trial of combined physiotherapy against hydrotherapy which showed an improvement in the core set measures including CHAQ in both groups. While Takken et al (18) in a randomised trial of an aquatic fitness program compared to standard therapy showed small non-significant improvements in fitness as measured by VO_{2peak} and function as measured by CHAQ.

The large randomised control trial of a high intensity aerobic training program compared to a far less intensive activity presented in Chapter 4 shows a similar pattern of results with both groups showing some improvements in functional measures which did not seem to be related to the intensity of exercise performed. One difference in this paper when compared to the others was that we also assessed sub-maximal VO_2 ($VO_{2submax}$) which has been suggested as a more useful exercise testing measure in patients with any chronic disease or limitation and has been shown to be a strong predictor of VO_{2peak} and may be a better reflection of functional fitness than VO_{2peak} in disease populations (19-26). Despite this no significant difference was seen in $VO_{2submax}$ between groups. The important feature of this study however was the clear result that a high intensity aerobic training program was very well tolerated by children with JIA and no worsening of disease activity was seen. Also of significance was the finding that CHAQ was improved in both groups but it is debatable as to whether this was as a result of the Hawthorn Affect (through increased attention from trainers and other study personnel resulting in an improved sense of well being).

We must recognise that the compliance with the program used in the randomised trial was quite poor meaning that is it possible that the required intensity, duration and frequency of training needed to demonstrate any improvements was not attained. This is a common theme in studies of exercise interventions in children with chronic diseases.

Nonetheless this study like the other large randomised trials of exercise interventions in JIA showed no worsening of disease activity and likely improvements in function which were in our study clinically significant. The caveat to this statement is that children with severe hip disease were unable to complete many aspects of exercise testing and training in the pilot study presented in Chapter 2. These patients may benefit from water based exercise programs which allow quite strenuous activity without the compressive forces through articular cartilage seen in land based programs (27, 28) and as shown by Takken

et al (18) may have similar benefits in terms of function to land based programs. Furthermore the findings of the pilot study in Chapter 2 suggest that some activities are better tolerated by children with JIA than others with the Fitball® particularly posing difficulties for most participants as the balance and control required to complete the Fitball® program proved too complicated for many participants and actually worsened symptoms in children with severe hip disease. Thus it may be that simple intuitive exercise activities rather than those which are complicated are best for children with JIA. It is possible to speculate that this may be a result of some impairment in proprioception and balance in this group of patients (30, 31). Furthermore, it may be that normal levels of activity commensurate with the age specific peer group may be of the greatest advantage to children with JIA.

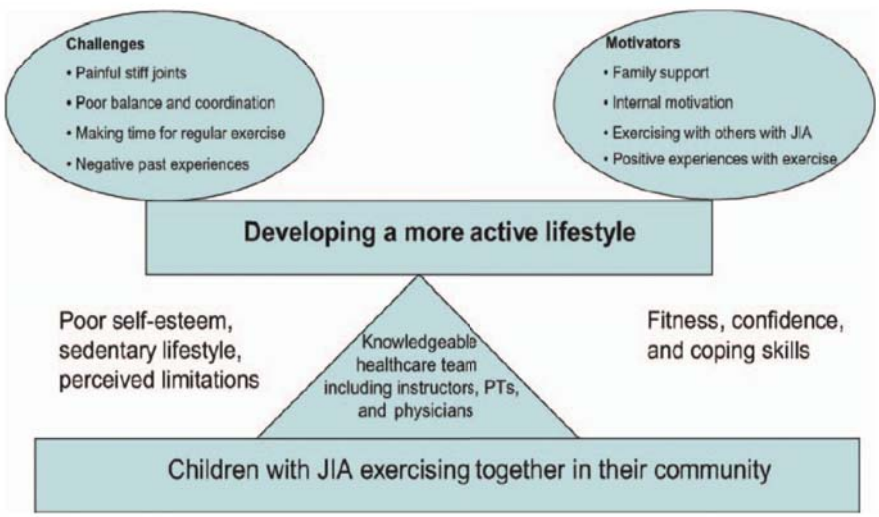

Figure 1 – For children with JIA to develop a more active lifestyle, the challenges they experience must not outweigh their sources of motivation. The base of this "balance scale" is the model in a community exercise program organized by a multidisciplinary healthcare team and lead by an instructor who is knowledgeable about their disease in order to provide individualized support and guidance.

