Physical fitness and training in chronic childhood conditions

Fysieke fitheid en training bij kinderen met een chronische aandoening

door

Marco van Brussel

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Fysieke fitheid en training bij kinderen met een chronische aandoening
(met een samenvatting in het Nederlands)

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door

Marco van Brussel
geboren op 7 juni 1979 te Zwolle

Promotoren:
Prof. dr. P.J.M Helders
Prof. dr. W. Kuis

Co-promotoren:
Dr. T. Takken
Dr. J. van der Net

“It is a grave mistake to submit children to the training programs of adults. After all, children are not simply little adults.”

Tudor Bompa (2000)

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Chapter

Introduction

Marco van Brussel

Research with children presents many challenges and much remains to be learnt about physiological responses to exercise and training in relation to age, growth, maturation and gender, especially in children with a chronic condition. Morphological parameters and physiological functions such as heart volume, lung function, aerobic capacity and muscular strength develop with increasing age and body size. Therefore, children can not simply be seen as miniature versions of adults. Furthermore, physical fitness and trainability also changes with growth and maturation. Variations in growth and maturation of a child can have profound effects upon aspects of physical activity, physical fitness and physical performance. Physical fitness in children can be measured by specially developed physiological test instrumentation, such as cardiorespiratory exercise tests. Single physiological tests can determine the current state of physical fitness in children with or without a chronic condition and compare this state with that of their peers. Serial physiological testing can provide a quantitative assessment of the improvement or decline in the condition of the child.[1] Possible applications of such testing included evaluation of training and/ or revalidation programs.

Physical fitness and training in (healthy) children

In current (paediatric) research, physical fitness has become synonymous with cardiorespiratory (or aerobic) fitness. Cardiorespiratory fitness is expressed as the maximal oxygen uptake (VO_{2max}). VO_{2max}, the highest rate at which an individual can consume oxygen during exercise, is widely recognized as the best single measure of adult's aerobic fitness.[4] Maximal oxygen uptake conventionally implies the existence of a VO_2-plateau. However, this response is not typical of children and adolescents[5, 6] and so it has gradually become more common to use the term VO_{2peak}, being the highest VO_2 elicited during an exercise test to voluntary exhaustion[a], to describe cardiorespiratory fitness of children.[7] The VO_{2peak} of children in relation to chronological age has been extensively documented. Figure 1.1 represents 4937 VO_{2peak} scores of untrained children with ages between 8–16 years.[8] This figure clearly indicates an almost linear increase in VO_{2peak} of the

[a] VO_{2peak} cannot increase with supramaximal loads above values observed in a standard progressive test in which a plateau is not observed.[2,3] This implies, that despite lack of a plateau, VO_{2peak} at exercise does, in fact reflect the limits of oxygen delivery in children.[10] Therefore, VO_{2peak} can be considered to reflect VO_{2max} if certain subjective and objective criteria (RER >1.0 and heart rate >180) are met. Therefore VO_{2peak} will be used throughout the whole thesis.

boys in relation to chronological age (r^2=0.75). The VO_{2peak} data of the girls show a similar but less consistent trend (r^2= 0.53), with a tendency to plateau at about 14 years of chronological age.

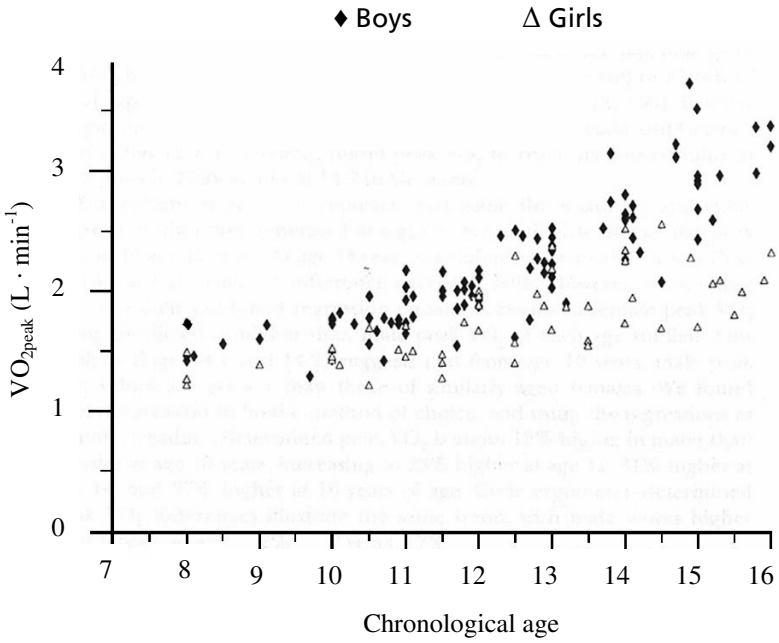

Figure 1.1: Relationship in children and adolescents between VO_{2peak} ($L \cdot min^{-1}$) and chronological age (redrawn after Armstrong et al.[8]).

The increase in cardiorespiratory fitness with age during childhood can be explained by investigating the components of VO_{2peak}. The VO_{2peak} can be described using the Fick equation[9] in which the oxygen consumption of exercising muscle reflects the product of oxygen delivery by cardiac output and it's cellular extraction as indicated by the difference in arterial and venous oxygen content:

Oxygen uptake (VO_2) = cardiac output x arterial-venous oxygen difference

In which the cardiac output is a product of heart rate and stroke volume and the arterial-venous oxygen difference is the difference in O_2 content of arterial and mixed-venous blood. Cardiac output increases linearly with VO_2 such that for every 1 $L \cdot min^{-1}$ increase in VO_2, cardiac output increases by about 5 $L \cdot min^{-1}$; this is similar for adults and children.[10] Stroke volume refers to the amount of blood pumped by the heart in each beat.

In order to increase the VO_2, and therefore also VO_{2peak}, either the cardiac output or the arterial-venous oxygen difference must rise. The understanding of children's cardiac function during exercise has been limited by the lack of safe, accurate and non-invasive means of assessing cardiac output.[10] Heart rate measurement during exercise can be performed with no difficultly, however this is not the case for stroke volume. Maximal heart rate during childhood is independent of age and gender[11-15], therefore maximal heart rate can be immediately dismissed as a defining determinant[16] and the increase of cardiac output in healthy children is entirely due to maximal stroke volume; which increases in parallel with growth of the left ventricle.[7] The maximal stroke volume during exercise show a clear difference between children and adults; children show a smaller stroke volume during maximal exercise.[17] It is known that stroke volume rise progressively in the initial phase of upright exercise up to moderate submaximal intensities (± 40-50% of VO_{2peak}) and then plateaus as exercise intensity increases.[10,16] This plateau of stroke volume is a consistent finding in the cardiovascular physiology, even in children.[18-25] The ability to reach maximal stroke volume could be a defining factor of the inter-individual differences in VO_{2peak}. As left ventricular end-diastolic dimension (the determinant factor of maximal stroke volume) increases as a child grows, increasing stroke volume during maximal exercise is also the sole factor responsible for ontogenetic changes in the limits of oxygen delivery until puberty.[16]

The arterial-venous oxygen difference represent the difference between the arterial oxygen content of the blood approaching the muscle cell and the venous oxygen content as it leaves. In other words, the amount of extracted O_2 from a given volume of blood passing the muscle cell.[16] Arterial-venous oxygen difference during maximal exercise changes little during childhood, and values are similar in unfit, fit and trained populations of healthy boys and girls.[26,27] Arterial-venous oxygen difference might increase in age, however the precise mechanisms are not exactly known. The arterial-venous oxygen difference can therefore also be excluded as a defining determinant. Using the physiological Fick-equation, the increase in VO_{2peak} during childhood in healthy children appears to be primarily due to factors which can influence the ability to reach maximal stroke volume and, therefore, cardiac output. However, from a peripheral (non-Fickian) perspective, there are also other factors than the above mentioned central factors that might influence the VO_{2peak} (Figure 1.2).

