Relationship between aerobic capacity and disease activity in children with Juvenile Idiopathic Arthritis: a review

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Abstract

Objective

To evaluate whether there is a relationship between aerobic capacity and disease activity in children with juvenile idiopathic arthritis (JIA), and to identify parameters which could provide more information about the aforementioned relationship in future studies.

Methods

A systematic literature search was performed. Studies on aerobic fitness in children with JIA were identified and examined for measures of aerobic fitness VO_{2peak} and “hard” measures of disease activity, including joint count (JC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or other markers of inflammation. Correlations between VO_{2peak} and disease activity were the main outcome measures for this review study.

Results

Seventeen studies were identified that reported aerobic capacity in children with JIA. Five studies described a possible correlation between aerobic capacity and joint count; three studies report no correlation, one study reports a negative correlation between JC and physical fitness score and one study reports a correlation between VO_{2max} and disease activity in JCA girls (r = -0.60).

Conclusion

Various studies investigated aerobic capacity in patients with JIA, including the effect of exercise training, on a variety of outcome measures; however no studies included “hard” measures of disease activity such as CRP or ESR. There is no equivocal evidence whether aerobic capacity is related to JC.

Introduction

Juvenile idiopathic arthritis (JIA) is a disease of unknown cause and the most common chronic rheumatic disease in children. It includes all forms of arthritis beginning before the age of 16 that persist for more than 6 weeks, and is characterized by inflammation of the synovium of unknown cause [1]. This results in joint swelling, pain, stiffness and fatigue which can lead to permanent disability in later life. Reported prevalence rates vary from 16 to 150 per 100 000 in developed countries [1].

Children with active JIA are often less physically active than their healthy peers. The inflamed joints are a source of pain which is aggravated by movement and discourages children from being active. Additional fear of further damaging the affected joints through physical activity by parents and children can result in prolonged hypoactivity. An inactive lifestyle can result in decreased aerobic and anaerobic fitness which in turn affects the overall physical and mental wellbeing of the JIA patients. Inactivity could also affect disease activity and puts these children at risk for developing other diseases related to a sedentary lifestyle later on in life [2, 3].

In the past years a number of studies examined the physical fitness of children with JIA. Several papers were published on the effect of exercise programs on various outcome measures and a number of excellent reviews have been published which provide a good overview of the results [4-21]. Although there is a fair amount of research into the relationship between aerobic capacity and JIA, these papers reveal that the main focus until now has been on daily activities, functional well being, joint pain, range of motion and psychological well being, and few studies have included measures of disease activity as outcome measurement.

The purpose of this review is to give an overview of what currently is known about the relationship between aerobic capacity and disease activity as measured by inflammation parameters or the number of active joints, and to identify missing knowledge and provide suggestions for future studies.

Methods

Articles on aerobic capacity and exercise in children with JIA were collected and screened for absolute measures of aerobic capacity (VO_{2peak}), “hard” measures of disease activity such as C-reactive protein (CRP), erythrocyte sedimentation rates (ESR) or joint count (JC), and a possible correlation with VO_{2peak}. (Table 1)

JIA subtypes

According to the International League of Associations for Rheumatology (ILAR) there are seven disease subcategories based on the symptoms in the first 6 months of the illness [22]. (Table 2) This subdivision is used mostly to identify homogenous groups of children with similar pathogenesis, clinical presentation, outcome, and in some cases, genetic background that can be used in research projects. It is less useful in a clinical setting due to the large variation in symptoms and disease progression between patients, even if they are in the same JIA subcategory.

Table 2. Frequency, age of onset and sex distribution of the International League of Associations for Rheumatology subsets of juvenile idiopathic arthritis. Adapted from Ravelli et al. [23].