Children with JIA have long been "sidelined" and not encouraged to participate in activity for a combination of reasons including their own perceptions of limitation and a poor understanding of their disease with similar deficiencies in knowledge in their teachers, parents and sporting coaches who would ordinarily encourage children without JIA to maintain appropriate levels of physical activity. In a qualitative study of the experiences of the fitness instructors involved in the exercise programs provided in Chapter 4 by Hutzal et al, they identified three main factors which may lead to increased activity in children with JIA : (a) encouragement and guidance from instructors who understand arthritis and support from family and peers; (b) Children with JIA need help and education to overcome their negative perceptions about exercise; and (c)

participation in a structured exercise program such as that used may result in the adoption of a more active lifestyle (29). They concluded that community based physiotherapists partnering with fitness instructors could result in positive influences on physical activity in children with JIA. These sentiments have been echoed by other authors (32, 33) and a schematic representation of the model proposed by Hutzal et al is shown in Figure 1.

Muscular strength is a significant contributor to anaerobic capacity and has been shown to be strongly related to function in children with JIA (34-36). This is thought to be due to the fact that many of the activities of daily living in childhood are anaerobic in nature (34-37). Despite this, in Chapter 4 we were unable to identify any improvements in anaerobic capacity as measured by the Wingate protocol despite the observed improvements in function in both groups. Chapter 6 presents the results of a small pilot study of the affect of intra-articular steroid injections on isokinetic and isometric muscle strength in the lower limbs showing a significant but unsustained improvement in knee extensor strength. This finding leads us to ask whether these improvements might be sustained by an active physiotherapy strengthening program after intra-articular injections and whether this might be translated into improvements in function.

Utility of measurements of fitness, function and activity

Exercise testing in patients with JIA might conceivably be performed for one of a number of reasons including: 1) to determine a patient's functional capacity and assess their ability to perform activities of daily living; 2) to determine response to an exercise intervention program particularly in research settings; or 3) to assess whether chronic disease progression is affecting the patient's physical capacity. As yet this aspect of sports science is still in evolution and the main uses this far has been in assessing response to training and assessing the relationship of fitness to function in patients with JIA.

In order to be able to use exercise testing measures in research and also clinical applications it is important that they conform to a number of requirements. They must be safe, valid, reliable and particularly for clinical applications feasible to perform. The gold standard in measurement of aerobic fitness remains the direct assessment of VO_{2peak} using a maximal exercise protocol. We used the $VO_{2submax}$ as the primary outcome measure for the randomised trial as it has been suggested as a feasible and possibly better measure of function. The papers presented in Chapters 2 and 4 show that both tests are well tolerated, and reliable in children with JIA which is in agreement with previously published data for the VO_{2peak} from Takken et al (38) but this thesis contains the first assessment of the reliability of $VO_{2submax}$ in children with JIA. The studies presented in Chapters 2 and 4 used a treadmill protocol to measure VO_{2peak} while Takken and colleagues used a bicycle protocol (38) nonetheless subjects were able to reach maximal heart rate and RER=1.1 to complete the test. Peak power (Want) measured using the Wingate test was also feasible in that subjects were able to complete the protocol. Patients with significant hip disease in the pilot study were able to complete testing but experienced pain while completing the protocols were excluded from the randomised trial.

If we accept that fitness in children with JIA is related to function and long term outcomes particularly cardiovascular risks, it is likely that fitness testing will become an important part of our assessment of patients in the future. Chapter 3 examined the reliability of some of these measures (VO_{2peak}, $VO_{2submax,}$ Want) in terms of their test retest characteristics and found them to be highly reliable in the JIA population. Overall these findings justify the use of these formal exercise testing measures in JIA populations in future studies.

While it is important to remember that the direct measurement of VO_{2peak} remains the gold standard in assessment of aerobic fitness and any method used to assess this indirectly will introduce the potential for error, field testing such as timed walking distances and shuttle runs are used quite frequently in assessing fitness in many different populations. These tests have the benefit of not suffering the logistic and financial disadvantage of requiring complicated equipment such as gas analysers or the expertise of an exercise physiologist associated with formal VO_{2peak} measurements. Thus less cumbersome means of testing may have an important role in clinical applications such as monitoring fitness after the prescription of an exercise program.