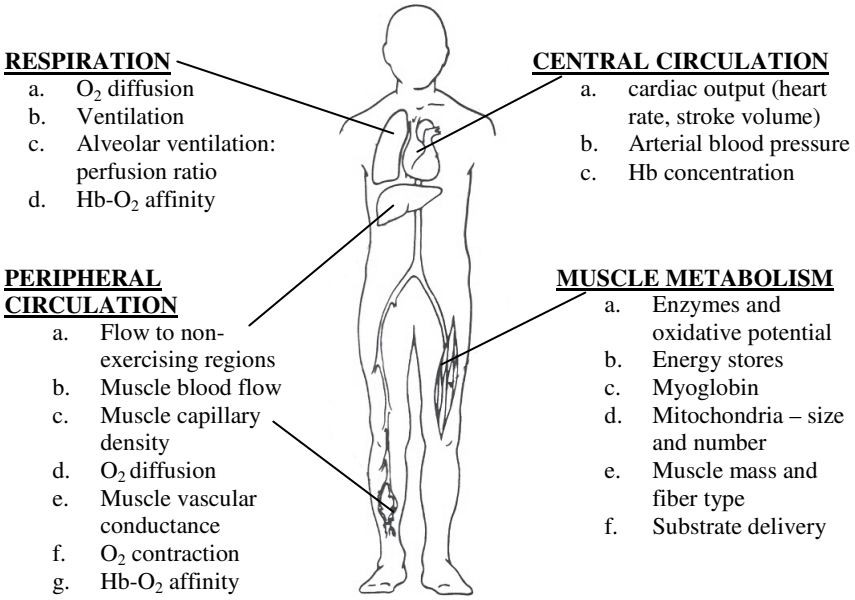

Figure 1.2: Possible central and peripheral limitations to oxygen consumption during exercise (redrawn after Saltin and Rowell[28]).

The peripheral factors are also referred as the muscle characteristics, such as peripheral diffusion gradients, mitochondrial enzyme levels, and capillary density. However, O_2 delivery, not skeletal muscle extraction, is viewed as the primary limiting factor for maximal oxygen uptake in healthy exercising humans.[29] Therefore the peripheral factors will not be discussed in this introduction; however, these peripheral factors might be determinant factors in pathological conditions.

As most physical activities involve transportation of body mass, to compare the cardiorespiratory fitness of children with a different body mass, VO_{2peak} is in most studies expressed as a ratio with body mass as millilitres of oxygen per kilogram body mass per minute ($mL \cdot kg^{-1} \cdot min^{-1}$)[7] Longitudinal studies show that $VO_{2peak/kg}$, in boys, is fairly consistent over the chronological age range 8-16 years.[30, 31] Girls` longitudinal data show that their $VO_{2peak/kg}$ continuously decline with chronological age.[30-32] Such a decline may reflect an increase in body adiposity (and hence a relative decrease in fat-free mass) of girls during adolescents.[33] Figure 1.3 shows the similar outcomes in cross-sectional studies.

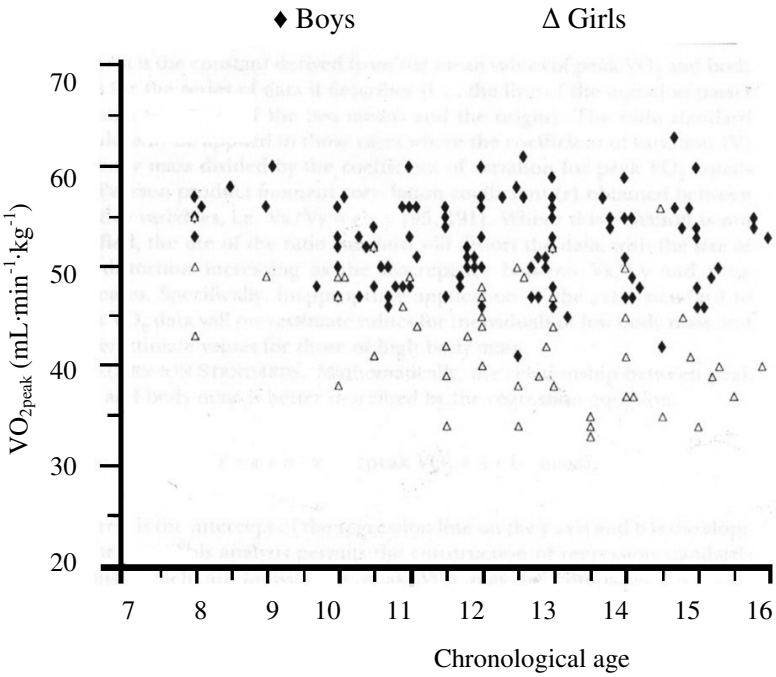

Figure 1.3: Relationship in children and adolescents between $VO_{2peak/kg}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) and chronological age.

Anaerobic fitness[b] during growth and development, has not received the same attention from researchers as cardiopulmonary (or aerobic) fitness[34], because cardiopulmonary fitness is better defined, easier to study, and has been linked to health outcomes.[16] However, the assessment of anaerobic fitness is important as daily activities involve both aerobic and anaerobic function. Young children are, during physical activity and sport, more attracted to short-burst movements rather than to long-term activities.[34] It is known that the ability to perform anaerobic-type activities is distinctly lower than that of adolescents, whose performance is lower than in adults.[35-39] The anaerobic fitness is lower in absolute and relative term, even when adjusted for body mass. There is a progressive growth-related increase in anaerobic fitness as shown in Figure 1.4, which represents 50 peak power scores of untrained Dutch children with ages between 8-18 years. This figure clearly indicates an almost linear increase of peak power in both boys and girls in

[b] In this thesis anaerobic fitness is measured by the Wingate Anaerobic cycling test (WAnT). In this 30-sec all-out cycling test, two outcomes of anaerobic power can be obtained: peak power (the highest value obtained within the first 5 seconds) and mean power (average power within 30 seconds).

relation to chronological age (r^2=0.73). The absolute values of anaerobic power increases progressively, with an acceleration at puberty in boys. The study of Armstrong et al. showed that between the ages of 12 and 17 years peak anaerobic power increased by 121% in males and 66% in females.[40]

However, it is known that children's capacity to perform these types of tests are a product of their biological rather than their chronological age.[16] In this thesis we will only focus upon the chronological age, because little research has been done to investigate the relationship between cardiorespiratory fitness or anaerobic fitness and maturation, perhaps of the difficulty in assessing maturation; also chronological age and gender matched peers were used as controls in our studies. It is not entirely clear why children have a poor anaerobic fitness when compared with adolescents and adults. Smaller muscle mass per body mass, lower glycolytic capability, and deficient neuromuscular coordination seem to be important factors for explaining the low anaerobic fitness in children.[33] Most data indicate that anaerobic power adjusted for body mass also rises during the paediatric years[16] (see Figure 1.5); this finding is different from VO_{2peak} adjusted for body mass, in which boy's show a fairly consistent and girls show a continuously decline of their $VO_{2peak/kg}$ with chronological age. Although improvements in neural adaptations with age, improved muscle coordination, improved capability to recruit motor units, complete myelination of nerve fibres help to explain age-related improvements in anaerobic fitness[41]; further research is needed to fully understand the development of anaerobic fitness.

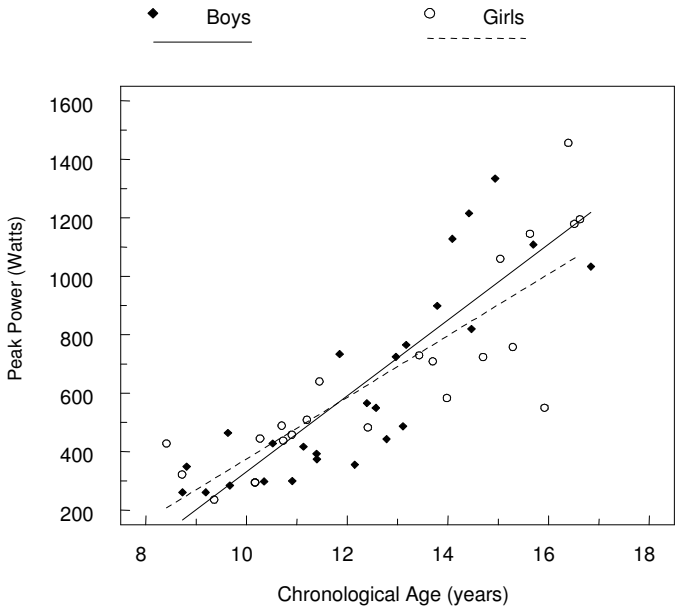

Figure 1.4: Relationship in children and adolescents between anaerobic fitness (Peak Power (Watts)) and chronological age from 50 healthy Dutch children.