	Frequency*	**Onset age**	**Sex ratio**
Systemic arthritis	4-17%	Throughout childhood	F=M
Oligoarthritis	27-56%	Early childhood, peak at 2-4 years	F>>>M
Polyarthritis rheumatoid-factor positive	2-7%	Late childhood or adolescence	F>>M
Polyarthritis rheumatoid-factor negative	11-28%	Biphasic distribution, early peak at 2-4 years and later peak at 6-12 years	F>>M
Enthesis related arthritis	3-11%	Late childhood or adolescence	M>>F
Psoriatic related arthritis	2-11%	Biphasic distribution; early peak at 2-4 years and later peak at 9-11 years	F>M
Undifferentiated arthritis	11-21%	-	-

*Reported frequencies refer to percentage of all juvenile idiopathic arthritis

JIA and exercise

Exercise therapy in the treatment of arthritis has been controversial for a long time. Inflammation of the joints causes pain that worsens during exercise, which was reason to advise people with arthritis to refrain from participating in any training program and advise bed rest instead [24]. However, it became clear that prolonged bed rest and inactivity resulted in reduced overall health, and exercise had positive effects on the general well-being of patients with rheumatoid arthritis [25].

One of the key questions in the treatment of children with JIA has been the role of physical activity and exercise. A number of different aerobic training programs have been proposed in the treatment of JIA, including aquatic training, aerobic floor exercises and qiqong, as well as anaerobic strength training programs [5, 26]. Although results vary, several studies have shown that exercise does not aggravate JIA, improves quality of life and provides benefits for the children, either physical, psychological, or both [1, 27]. Exercise related increased circulation and movement in the joints can help the patient being fit and maintaining a good range of motion in their joints; furthermore, a recently published meta analysis concluded that exercise has a favorable effect on functional ability, quality of life and aerobic capacity, though none of these effects were statistically significant [1].

Aerobic capacity

The most reliable and valid way of quantifying aerobic and cardiovascular fitness is by measuring the maximal oxygen uptake (VO_{2max}) during a cardiopulmonary exercise test (CPET). In a progressive exercise test the participant exercises until voluntary exhaustion, which is characterized by oxygen uptake reaching a plateau even though the workload increases. The CPET has proven to be very accurate in adults, but the plateau phase is often not seen in children and it is not sure that a maximum can be measured accurately.[10] VO_{2peak} is therefore often used instead of VO_{2max} to quantify the aerobic fitness in children. Most studies agree that children with JIA have a significantly lower VO_{2peak} than their healthy peers [1, 10, 18, 20, 26], though this is not seen in every study[11, 16]. The difference in VO_{2peak} tends to disappear when the disease is in remission, though the evidence for this is not conclusive [10, 16]. Also there can be great differences concerning the aerobic capacity between the subgroups of JIA [4].

Disease activity

There is a connection between biomarkers of inflammation and disease severity in rheumatoid arthritis [28]. Disease activity measures include non specific inflammation markers (CRP, TNFalpha, IgM, ESR), the number of active and swollen joints, and other parameters. A high degree of inflammation is a sign of increasing disease severity, however it is not clear what the effect of increased disease activity on physical fitness is.

In a study by Golebiowska et al [18] on VO_{2peak} and post-exercise lactate and pyruvate levels in children with JIA, some additional clinical data was recorded. Disease duration, stage of disease, number of affected joints, activity of disease and hemoglobin levels were also analyzed. They found that girls with JIA with moderate to high disease activity had lower VO_{2max} compared with the control group, while the VO_{2max} of girls with inactive JIA was similar to that of the controls. There was no significant correlation between disease activity and VO_{2max} in boys. Both boys and girls with moderate to high disease activity had a lower VO_{2max} compared with their controls. They concluded that the activity of disease is the most important factor limiting aerobic capacity in children with juvenile arthritis, however they do not know whether this is caused by hypoactivity or cardio respiratory dysfunction and inflammatory changes in the muscles, or a combination of both.

Giannini et al [19] published a study in the same year describing the exercise response in children with juvenile rheumatoid arthritis and healthy controls. Data on the severity of the articular disease was collected and consisted of the number of joints with active arthritis and the articular severity score determined by swelling, pain on passive motion, tenderness and passive limitation of motion. No other measures of disease activity were included. Results showed a lower VO_{2peak} in the patient polulation, however there was no correlation between aerobic capacity and disease severity. JIA subtypes were recorded but not taken into account in the analysis. The authors concluded that deconditioning occurred in the children with JIA regardless of disease severity.