The 6 minute walk test has been shown to have a very poor correlation with $VO_{2peak\ in}$ JIA (39) and there is no validation data for other approaches such as the shuttle run which has been shown to be valid in normal populations and patients with cerebral palsy (40-43). No such data on the shuttle run is available on children with JIA. Chapter 5 assesses the use of maximal power output or peak work rate (W_{peak}) from a cycle task as a means of predicting of $VO_{2peak.}$ This approach has the advantage of not requiring complicated equipment but still maintaining much of the standardisation seen in formal exercise testing. The study showed a significant correlation between VO_{2peak} and W_{peak} and provides a prediction equation for VO_{2peak} in children with JIA. This simplified method of estimating aerobic capacity may prove a useful means for monitoring fitness in research and clinical settings.

Along with exercise testing measures, Chapter 3 also assessed the reliability of functional measured such as the CHAQ and Revised ASK and also the HAES as a measure of physical activity. The CHAQ has been extensively investigated as a measure of function in JIA and our study confirms earlier findings reporting it's reliability in this role (44). The Revised ASK was also shown to have a excellent reliability as a measure of function in JIA but as yet there is no data to demonstrate it's sensitivity to change in function. Thus CHAQ should remain the preferred measure of function in JIA until this data is available. The HAES, however, was shown to have a fairly poor reliability in our population which is in contrast to other work in CF patients showing a good reliability and validity when compared to accelerometer measurements (10). These results might reflect a slightly lower age group selected in our population that the CF population or might simply indicate what difficulties children might experience with a recall questionnaire of activity such as the HAES. Nonetheless the validity of the HAES has still not been assessed in JIA patients against prospective activity diaries or acclereometry.

Main conclusions and clinical significance

It is clear that children with JIA are deconditioned when compared to their peers who do not suffer from JIA. The evidence would suggest that this deconditoning is significant and may place them at some long term disadvantage from a health point of view.

There is no evidence that even very intense physical activity will exacerbate arthritis symptoms in all but those with the most severe hip disease and thus children should generally not be sidelined from participating in sports and other physical activities. This represents a challenge to the longstanding misconception that exercise might cause deterioration in the disease.

It seems that fitness training of any sort has benefits for children with JIA particularly in terms of their overall function even if specific improvements in fitness measures are not demonstrable. Many of these benefits might be psychological and related to fitting in and feeling "normal". The encouragement of physical activity in children with JIA which is on-par with their peers may translate into increased physical activity and the benefits particularly from the point of view of cardiovascular health into adulthood.

Exercise testing measures are generally safe and reliable in patients with JIA and are likely to become an invaluable tool in the assessment and long term follow-up of children with JIA. While formal exercise testing remains the best means of assessment less intensive measures with good extrapolation to VO_{2peak} including the W_{peak} may represent more feasible means for the widespread use of exercise measures in management.

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Summary

This thesis considers the field of exercise testing and training in children with Juvenile Idiopathic Arthritis (JIA). The papers contained within the thesis examine the feasibility and affects of fitness training and the treatment of active JIA on exercise testing parameters and function. It also examines the reliability of exercise testing and measures of function and activity in patients with JIA.

Chapter 1 describes the understanding of fitness, it's assessment and evidence for fitness testing and training in children with JIA prior to the work presented in this thesis. It also explores the potential detrimental affects of low levels of physical activity and fitness in this population.

Chapter 2 presents the results of a pilot study of nine patients undertaking a 12 week circuit training program of pool, stationary bike, treadmill and Fitball. It was designed to assess the safety of exercise testing and fitness training in children with JIA. The study also endeavoured to assess the training affect of this program to help with the development of a larger randomised controlled trial which is presented in Chapter 2. This pilot study determined that it was safe and feasible for children with JIA to participate in a fitness training unless they had severe hip disease which was shown to worsen symptomatically during the program and prevented these children from completing the study.