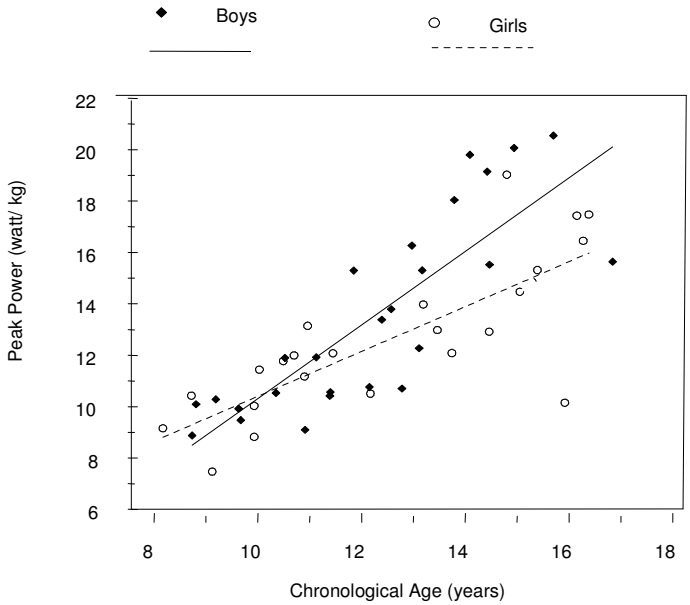

Figure 1.5: Relationship in children and adolescents between anaerobic fitness adjusted for body mass (Peak Power (Watts $\cdot kg^{-1}$)) and chronological age from 50 healthy Dutch children.

Aerobic versus anaerobic

For physical activity muscle contractions are necessary. Energy for muscular contraction is derived from the hydrolysis of adenosine triphosphate (ATP). In resting muscles, small quantities of ATP are available, however, when contractions start, there is an immediately need for the re-synthesis of ATP. ATP can be re-synthesized through a number of systems or pathways, namely 1) the hydrolysis of creatine phosphate (CP), 2) glycolysis, and 3) the oxidation of carbohydrate, lipids and protein (the Krebs Cycle).[42] The first two pathways do not necessarily require O_2 and are therefore called anaerobic. The latter pathway requires O_2 and is called aerobic. Muscle contractions utilizing anaerobic energy turnover (energy from glycolysis) cannot be sustained longer than 40 to 50 seconds.[33] In contrast, muscle contractions utilizing aerobic energy turnover can last many minutes, hours or even days; although at a lower intensity than with anaerobic capacity. Even though most activities utilize both aerobic and anaerobic pathways (Figure 1.6), in the terminology of sport scientists and exercise physiologists, activities are subdivided into "aerobic"-type and "anaerobic"-type activities.[33]

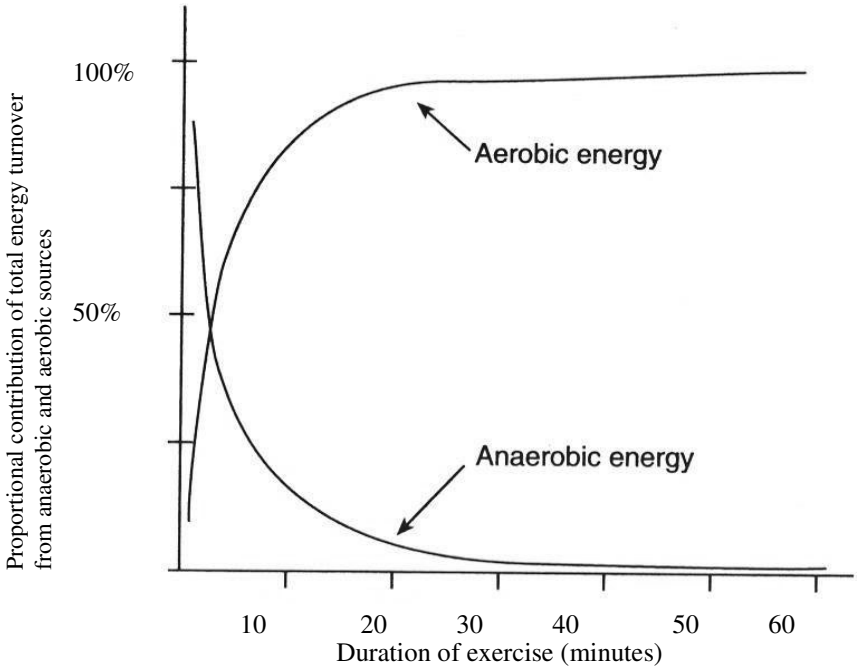

Figure 1.6: Schematic representation of the percentage contribution of aerobic and anaerobic energy to total energy turnover in relation to the duration of maximal exercise (redrawn after Sargeant et al.[43]).

Aerobic activities include distance running, swimming, cycling, and other endurance-requiring tasks. The anaerobic activities include sprinting, jumping, and other activities in which the required power intensity is high and the duration short. Bar-Or and Rowland[16] suggested that children, prepubescents in particular, are metabolic non-specialists. This means that children are less specialized as anaerobic or aerobic performers. However, Blimkie[44] challenge the concept of metabolic non-specialisation, by stating: "Perhaps children are less trainable than adults on both the aerobic and anaerobic metabolic fronts, and it is this difference in trainability that differentiates the apparent metabolic non-specialization in children. If this is the case, then, regardless of the underlying mechanisms influencing relative trainability, it could be argued that children are indeed metabolic non-specialists. Evidence supporting differences is trainability of aerobic and anaerobic capacities in children however, are equivocal, and the role of relative trainability in relation to metabolic profile differentiation needs to be further investigated. Until confirmed at the muscle cell level, our understanding of the metabolic differentiation between children and adults remains incomplete and the concept of metabolic non-specialization of children must remain an interesting but unproven hypothesis".[44]

Exercise training is the process by which repeated systematic exercise leads to functional and morphological adaptations in the body tissues and –systems[33] or for the preservation of these adaptations. These functional and morphological changes in adults, before and after an exercise training program, can only be attributed, with fair certainty, to the followed training regime. This principle does not apply for children and adolescents. In children and adolescents changes caused by growth, development and maturation, often masks and outweigh those induced by a physical training program. Therefore a control group is essential when a physical training intervention is studied in children. Many of the physiological changes as a result of physical training can also be seen as an effect of the natural process of growth and maturation. So the question not only is whether children are trainable, but also whether the physiological changes are the net result of this training or is only due to growth, development and maturation. In general, there are three distinct forms of physical training, namely: aerobic, anaerobic, and muscle strength training.

In the past there were many questions concerning the efficacy of aerobic training in children before reaching adolescence, because of the low secretion and circulating of anabolic hormones (e.g. testosterone, IGF-1, and

growth hormone). Several studies demonstrated that with a comparable training regime, children illustrate a smaller increase in physical fitness compared to adults (Figure 1.7). Whereas, the adults show an average increase of 15% in VO_{2peak}, children show a average increase of 5-6 % in VO_{2peak}[2,3]; in which boys and girls show comparable increases until adolescence. When only studies showing significant improvements in VO_{2peak} were included, as recommended by Rowland[45], the average improvement was 10.1% for prepubertal and 8.8% for adolescent individuals.[3]

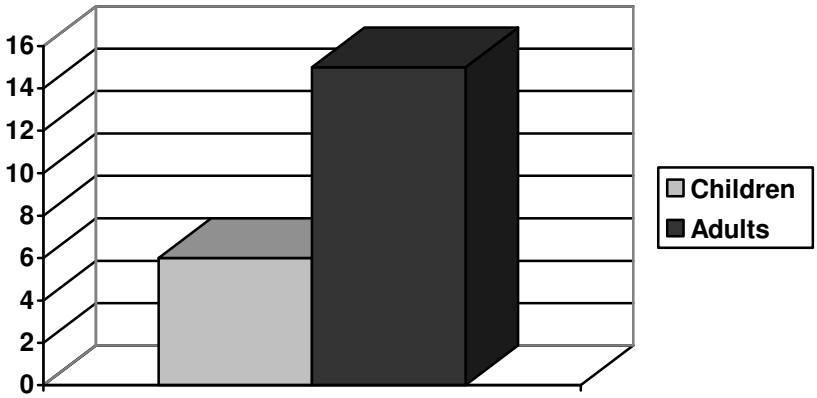

Figure 1.7: Percent increase of VO_{2peak} after aerobic training when comparing children (<18 years of age) and adults (>18 years of age).[2, 3]

Possible explanations could be that children might train less effectively than adults or that the stimulus intensity needs to be higher for children because of their relatively higher ventilatory threshold[c] (in other words: children need a higher training intensity to burden their aerobic systems).[16] Moreover, children are more active and relatively more trained compared to adults and therefore are showing less training gains. Therefore, inactive children show a greater 'window of opportunity'. The relative increase is dependent upon the overall training characteristic (frequency, intensity, time (duration) and program length, and type, the so-called F.I.T.T-factors) and the initial baseline capacity.[46] Intensity seems to be a key factor in training design.[3] The results in the review of Baquet et al.[3] indicated that intensity higher than 80% of maximal heart rate is needed to obtain significant increase in VO_{2peak}. The

[c] Ventilatory threshold: Exercise workload at which ventilation and lactate accumulation begin to increase at progressively greater rates. Ventilation increases in a linear fashion up to this threshold point. Then the decrease in pH leads to an increased drive to breathe, so here ventilation goes up at a much faster rate.

following F.I.T.T-factors can be extracted from the literature as training guidelines for cardiorespiratory in healthy children.[3] The frequency should be at least 3-4 times a week, the intensity should by heavy and the duration about 30–60 minutes per session in which activities should use the large muscle groups. The training program should last for, at least, 4 weeks in healthy children. In contrary to adults[47], heart rate reserve does not match the oxygen uptake reserve.[48] Therefore, the guidelines of the American College of Sports Medicine (ACSM) for adults should be adapted for children. Table 1.1 show the guidelines for the training intensity in children on basis of the recent findings of Hui & Chan.[48]

Table 1.1: Training guidelines on basis of heart rate and peak oxygen uptake in children.