In a study concerning the relationship between physical fitness and other indices of health status in children with chronic arthritis, Malleson et al [11] found no differences in aerobic capacity between children with arthritis and their healthy controls. However, they did report an unspecified negative association between VO_{2peak} controlled for age, sex and skinfolds, and disease severity ($p=0.04$), and reported a trend towards lower VO_{2peak} with increasing disease activity.

Klepper et al. published several studies concerning the relationship between physical fitness and JIA [13-15, 27, 29, 30]. In 1992 the authors looked at physical fitness levels in children with poli-articular JIA using the Health Related Physical Fitness Test (HRPFT). Children with JIA scored significantly lower on a 9 minute run/walk test, which indicates lower physical fitness, however VO_{2peak} was not measured directly. The extent and severity of the disease was measured by articular severity scores and joint count, both of which were not related to physical fitness [13].

In 1999 Klepper reported the effects of 8 weeks of training on disease signs in children with chronic arthritis [15]. Aerobic fitness and disease activity measures were compared before and after an 8-week 24 session program of low impact aerobic exercise, again using the HRPFT 9 minute walk test. Aerobic fitness improved and there was a significant reduction in pre- and post-exercise mean joint count (72%) and articular severity index (80%), suggesting that improvements were significant for the whole group and in most individuals [15]. Unfortunately VO_{2peak} was not measured directly and correlating improvements in joint count to changes in aerobic capacity was not possible.

Discussion

Analyzing all sub classifications as a whole could hide an existing effect in one of the disease categories. Metin et al. demonstrated this in a study assessing aerobic capacity and subgroup differences in JIA patients [10]. They found lower VO_{2peak} values in the JIA group compared to controls, but also found that the enthesis related subgroup reached significantly higher VO_{2peak} levels than the systemic, poliarticular and oligoparticular subgroup as shown in Figure 1.

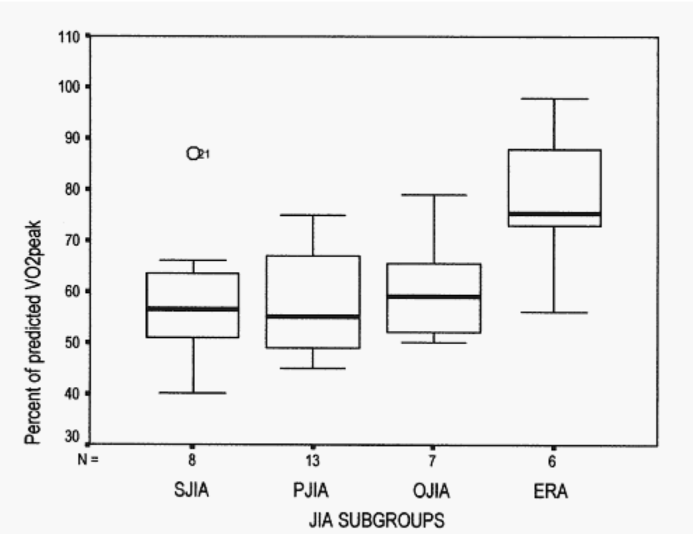

Figure 1. Peak VO_2 in different subgroups of JIA. Figure from Metin et al. [10].

The difference in disease severity between these four subgroups could explain this. ERA is often remitting and can be mild, while the PJIA, SJIA and OJIA are characterized by a more serious disease course [23]. It is possible that the ERA subgroup was not too limited in their daily activities by pain, fatigue and swollen joints and remained active, preventing muscle atrophy and maintaining their fitness levels. The ERA subgroup was also able to exercise significantly longer than the other groups. Measures of disease activity that would have provided additional information on the relationship between VO_{2peak} and the disease severity were not included [10]. Due to differences in mean VO_{2peak}, differentiation between subgroups of JIA in the relationship between aerobic capacity and the disease outcome measure is necessary. Certain forms of JIA are more limiting when it comes to exercise potential and physical activity than others due to variations in the number of swollen and active joints, pain and overall well being. When all patients with JIA are analyzed as one group, the disease category or subgroup can act as a confounder.