Chapter 3 examines the reliability of exercise testing, functional and activity questionnaires in the patients with JIA. Test retest reliability and limits of agreement between repeat measures are reported for peak VO_2 (VO_{2peak}), submaximal VO_2 ($VO_{2submax}$), anaerobic power measured by the Wingate Test (Want), Child Health Assessment Questionnaire (CHAQ), Revised Activity Scale for Kids (ASK) and the Habitual Activity Estimation Scale (HAES). All measures tested excluding the HAES proved to be reliable in this study.

Chapter 4, presents a large randomised and controlled trial of an exercise intervention in children with JIA. It includes 80 subjects with the experimental group undertaking a 12 week intensive aerobic training program and the control group a gentle exercise program based on qigong. Exercise was well tolerated by both groups but compliance was somewhat disappointing. The study showed no difference between the groups in any fitness measures at the conclusion of the study. However, there were significant improvements in the CHAQ in both groups and importantly no worsening in arthritis activity or symptoms.

Chapter 5 examines whether peak work rate (W_{peak}) which is a mixed measure of aerobic and anaerobic capacity can be used to predict aerobic capacity (VO_{2peak}) in patients with JIA. The benefits of using W_{peak} to assess fitness rather than VO_{2peak} is that it does not require complicated equipment and analysis techniques. In this study we were able to show that W_{peak} is highly predictive of VO_{2peak} and were able to formulate a prediction

equation which showed only small differences to similar equations formulated for children without JIA.

Chapter 6 presents a small pilot study of isometric and isokinetic muscle strength measurements of the quadriceps and hamstrings around inflamed knee joints in JIA patients before and after intra-articular steroid injections. This study aimed to assess the feasibility of larger trial examining the affect of intra-articular injections on muscle strength locally in terms of the affect size observed and patients' ability to comply with testing procedures.

Chapter 7 provides a general synthesis of the proceeding chapters and the contribution of the thesis to the literature and our understanding of exercise testing and exercise interventions in patients with JIA.

Samenvatting

Dit proefschrift bestudeert inspanningstests en fysieke training bij kinderen met Juveniele Idiopathische Artritis (JIA). De verschillende hoofdstukken van dit proefschrift beschrijven de haalbaarheid en de effecten van fitnesstraining als behandeling van een actieve JIA op zowel inspanning als functionele capaciteit.

Ook de betrouwbaarheid van inspanningstests en de metingen van functionele capaciteit en fysieke activiteit van patiënten met JIA wordt onderzocht.

Hoofdstuk I beschrijft het begrip fitness, het onderzoek en het wetenschappelijk bewijs van fitness training bij kinderen met JIA in de periode vóór het in dit proefschrift gepresenteerde werk. Tevens verkent dit hoofdstuk de potentiële schadelijke gevolgen van een de kort aan fysieke activiteit en fitheid in deze patiëntengroep.

Hoofdstuk II laat de resultaten zien van een pilot-studie bij negen patiënten met JIA na een twaalf weken durend trainingsprogramma waarbij gebruik gemaakt werd van respectievelijk een zwembad, hometrainer, tredmolen en Fitball. Het doel was een inschatting te maken van de veiligheid van inspanningstests en fitnesstraining bij kinderen met JIA. Met de studie is ook geprobeerd om de opgedane kennis te gebruiken bij het opzetten van een groter gerandomiseerd gecontroleerd onderzoek dat is weergegeven in hoofdstuk IV

De pilot-studie stelde vast dat het voor kinderen met JIA veilig en doenlijk was om deel te nemen aan een fitnesstraining, tenzij zij ernstige heupafwijkingen hadden die aantoonbaar symptomatisch verergerden gedurende het programma en zij daardoor het onderzoek niet konden afronden.

Hoofdstuk III onderzoekt de betrouwbaarheid van inspanningstests en het gebruik van vragenlijsten naar het functioneren en de fysieke activiteit van patiënten met JIA.

Test-hertest betrouwbaarheid en ‘limits of agreement’ tussen herhaalde metingen zijn vermeld waar het gaat om ‘peak VO2’ (VO2 peak), submaximale VO2 (VO2submax) anaerobe kracht gemeten met behulp van de Wingate Anaerobe test (Want), Child Health Assessment Questionnaire (CHAQ), Revised Activity Scale for Kids (ASK) en de Habitual Activity Estimation Scale (HAES). Alle meetinstrumenten die getest werden met uitzondering van de HAES bleken in deze studie voldoende betrouwbaar.