Intensity	$\%VO_{2peak}$	$\%HR_{reserve}$	$\%HR_{max}$
Very easy	<20	<29	<54
Easy	20-39	29	54
Moderate	40-59	47	66
Heavy	60-84	65	77
Very heavy	>85	87	91
Maximal	100	100	100

Abbreviations: $\%VO_{2peak}$: Percentage of VO_{2peak}, $\%HR_{reserve}$: Percentage of heart rate reserve, $\%HR_{max}$: Percentage of maximal heart rate.
Table based upon[48, 49]

Few studies in children have examined the influence of exercise training on anaerobic fitness.[50-53] The reason might be that anaerobic fitness does not have the strong causative relationship with health as has been shown for VO_{2max}.[7] However, anaerobic fitness contributes to a great extend to performances in many activities of daily childhood living, such as play, leisure and sport activities which are initially short term activities and of a high intensity in nature.[54] The studies[50-53] have indicated that children's anaerobic power can improve after anaerobic training; however the increases have been small. To our knowledge, guidelines for anaerobic training programs have not been published, certainly not that are based on a strong empirical foundation. There is too little information to conclude whether differences in maturity, age or gender of children will affect anaerobic trainability.[46] Further research in this area is needed.

Muscle strength training tends to be safe and effective[55-62], even in children as young as 5-6 years of age.[58] One of the greatest differences between the response of strength training in children and those of adolescents and adults, is that the increased muscle strength in children is not accompanied by an increase of muscle size (hypertrophy).[63-65] This phenomenon can be explained by an inadequate level of circulating testosterone in pre-adolescents. The testosterone levels in pre-adolescent boys and girls are between 20 and 60 ng/ 100 ml.[66] During puberty these levels will increase up to 600 ng/ 100 ml in male adolescents, whereas the levels in female adolescents remain the same.[66] Nevertheless, many studies[64, 65, 67-72] clearly indicated that both boys and girls can improve their muscle strength above (and far beyond) natural growth and maturation. It seems that pre-adolescents have more potential for increasing muscle strength by neural factors such as increased activation of motor-units and changes in motor-unit coordination, recruiting and firing.[63, 64, 73]

Table 1.2: Training advice for muscle strength training[58] in children.

Frequency	2-4 times a week
Intensity	70% of 1 repetition maximum (RM)
Number of repetitions	13-15
Number of sets	1-3
Number of different exercises	6-8

Physical fitness and training in children with a chronic condition

Increased physical activity is considered beneficial for health. However, children with chronic conditions are often constrained from participation in sports activities or exercise programs as a consequence of real or perceived limitations imposed by their condition. The condition itself often causes hypoactivity, which leads to a deconditioning effect, a reduction in the functional ability of the child, and further hypoactivity[33] as seen in Figure 1.8. This descending spiral can occur in any chronic condition or disability.[33]

Exercise therapy (e.g. a physical training program) might prevent or slow down this deconditioning due to hypoactivity, and break up this descending spiral. Besides the chronic condition itself, other factors such as parental overprotection, social isolation by peers, fear and ignorance can also lead to hypoactivity (Figure 1.8). It is important to recognize these other factors as well. However, exercise physiologists mainly deal with the physiologic aspects; therefore the aforementioned psychological and behavioural factors are not further addressed in this thesis. Furthermore, specific disease related pathophysiological factors are also beyond the scope of this introduction.

Not only the physical fitness and functional ability might decrease due to hypoactivity, but these children also are at additional risk for a range of health conditions associated with a hypoactive life style. For this reason it is of great importance to know and describe the ever changing physical fitness during childhood, analyse its development, and when necessary provide, individual tailored interventions. Hardly ever will exercise therapy influence the basic pathophysiological process it self, the benefits of exercise are generally indirect. Bar-Or & Rowland[33] stated that "treatment of children through enhanced physical activity is unique: *"By prescribing exercise we are signalling to the child that he or she can, and should, act like his or her healthy peers."*

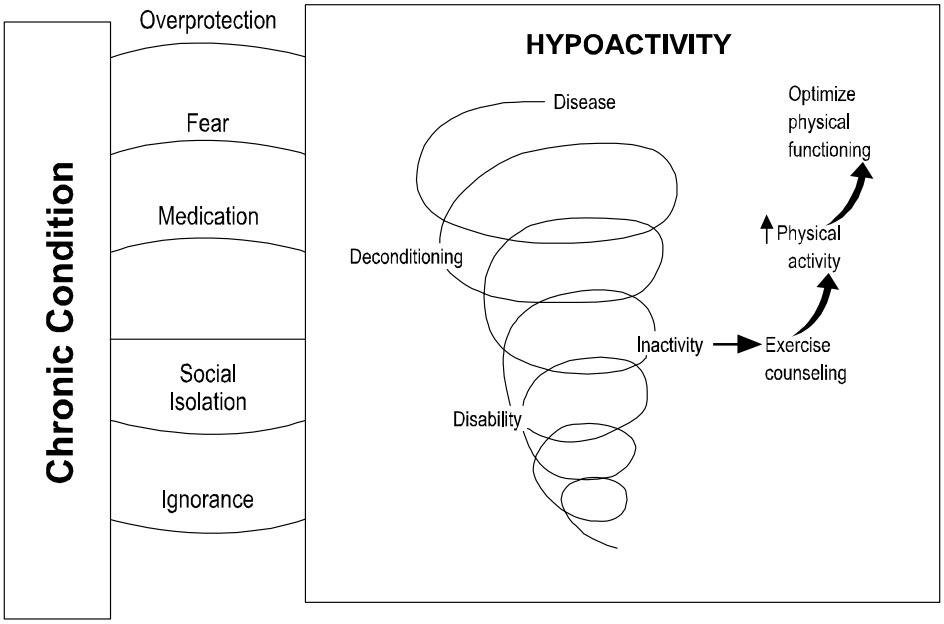

Figure 1.8: Direct and indirect links between condition and hypoactivity (redrawn from Bar-O [33]) combined with the relationship between condition, deconditioning, inactivity and disability (redrawn from Painter[74])

Aims & Outline

Despite the dramatic increase in published research over the last decades has enhanced understanding of the physiology of the exercising child; however in relation to research with adults data are still sparse. The understanding of the physiology of the exercising child with a chronic condition is even sparser; therefore we tried to add relevant studies for understanding the physiology of physical fitness and training in these children.

As shown in the first part of this introduction, physical fitness has become synonymous with cardiorespiratory (or aerobic) fitness. Anaerobic fitness during growth and development, has not received the same attention from researchers as cardiopulmonary fitness. However, the assessment of

anaerobic fitness is important as daily activities involve both aerobic and anaerobic function. Therefore, in this thesis, besides the aerobic capacity, we also evaluated the anaerobic capacity of the individual in the intervention studies (chapter 3, 5 and 6). After the determination of the level of fitness per chronic condition, it is important to investigate whether these children are trainable, and therefore capable to break through the descending spiral of deconditioning, or whether these children already function at their maximal level of physical fitness. When these children are trainable, the following logical causality (and probability the most important) is to provide possibilities for participation in sports and leisure activities. The demand for such participation is a frequent heard question in the clinical setting of our hospital.