Another issue to consider is that aerobic capacity is a dynamic process. Disease activity at the time of study has limited effect on physical fitness since aerobic capacity is determined by how active a child has been in the weeks and months before the moment of testing. Any effects of physical activity on disease activity could be delayed, so if we conduct a study at a certain point in time it is possible to misinterpret a possible relationship or miss the effect. Because of this, cross sectional studies are not the best way to find correlations between physical capacity and disease parameters. Repeated measurements provide information on the dynamics of both physical fitness and the disease process. A longitudinal cohort study should be preferred over a cross sectional study.

According to a recently published study exercise has an influence on the expression of neutrophil activity in healthy men [31]. Radom-Aizik et al. show that thirty minutes of heavy constant exercise altered the expression of a number of neutrophil genes known to be involved in arthritis, suggesting a link between physical activity and disease [31]. This is not evidence that exercise has an actual effect on the function of neutrophils, or that this altered expression is seen in a situation of chronic inflammation or that these results can be translated to children with JIA, however it does indicate that there might be advantageous temporary effect of exercise on the inflammation process.

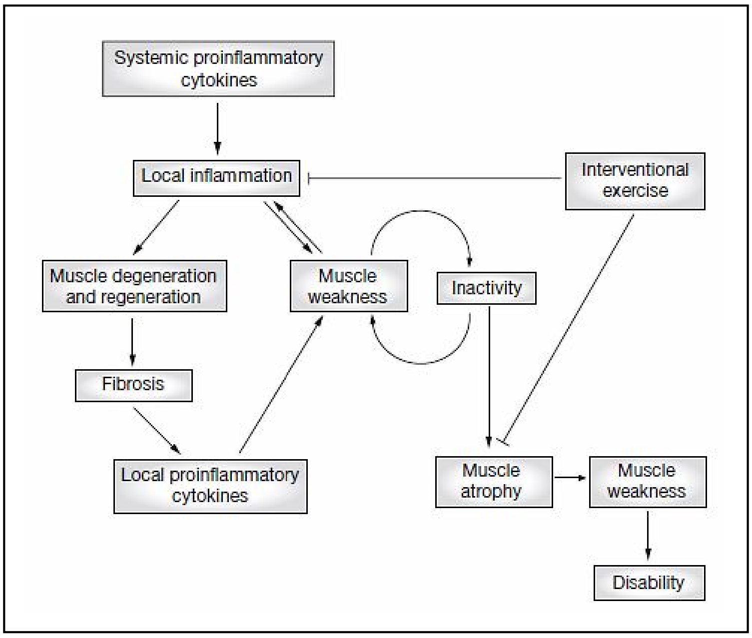

Figure 2. Mechanism for going from inflammation to disability and the potential points of intervention for exercise. Figure from Lundberg et al. [32].

In a recently published article by Lundberg et al. on the molecular effects of exercise in patients with inflammatory disease [32], they report that exercise has the potential to revert some of the key processes in inflammation induced muscle loss. (Figure 2) Reduced disease activity scores and ESR were observed following different types of exercise, after short and long term programs, at various disease phases and in patients with high disease activity [32]. Collecting data on inflammation markers in studies on exercise capacity and exercise training in patients with JIA could show whether this is also correct for children with JIA and might be helpful in optimizing the exercise prescription.

Conclusion

There is still a lot unclear regarding the relationship between aerobic capacity and disease activity in children with JIA. Various studies investigated aerobic capacity in patients with JIA and the effect of training on a variety of outcome measures, however none included "hard" measures of disease activity such as CRP or ESR. Some studies did report the number of active joints, but none have linked joint count to VO_{2peak}. Providing information on disease status and inflammation markers could help elucidate the effect of exercise/physical activity on well being and physical fitness.