Hoofdstuk IV presenteert een groot gerandomiseerd en gecontroleerde trial van een trainingsprogramma voor kinderen met JIA. Het gaat hier om 80 kinderen waarvan de experimentele groep een twaalf weken durend intensief aeroob trainingsprogramma ondergaat en de controlegroep een licht oefenprogramma gebaseerd op Qigong. De programma’s werden door beiden groepen goed verdragen. De juiste uitvoering/inzet liet wat te wensen over.

Het onderzoek vertoonde geen enkel verschil tussen de twee groepen op de fitness parameter. Er waren echter significante verbeteringen te zien in de CHAQ van beide groepen en, belangrijk, geen verslechtering in de activiteit van de artritis of in de symptomatologie.

Hoofdstuk V onderzoekt of de maximaal behaalde belasting (Wpeak), een gecombineerde weergave is van de aerobe en anaerobe capaciteit, gebruikt kan worden om voorspellingen te doen over de aerobe activiteit (VO2peak) bij patiënten met JIA. De voordelen van het gebruik van Wpeak boven dat van VO2peak bestaat daarin dat er geen ingewikkelde instrumenten of analysetechnieken nodig zijn. We hebben aangetoond dat Wpeak in hoge mate VO2peak voorspelt en hebben een voorspellingsformule geformuleerd die slechts kleine verschillen laat zien met overeenkomstige formules die geformuleerd werden voor kinderen zonder JIA.

Hoofdstuk VI behandelt een kleine pilot studie naar isometrische en isokinetische spierkrachtmetingen van de quadriceps en de hamstrings rond de ontstoken kniegewrichten van JIA patiënten vóór en na het toedienen van intra –articulaire steroïd injecties.

Deze studie, bedoeld om een inschatting te maken van de haalbaarheid van een groter onderzoek naar het effect van intra-articulaire injecties op de plaatselijke spierkracht en van de haalbaarheid naar het meedoen van patiënten aan testprocedures.

Hoofdstuk VII geeft een algemene samenvatting van de voorafgaande hoofdstukken en de bijdrage die dit proefschrift levert aan de literatuur en onze kennis van inspanningstests en inspanningsprogramma's bij kinderen met JIA.

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I cannot forget the input of my parents Sylvia and Lakhmir who instilled the importance of education from an early age and supported my education from kindergarden to the completion of paediatric rheumatology specialisation. For this, their love and much, much more I am forever grateful.

To my girls, my wife Anne and daughter Maya who both provide the inspiration for each day, I love you dearly.

Curriculum Vitae

Davinder Singh-Grewal was born in Sydney Australia and graduated with first class honours from the University of Sydney in 1996 with a Bachelors of Medicine and Bachelors of Surgery (MBBS). He entered paediatric physician training at The Children's Hospital at Westmead in Sydney and obtained the Diploma in Child Health (DCH) with a high distinction in 1999 and then Fellowship of the Australasian College of Physician as a Paediatrician (FRACP) in 2003.

In 2003 he also entered the Rheumatology fellowship program at The Hospital for Sick Children in Toronto Canada and completed a three year fellowship there. During this fellowship he completed a Masters in Medical Science majoring in Clinical Epidemiology (MMedSci). He conducted much of the research presented in this thesis during that fellowship at Sick Kids in Toronto and obtained qualification as a paediatric rheumatologist.

In 2006 he returned to Sydney Australia to work as a consultant paediatric rheumatologist, and has also spent 6 months working at The Great Ormond Street Hospital in London as a locum consultant in Rheumatology in 2008.

He has authored numerous peer reviewed journal articles and invited papers and presents at numerous international and national meetings through his career.

He now lives again in Sydney, Australia with his wife Anne and 2 year old Daughter Maya and is appointed as a staff specialist at The Children's Hospital at Westmead, The Sydney Children's Hospital at Randwick and the John Hunter Children's Hospital in Newcastle. He continues to be actively involved in research, teaching and advocacy for children with rheumatic disease.

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