This thesis describes three different types of chronic disorders, namely Acute Lymphoblastic Leukaemia (ALL), Juvenile Idiopathic Arthritis (JIA), and Osteogenesis Imperfecta (OI). ALL is an acquired acute condition with chronic consequences, JIA is an acquired chronic condition, and Osteogenesis Imperfecta is a genetic and heritable chronic condition. Determination of the level of physical fitness in these children seems of clinical relevance, because this variable appears to be a powerful predictor of mortality in both healthy and diseased adults[75,76]; for example, a reduction of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (relative VO_{2peak}) is associated with a 12% decrease in the survival rates of diseased people.[76] Therefore, it is important to understand and distinguish the different direct and indirect causes for the decreased levels of fitness.

Limited research has focused on the physical fitness of children with cancer or on survivors of childhood cancer. From these individual studies it is unclear whether the VO_{2peak} in children with ALL is significantly decreased when compared to healthy controls.[77-79] Therefore, we performed a systematic review and an intervention on the physical fitness in survivors of childhood leukaemia in this thesis.

Aerobic fitness in children with JIA has been studied extensively in recent years.[80-88] Most of these studies suggest that patients with JIA have impaired aerobic fitness[89], presumably as a result of decreased physical activity secondary to disease symptoms.[90] However, all studies included small cohorts of children which make the outcomes of these studies not as strong as with a large cohort. Surprisingly little is known about the anaerobic capacity in these children.[86, 91-94] Therefore, the aerobic and anaerobic capacity in a large cohort of children and adolescents with JIA has been studied. Furthermore, we studied the efficacy of exercise therapy by means of a Cochrane review.

The study of Takken et al.[95] is the only known study that describes physical fitness in children with Osteogenesis Imperfecta. They reported that exercise capacity and muscle strength were significantly reduced in children and adolescents with OI type I compared to their healthy peers. They also reported a significant decrease fatigue. To our knowledge, physical intervention studies have not been performed in children with OI. To study whether children with OI were able to complete a training program safe and effectively and were able to decrease their experienced fatigue, and therefore might break their descending spiral of deconditioning, we studied the effects of a physical training program in children with OI by performing a randomised controlled trial.

The aims of this thesis were:

- To review whether there are deficits in physical fitness in survivors of ALL.
- To determine if there are deficits in physical fitness and function in Dutch survivors of childhood ALL 5-6 years after cessation of chemotherapy compared to a group of control subjects.
- To review whether exercise therapy is effective on functional ability, quality of life and aerobic capacity in patients with JIA.
- To determine whether there are deficits in aerobic and anaerobic exercise capacity in a large cohort children with JIA compared to healthy controls
- To determine whether there are deficits in aerobic and anaerobic exercise capacity in adolescents with JIA compared to age- and sex-matched healthy individuals.
- To study the effects of a physical training program on exercise capacity, muscle strength, and subjective fatigue levels in patients with mild to moderate types of OI.

In the first chapter a brief introduction on physical fitness and training is given. In chapter 2, we describe the findings of our review about the physical fitness in survivors of childhood leukaemia. Chapter 3 describes the physical function and fitness in long-term survivors of childhood leukaemia. In chapter 4, we describe the findings of our review about exercise therapy for treating juvenile idiopathic arthritis. Chapter 5 and 6 describes the aerobic and anaerobic exercise capacity in children and adolescents with Juvenile Idiopathic Arthritis. In chapter 7, we describe the randomised controlled trial about physical training in children with Osteogenesis Imperfecta. Chapter 8 is the general discussion and the summary of this thesis.

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2
Chapter

Is physical fitness decreased in survivors of childhood leukaemia? A systematic review

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Abstract

Objective

The aim of this review is to determine whether physical fitness, assessed by peak oxygen uptake (VO_{2peak}) measurement, is reduced in survivors of acute lymphoblastic leukaemia (ALL) compared to healthy children.

Methods

A systematic literature search (up to June 2004) was performed using Medline, Sportdiscus, Cinahl, Embase, Cochrane and PEDro database and reference tracking. The VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) reached during a maximal exercise test until volitional exhaustion was used as the main outcome for this review.

Results

In all, 17 studies were identified in the literature. Data from three studies (102 ALL survivors, age ranging from 7 to 19 years) were pooled in a meta-analysis. Although there was a significant heterogeneity between the included studies (P=0.0006), the standardized mean difference (SMD) value of -0.61 (P=0.07) indicated that VO_{2peak} tended to be reduced in survivors of childhood ALL compared to healthy control subjects, that is, decrease of -5.97 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% confidence interval (CI): (-12.35, 0.41); P=0.07) or -13% (95 % CI: (-27, 0.004)).

Conclusion

Physical fitness tends to be reduced in survivors of ALL during childhood, which suggests the need for this population group to engage in regular physical activities with the purpose of increasing their functional capacity. Although more research is needed, this functional improvement might ameliorate the quality of life of ALL survivors as physical and outdoors activities are an essential part of daily routine during childhood.

Introduction

The peak oxygen uptake (VO_{2peak}) attained during a graded maximal exercise to volitional exhaustion is considered by the World Health Organization as the single best indicator of aerobic physical fitness.[1] This variable, commonly expressed as the volume of oxygen consumed per unit of time relative to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$), is also a valid indicator of health status[2] and a powerful predictor of mortality in both healthy and diseased individuals.[3,4] The improvements in exercise capacity and VO_{2peak} brought about by training are related to improved quality of life (QOL), particularly in patients with exercise capacity limited by various disease processes.[5]

In adult cancer patients/survivors, it is not untypical to measure VO_{2peak} levels considerably lower (~50%) than predicted, which reflects the sedentary life habits and poor physical condition of this population group.[6] Poor physical condition self-perpetuated by sedentarism is largely responsible for the disrupting symptoms of fatigue that these individuals experience during normal activities of daily living, with subsequent impairment in QOL.[6] In turn, increases in functional capacity brought about by regular exercise training are reflected by higher VO_{2peak} levels and result in improved OQL, that is, normal activities can be carried out with no fatigue.[7–10]

Less research has focused on the physical capacity and VO_{2peak} of children with cancer or survivors of cancer during childhood. Most studies have been performed on children which are survivors of acute lymphoblastic leukaemia (ALL) and it is unclear whether their VO_{2peak} is significantly decreased compared to healthy controls. For instance, Vizinova et al.[11] showed no significant difference between ALL survivors and controls, while other authors found significantly decreased VO_{2peak} levels in the former.[12–14] Outdoor physical activities involving cardiorespiratory work of moderate intensity are an essential part of the daily routine of children.[6] Thus, it would be interesting to assess if functional capacity, assessed by VO_{2peak} measurement, is significantly decreased in children survivors of ALL. If this is the case, exercise training prescription is necessary to improve their QOL and more research is warranted in this field.

It was therefore our purpose to determine whether the physical fitness of ALL survivors, assessed with VO_{2peak}, is decreased compared to healthy age-matched children.

Materials and methods

Search strategy

Publications were selected based on a literature search from 1966 until June 2004 using the Medline, Pubmed, Sportdiscus, Cinahl, Embase, Cochrane, and PEDRO database. Search terms 'physical fitness', 'exercise testing', 'exercise', 'exercise capacity', 'exercise tolerance', 'child', 'survivors', 'acute lymphoblastic leukaemia', and 'leukaemia' were used. References of the selected papers were tracked to find additional publications on this subject.

Selection of publications and types of outcome measures

We first selected all publications that reported one or more of the following outcome variables in ALL survivors: VO_{2peak} (in $ml \cdot kg^{-1} \cdot min^{-1}$), maximal heart rate, respiratory exchange ratio (RER), and exercise testing on a treadmill or cycle ergometer. Thereafter, we included in this study only those publications reporting: (1) data of survivors of childhood ALL included within the same homogeneous group (i.e., excluding survivors of any other type of cancer during childhood) and their corresponding healthy controls, (2) VO_{2peak} values (in $ml \cdot kg^{-1} \cdot min^{-1}$) measured during a graded maximal exercise to volitional exhaustion, (3) description of methodology (gas-exchange analysis) for VO_{2peak} measurement, and (4) description of subjects' characteristics (both ALL survivors and controls). Data were extracted from the publications by two independent reviewers and entered into Review Manager 4.2.3 (Update Software, Oxford, UK).

Statistics

DerSimonian and Laird Random Effects Model were used for analyzing the results on VO_{2peak} because of the significant heterogeneity between the studies. The data were pooled using standardized mean differences (SMDs). SMD is the difference between two means divided by an estimate of the within-group standard deviation, and can be considered as an effect size, for example, negative values for SMD would indicate a lower physical fitness of childhood survivors of ALL compared to healthy controls. The level of statistical significance was set at $P<0.05$.