Recommendations for future research

- Include "hard" measurements of disease activity in future studies of exercise in patients with JIA.
- Stratify the patients with JIA in different disease categories. Analyzing the subgroups separately allows effects that are only present in one or a few categories to be uncovered, while they would get lost when data is grouped together.
- The inclusion of data on physical activity and disease activity in the months prior to the time of testing. Aerobic capacity is a dynamic measure that is determined by physical activity during the weeks / months prior to testing. Information on activity levels during this time helps provides a framework for interpreting VO_{2peak}. This is also true for disease activity. A flair of disease activity in the time preceding the time of testing could limit physical activity and influence the aerobic capacity.
- Longitudinal follow-up studies are more suited to acquire data on both aerobic capacity and measures of disease activity and their variation and association over time than cross sectional studies.

Table 1. Characteristics of included studies.

Study	JIA patients/ controls	Patients age	Disease subgroups	Ergometer	VO_{2peak} determination	Protocol	Correlation with disease activity
Giannini 1991 [20]	16 / 16	8 - 13 yrs	OJIA, PJIA	Cycle ergometer	Direct	25 Watt/2 min	No correlation VO_{2peak} and JC
Golebiowska 1991 [33]	25 / 19	10 - 18 yrs	OJIA, PJIA, SJIA	Treadmill	Direct	Riopel[=]	NA
Giannini 1992 [19]	30 / 30	7 - 17 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	25 Watt/2 min	No correlation VO_{2peak} and JC
Golebiowska 1992 [18]	45 / 61	4 - 19 yrs	OJIA, PJIA, SJIA	Treadmill	Direct	Riopel[=]	Correlation VO_{2max} an disease activity in JCA girls r = -0.60
Klepper 1992 [13]	20 / 20	6 - 11 yrs	PJIA	9-min run-walk	Estimation	HRPFT	No relationship JC and fitness score
Malleson 1996 [11]	30 / 15	8 - 17 yrs	OJIA, PJIA, SJIA, JSpA, Juvenile psoriatic arthritis	Cycle ergometer	Direct	15 Watt/min	Negative association VO_{2peak} and disease severity p = 0.04
Hebestreit 1998 [16]	10 / 10	6 - 18 yrs	JSpA (HLA-B27^{+})	Cycle ergometer	Direct	NA	NR
Klepper 1999 [15]	25 / 0	8 - 17 yrs	PJIA	9 min run-walk	Estimation	HRPFT	NR
Takken 2002 [21]	23 / RV	6 - 14 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	20 Watt/3 min	NR

Takken 2003 [5]	54 / 27	5 - 13 yrs	NA	Cycle ergometer	Direct	20 Watt/3 min	NR
Takken 2003 [6]	49 / RV	8.8 ± 2.2 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	20 Watt/3 min	NR
Takken 2003 [7]	18 / RV	7 - 14 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	20 Watt/3 min	NR
Metin 2004 [10]	34 / 21	7 - 16 yrs	OJIA, PJIA, SJIA, ERA	Cycle ergometer	Direct	10 Watt/min	NR
Singh-Grewal 2006 [9]	9 /	8 – 11 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	Resistance/ 2 min▲	NR
Van Brussel 2007 [4]	62 / 50	6 - 15 yrs	OJIA, PJIA, SJIA	Cycle ergometer	Direct	20 Watt/min	NR
Lelieveld 2007 [12]	22 / RV	16 - 18 yrs	NA	Cycle ergometer	Direct	20 Watt/min (SLBE)	NR
Singh-Grewal 2007 [26]	80 / 0	8 – 16 yrs	NA	Treadmill	Direct	Speed or incline / min∞	NR

Abbreviations: JC = joint count; HRPFT = Health Related Physical Fitness Test; OJIA = oligoarticular JIA; PJIA = polyarticular JIA; SJIA = systemic JIA; ERA = enthesitis-related arthritis; JspA = Juvenile spondylarthropathy; NA = not available; = = Riopel protocol consists of keeping the treadmill belt speeds at 5.6 km/hr and elevating the slope of the belt by 2° every minute until volitional exhaustion of the patient; ▲ = Resistance was increased every 2 minutes with increments selected by the investigator based on the child's HR and overall appearance; SLBE = Simple Limited Bicycle Ergometer test; ∞ = Treadmill speed or incline increased every minute until volitional exhaustion. Performed by experienced tester based on child’s performance; RV= Reference Values.

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