Results

A total of 17 published studies (two of which were written in the Czech[11] and Polish language[15]) were identified in the literature. Of them, 14 did not meet the criteria described above for inclusion in the meta-analysis (Table I).

The study by Matthys et al.[13] was excluded because they included in the same group ALL survivors and childhood survivors of several type of cancer other than ALL. The studies from Ostanski et al.,[15] Black et al.,[16] Kadota et al.,[17] Lipshultz et al.,[18] Pihkala et al.,[19] Calzolari et al.,[20] Turner-Gomez et al.,[21] and Zalewska-Szewczyk et al.[22] were excluded from the meta-analysis, because of missing or incomplete description of the methodology (gas analysis) for VO_{2peak} measurement. The study by Prestor et al.[23] lacked a clear description of the patients. Johnson et al.[24] reported only the results of submaximal testing and did not report VO_{2peak} values directly measured during a maximal graded test to exhaustion. Jenney et al.[25] expressed the results as percent predicted values, and did not report absolute values of VO_{2peak}. Sharkey et al.[26] did not describe their control subjects, and McKenzie et al.[29] studied only patients treated for solid tumor cancers.

A total of 102 childhood survivors of ALL and 99 control subjects from three studies were included in this review (Table II). For the study that reported VO_{2peak} values separately for girls and boys[14], VO_{2peak} data were also entered separately into the meta-analysis. One study reported values separately for patients with and without normal stress echocardiography.[12] The VO_{2peak} data for this study were also entered separately into the present meta-analysis. All included studies used a calibrated metabolic cart for gas-exchange analysis. Despite variations between studies in exercise mode (subjects pedalling on a cycle ergometer[11] or running/walking on a treadmill[12,14]) and protocols (i.e., different rates of workload increases to attain exhaustion) and instrumentation (i.e., different commercial models of metabolic carts for gas-exchange measurement), the measurement of VO_{2peak} values was based on the same methodology in all the three included studies. None of the studies included in the meta-analysis specified the number of patients who underwent bone marrow transplantation (BMT). This is to be kept in mind as BMT is associated with reduced VO_{2peak} levels in survivors of childhood ALL.[25] The results of the meta-analysis are displayed in Table III. Although there was a significant heterogeneity between the included studies (P=0.0006), the SMD value of -0.61 (P=0.07) indicated that VO_{2peak} tends to be reduced in survivors of childhood ALL compared to healthy control subjects, that is, decrease of

-5.97 ml·kg^{-1}·min^{-1} (95% confidence interval (CI): (-12.35, 0.41)) or -13% (95% CI: (-27, 0.004)).

Table I: Studies excluded from the meta-analysis.

Study	Sample size (survivors/ controls)	Subject's age (years)	Disease subgroups	Ergometer	VO_{2peak} determination
Matthys et al[13]	35/50	10-19	ALL, ANLL, NHL, HL, WT, NB, MB, RS, TC survivors	Cycle ergometer	Direct
Ostanski et al[15]	36/28	12-24	ALL	Treadmill	Direct
Black et al[16]	56/RV	9-27	ALL, AML	Cycle ergometer	Direct
Kadota et al[17]	12/NR	13-27	HL	Cycle ergometer	Direct
Lipschultz et al[18]	115/NR	4-32	ALL	Cycle ergometer and treadmill	Direct
Pihkala et al[19]	30/38	8-25	ALL, AML, HD, spinal cord glioma Askin tumor	Cycle ergometer	Direct
Calzolari et al[20]	15/RV	9-19	ALL, ANLL	Cycle ergometer	Direct
Turner-Gomes et al[21]	12/RV	8-24	ALL	Cycle ergometer	Direct
Zalewska et al[22]	50/20	5-20	ALL, ANLL	Cycle ergometer	Direct
Johnson et al[23]	13/15	9-17	Childhood cancer	Cycle ergometer	NR
Prestor et al[24]	46/NR	5-23	ALL	Cycle ergometer	NR
Jenney et al[25]	57/128	6-30	ALL, ANLL	Cycle ergometer	Direct
Sharkey et al[26]	10/NR	19± 3	ALL, Ewing' tumor, RS, NT	Cycle ergometer	Direct
McKenzie et al[29]	34/15	8-18	Solid tumor	Cycle ergometer	Direct

RV= reference values; NR= not reported; ALL= acute lymphoblastic leukaemia; ANLL= acute nonlymphoblastic leukaemia; AML= acute lymphoblastic myoblastic leukaemia; NHL= non-Hodgkin's lymphoma; HL= Hodgkin's lymphoma; WT= Wilm's tumor; NB= neuroblastoma; MB= medulloblastoma; RS= rhabdomyosarcoma; TC= thyroid carcinoma.

Study	Sample size (survivors/ controls	Disease subgroups	Controls	Subjects' mean (sd) age (years)	Physical activity of controls	Anthracycline dose (mg/m^2)	Cranial irradiation	Mean (sd) age (years) at diagnosis	Mean (sd) length of time (years) after treatment	Ergometer/ protocol
Vizinová et al [11]	29/29	ALL survivors (13 boys and 16 girls)	Age and sex-matched healthy children	ALL survivors: 12 (3) (range: 8-16); Controls: NR	Not engaged in specific physical training	Mean: 224 (sd=39.4)	None	NR	4.8 (2.1)	Cycle ergometer/ BW
Hauser et al [12]	38/38	ALL survivors (22 boys and 16 girls)	Healthy children matched by age and body surface area	All survivors: 6 (2); range: NR; Controls: 6 (2)	Normal physical activity of daily life	Mean: 107; range: 32.4-412.5	NR	NR	NR (>6 Months)	Treadmill/ Bruce protocol
Warner et al [14]	35/32	ALL survivors (14 boys and 21 girls)	Siblings of ALL survivors	All survivors: 13 (3) (boys); 12 (3) (girls) (range 7-19); contols: 13 (3) (boys); 12 (3) (girls)	NR	Range: 0-330	5 patients 24 Gy, 30 patients <18Gy	3.2 (1.4)	6.6 (3.3) (>1.5 in all subjects	Treadmill/ Balke protocol

Sd= standard deviation; NR= not reported; ALL= acute lymphoblastic leukaemia; BW= protocol based on weight.

Table II: Studies included in the meta-analysis.

Table III: Forrest plot with the comparison of VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) values of ALL survivors with controls.

Review: ALL survivors
Comparison: Aerobic capacity
Outcome: VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)

Study or sub-category	N	ALL patients(SD)	N	Healthy controls (SD)	SMD (random) 95% CI	Weight %	SMD (fixed) 95% CI
Warner (female)	21	30.50(6.10)	14	41.30(9.20)		19.07	-1.41(-2.17, 0.65)
Warner (male)	14	39.90(3.50)	18	47.60(8.40)		19.39	-0.89(-1.63, 0.15)
Hauser (abn. str)	10	35.40(11.60)	19	50.20(12.60)		18.19	-1.17(-2.00, -0.34)
Hauser (norm. str)	28	49.50(10.90)	19	50.20(12.60)		21.29	-0.06(-0.64, 0.52)
Vizinova	29	37.40(7.80)	29	35.60(4.30)		22.06	-0.27(-0.24, 0.79)
Total (95% CI)	102		99			100.00	-0.61(-1.27, 0.061)

Test for hetrogeneity:
Chi^2= 19.59, df= 4 (P=0.0006), I^2=79.6%
Test for overall effect: Z= 1.79 (P=0.07)

-4 -2 0 2 4
Favours control Favours ALL

N=number of subjects; SMD= standardized mean difference; weight (%)= the contribution of the study to the overall result; favours control= controls have a higher VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) compared to survivors of childhood ALL; favours treatment= survivors of childhood ALL have a higher VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) compared to controls. Forrest plot with I^2 is measuring the extent of inconsistency among results.

Discussion

The results of the present systematic review indicate that the VO_{2peak} values (and thus fitness levels) of survivors of childhood ALL tend to be reduced (average of ~ -6 $ml \cdot kg^{-1} \cdot min^{-1}$ or -13%) compared to healthy controls. Besides the decrease in QOL associated with lower VO_{2peak} levels, the aforementioned average decrease in the VO_{2peak} of ALL survivors is of clinical relevance as this variable is a powerful predictor of mortality in both healthy and diseased individuals[3,4], for example, a -3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ reduction is associated with a 12% decrease in the survival rates of diseased people.[4]

There existed some heterogeneity between studies, mainly attributable to the study of Vizinova et al.[11] These authors did not find significant differences between ALL survivors and control subjects. It must be, however, noticed that ALL survivors were encouraged to be physically active, whereas the children of the control group followed a sedentary lifestyle. The second factor that contributed to the heterogeneity between studies arises from the inclusion of ALL survivors with normal stress echocardiography in one of the studies.[12] Indeed, Hauser et al.[12] found no significant differences in exercise

capacity between ALL survivors with normal stress echocardiography results and healthy control children. This finding suggests that impaired cardiac function is responsible, at least partly, for the reduced functional capacity of ALL survivors, as discussed below. On the other hand, the wide CI we obtained (impairment -13%, 95% CI: (-27, 0.004)) indicates a considerable variation in the physical fitness levels of ALL patients after successful treatment. This might be due to differences in treatment and response to treatment in leukaemia patients. For instance, Sharkey et al.[26] found normal exercise capacity in patients receiving minimal doses of anthracycline and no irradiation.

In humans, decreases in VO_{2peak} are largely attributable to impaired cardiac function as VO_{2peak} mainly reflects (and is largely limited by) maximal O_2 supply to muscles (i.e., maximal cardiac pump capacity) rather than maximal rate of O_2 utilization by muscle mitochondria.[27,28] Anticancer therapy may affect central cardiac dynamics and thus blood supply to body tissues, particularly exercising muscles. Anthracyclines can induce myocardial damage (e.g., doxorubicin-induced cardiomyopathy) with subsequent decreases in cardiac output.[29,30] Sedentary habits (especially bed rest) induce cardiac atrophy and further reduce stroke volume and thus cardiac output in young adults[31] and children.[32] Since sedentary ALL survivors with reduced VO_{2peak} are able to reach normal values of maximal heart rate during exercise,[13,14] impaired stroke volume is largely responsible for their reduced cardiac output and thus decreased VO_{2peak} (as cardiac output is the product of heart rate by stroke volume). Anticancer therapy can also alter the exercise capacity of ALL survivors due to its deleterious effects on lung function. Craniospinal irradiation, cyclophosphamide or lung infections during or subsequent to treatment for leukemia (e.g., bacterial, or due to respiratory syncytial virus, candida, pneumocystis or cytomegalovirus) can reduce total lung capacity.[25] Lung function impairment in ALL survivors is reflected by the occurrence of arterial desaturation (oxygen saturation values <90%) during exercise.[13]

Besides insufficient pumping of oxygenated blood to working muscles, several phenomena at the peripheral (muscle tissue) level might severely limit the maximal capacity of muscle fibres to consume oxygen and further decrease the VO_{2peak} of ALL survivors. Muscle atrophy is a common problem in this population group due to the catabolic effects of several chemotherapeutic agents as vincristine or corticosteroids.[14,33] Muscle atrophy implies a smaller muscle mass to consume oxygen during exercise. In addition, the metabolic function of muscle fibres can be altered. Impaired aerobic metabolism (due to decreased mitochondrial volume and/or mitochondrial

myopathy) or reduced capillarization can occur after immunosuppressive therapy.[34] Muscle atrophy and altered muscle function are further aggravated by sedentary habits due to the catabolic effects that sedentarism and prolonged bed rest induce on skeletal muscle tissue.[6] As a result, muscle atrophy and early fatigue during low-to-moderate physical tasks become self-perpetuating conditions.[6]

Although more research is needed, some data suggest that the total daily energy expenditure of ALL survivors is indeed reduced compared to healthy children, leading to further deconditioning. Particularly, female patients show a greater impairment after treatment with anthracyclines, which results in further deterioration of functional capacity and increased body fat compared to males.[13,14,16] For instance, Matthys et al. estimated the physical activity of ALL survivors with a questionnaire. Sport leisure time was lower in girl survivors of cancer (the majority, but not all, of which was ALL) than in their corresponding controls. Their VO_{2peak} levels were also lower (-8 $ml \cdot kg^{-1} \cdot min^{-1}$).[13] Warner et al.[35] measured total daily energy expenditure (TDEE) and physical activity levels (=TDEE/basal metabolic rate) in long-term survivors of ALL and compared them with results from survivors of other malignancies and healthy sibling control subjects. The median TDEE was reduced in the ALL group (150 kJ kg day^{-1}) compared with other malignancies and controls (207 and 185 kJ kg day^{-1}, respectively). In turn, this reduction was accounted for mainly by a relative decrease in their levels of physical activity. Total energy expenditure and physical activity were in turn correlated with percentage body fat, indicating that obesity in survivors of ALL may, in part, be explained by a decrease in their TDEE as a consequence of their low physical activity levels. The detrimental effects of sedentarism are aggravated by the fact that diseased children may underestimate their own potential for performing physical tasks due to low self-esteem or overprotection by their parents.[13] Only physical training can break the 'vicious circle' of sedentary habits and subsequent exercise intolerance.[6]

Finally, it must be kept in mind that glucocortocoid therapy can increase adiposity and body mass in children receiving treatment for ALL.[36] As VO_{2peak} is expressed relative to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$), the decreased VO_{2peak} levels of ALL survivors might be partly attributable to the aforementioned side effects of glucocorticoid treatment. Nevertheless, the difference in VO_{2peak} levels between the ALL survivors and controls included in our meta-analysis cannot be fully explained by differences in body mass, as the mean values of this variable were very similar in both groups of subjects studied by Vizinova et al.[11] (ALL survivors: 46.2 kg; controls: 45.1 kg) and Warner et al.[14] (boys

survivors of LLA: 50.9 kg; controls: 51.0 kg), except for the girls included in the report by Warner et al.[14] (ALL survivors: 49.0 kg; controls: 45.5 kg). Although Hauser et al.[12] did not report body mass, they stated that their controls and ALL survivors were 'matched for age and body surface area'.

Conclusions and perspectives

The physical fitness (as reflected by VO_{2peak} levels) of ALL survivors tends to be reduced compared to healthy children. Impaired physical fitness leads to early fatigue during physical activities and can severely deteriorate the QOL of ALL survivors, which suggests the need for these children to engage in regular physical activities. Exercise physiologists could assist oncologists in prescribing exercise programs for attenuating cancer-related fatigue and help improve the physical fitness and QOL of children surviving cancer.[6] Furthermore, there are scientific indications that exercise training improves the function of several anti-cancer immune system components,[37] and can attenuate tumor development.[38]

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3
Chapter

Physical function and fitness in long-term survivors of childhood leukaemia

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Abstract

Objective

To evaluate the physical function and fitness in survivors of childhood leukaemia 5–6 years after cessation of chemotherapy.

Materials and methods

Thirteen children (six boys and seven girls; mean age 15.5 years) who were treated for leukaemia were studied 5–6 years after cessation of therapy. Physical function and fitness were determined by anthropometry, motor performance, muscle strength, anaerobic and aerobic exercise capacity.

Results

On motor performance, seven of the 13 patients showed significant problems in the hand-eye co-ordination domain. Muscle strength only showed a significantly lower value in the mean strength of the knee extensors. The aerobic and the anaerobic capacity were both significantly reduced compared to reference values.

Conclusion

Even 5–6 years after cessation of childhood leukaemia treatment, there are still clear late effects on motor performance and physical fitness. Chemotherapy-induced neuropathy and muscle atrophies are probably the prominent cause for these reduced test results. Physical training might be indicated for patients surviving leukaemia to improve physical fitness levels and muscle strength.

Introduction

Childhood leukaemia has an increasing number of survivors; therefore more emphasis is focused on the long-term effects of disease and treatment. The success rate is attributed to the usage of more intensive systemic therapy. The chemotherapeutic treatment for children with leukaemia has short- and long-term effects on the neuromuscular and cardiovascular systems. *Vincristine*®-induced peripheral neuropathy is a well-defined complication of treatment for ALL.[1] Children with leukaemia show decreased muscle strength early in treatment.[2,3] The magnitude of this decreased muscle strength and its impact on function and physical fitness are currently not well understood.[2]

In children with leukaemia several scientific studies have been conducted investigating physical fitness.[4–7] In these studies, the main focus was on cardiac- and pulmonary function. There is increasing evidence indicating that there are factors other than cardio-pulmonary factors, which limit the physical fitness of leukaemia patients.[7, 8]

Obesity is an often occurring phenomenon after childhood leukaemia treatment.[9–11] Warner et al.[7] found in leukaemia patients a strong negative relationship between exercise capacity, including sub-maximal oxygen consumption and adiposity. According to Warner et al. this could be caused by a reduction in quantity and quality of mitochondria in the muscles of leukaemia patients.[7] This leads to a reduced oxygen uptake during sub-maximal exercise as well as the reduced capacity in leukaemia patients to oxidize fats as a fuel. This reduced oxidation of fats could lead to a form of adiposity.[7]

In the literature there are several publications on exercise capacity in leukaemia patients after being treated medically.[5,12,13] However, no studies investigated the anaerobic exercise capacity of these patients, although it has been shown that the anaerobic exercise capacity might be very important in the performance of daily childhood activities with chronic conditions.[14] Also a decreased anaerobic performance in survivors of solid tumour cancers was previously reported.[15]

The objective of this study is to determine whether physical function[a] and physical fitness is reduced in survivors of leukaemia 5–6 years after their final treatment, compared to reference values of healthy children and adolescents.

[a] Physical function refers to the capacity to perform activities of daily living. Physical fitness refers to the exercise capacity as measured under laboratory conditions (i.e. muscular strength, cardiopulmonary fitness).

Material and methods

Patients

Thirteen patients being treated for acute lymphoblastic leukaemia (six boys, seven girls) at the Wilhelmina Children's hospital, Utrecht, the Netherlands, participated in this study. Their characteristics can be appreciated from Table I.

Children who started chemotherapy in 1996 were treated according to the Dutch Childhood Leukaemia Study Group (DCLSG) protocol ALL-8[16] and children who started chemotherapy in 1997 were treated according to the DCLSG protocol ALL-9.[17] One patient with T-cell non-Hodgkin Lymphoma (T-NHL) was also treated according to protocol ALL-8 and was included in this study. Excluded were children with High-Risk ALL, receiving more intensive chemotherapy and children who were mentally disabled. Six of 13 were treated according to DCLSG protocol ALL-8 and seven of 13 according to Dutch Childhood Leukaemia Study Group protocol ALL-9. Children treated with protocol ALL-8 received 8 x 1.5 $mg \cdot m^{-2}$ *Vincristine* over two periods of 4 weeks. Children treated with protocol ALL-9 received 34 x 2.5 mg/dose *Vincristine* during the whole treatment period of 2 years (Table II). In protocol 8, both dexamethasone and prednisone were used as corticosteroidtherapy, in protocol 9 dexamethasone alone was used; the equivalent doses of steroids was 5–6 times higher in protocol 9 compared to protocol 8. On the other hand, the latter protocol contained more cytostatic agents (*daunorubicine, ara-C, 6-thioguanine*). Neither protocols included cranial irradiation. The eligible patients were participants in a previous study (n=18) from the group.[3] Thirteen patients of the original cohort participated in this study. Five did not participate: three for personal reasons, one for coming to the hospital too often and one left the country. The characteristics (age, gender and type of ALL) of these five patients did not differ from the other 13 patients. Informed consent was obtained from the parents and/or from the children if they were older than 12 years of age.

Skin-fold and muscle strength measurements were performed by the second author (TT) who is an experienced exercise physiologist and has significant familiarity with these measurements. All other measurements were performed by the first author (MvB). The medical-ethics committee of the University Medical Centre Utrecht approved all study procedures.

Table I: Anthropometric parameters and time of treatment of the 13 ALL survivors.

Variables	Mean	SD	Range	
Age (years)	15.5	5.8	8.6 - 23.7	
Weight (kg)	54.24	19.5	25.1 – 80.7	NS
Height (meters)	1.54	0.2	1.26 - 1.8	NS
BMI ($kg \cdot m^{-2}$)	20.75	3.8	15.1 - 26.1	NS
Σ7SF(mm)	96.3	46.6	49 - 182	NS
Time off treatment (months)	61.9	6.8	46-73	

Abbreviations: NS: not significantly different from reference values; BMI: body mass index; Σ7SF: sum of the seven skinfolds.

Table II: Patient characteristics and outline of treatment according to protocol ALL-8 and ALL-9.[27]

	Treated with protocol ALL-8	Treated with protocol ALL-9
Number	6	7
Male to female ratio	3:3	3:4
Age (years)	17.9	13.5
Medication		
Induction	VCR/Pred/DNR/L-ASP+ MTX/ Ara-c/Pred i.th	VCR/Pred/L-ASP+ MTX/Ara-C/ Pred i.th.
Intensification	MD-MTX/6MP + MTX/Ara-c/ Pred i.th	MD-MTX/ 6MP + MTX/Ara-c/ Pred i.th.
Reinduction	VCR/Dexa/Adria/L-Asp/6MP, Ara-C, 6TG + MTX/Ara-c/Pred i.th.	none
Maintenance	6MP/MTX	6MP/MTX+ Q 5 weeks: VCR/Dexa

Abbreviations: VCR: vincristine, Pred: prednisone, DNR: daunorubicine, L-Asp: L-asparaginase, Ara-C: cytosine-arabinoside, MTX: methotrexate, Adria: doxorubicine, 6TG: 6-thioguanine, 6MP: 6-mercaptopurine, Dexa: dexamethasone, i.th: intrathecal

Anthropometry

The participants' body mass and height were determined using respectively an electronic scale and a stadiometer; subcutaneous adiposity was determined from skin-fold measurements using Harpenden skin-fold callipers (Holtain, Crymych, UK). The measurements were taken at seven sites (at the right side of the body); triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf and thigh in accordance with the American College of Sports Medicine guidelines.[18] No percentage of body fat was calculated because there are no validated prediction formulae for leukaemia patients.[11] Therefore, the sum of the seven skin-folds was used as an index for body fat after Pollack et al.[19] Body Mass Index was calculated as body mass/ height^2. The BMI of the included patients were compared and to international cut-off points for body mass index for overweight and obesity.[20]

Motor performance

The movement assessment battery for children (Movement ABC test I) tested the motor performance of the patients.[21,22] The Movement ABC screens motor performance of children between 4–12 years. The Movement ABC I consist of test items for four age groups: 4–6 years, 7–8 years, 9–10 years and 11–12$^+$ years. As described in the manual, the instrument can be used for children above this age as well. [22] In the Dutch version of the Movement ABC the upper age band is therefore listed as 11–12$^+$. Children above 12 years of age were compared with the normative percentile scores of the age band 11–12$^+$.[22]

The test can be divided into two parts: a checklist and a motor performance test. The motor test measures three different aspects of motor performance, i.e. manual dexterity, ball skills, dynamic and static balance. Percentile scores of the child's motor abilities were compared with a normative age-matched sample of children.[21] A score below the 5th percentile indicates that the child has significant movement difficulties. In scores between the 5th and 15th percentile, the child is at risk for these difficulties. The motor performance is adequate in scores above the 15th percentile.[21] Children were evaluated using the score forms for their appropriate age group.

Strength measurement

Muscle strength was measured with a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, the Netherlands) in six different muscle groups (shoulder abductors, knee extensors, foot dorsal flexors, wrist extensors, hip flexors and grip strength). Maximum muscle strength was tested using the 'break' method, in which the examiner gradually overcomes the muscle strength of the patient and stops at the moment the extremity gives way. Grip strength was measured using the 'make' method. With the subjects sitting and the arms held 90° flexion at their sides, the dynamometer was gripped as hard as possible for 3 seconds without pressing the instrument against the body and without touching the elbow to the body.

During the test, the examiner manually stabilized the body parts proximal to the tested limb segment. Each person was tested once and in this session every muscle group was measured three times and the highest score was recorded. The highest value was used for comparison. Reference values for muscle strength (mean and SD for age and gender) were obtained from Beenakker et al.[23] and van der Ploeg et al.[24] and grip strength from Engelbert et al.[25] and used for analyses.

Exercise capacity

Wingate anaerobic exercise test. The Wingate Anaerobic test (WAnT) as described by Bar-Or[26] was performed on a calibrated electromagnetic braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The ergometer was upgraded and calibrated by the manufacturer to a maximal resistance of 800W instead of the standard 400W. External resistance was controlled and the power output was measured using the Lode Wingate software package. The seat height was adjusted to the patients' leg length (comfortable cycling height). The external load (torque; in Nm) was determined, dependent of bodyweight (at 0.53 bodyweight and 0.55 bodyweight for girls and boys under 14 years of age and 0.67 bodyweight and 0.7 bodyweight for older girls and boys, respectively) according to the user manual. The patients' feet were placed in the Velcro toe-straps and the exercise protocol was explained. The patients were instructed to exercise for 1 minute at the cycle ergometer with an external load of 15W at 50–60 rpm.

Thereafter, the sprint protocol started. The patients were instructed to cycle all-out for 30 seconds. Power output during the WAnT was corrected for the

inertia of the mass of the flywheel (23.11kg·m^{-2}). Measured variables were mean power and peak power. Mean power represents the average power output over the 30 seconds sprint. Peak power is the highest recorded power output achieved during the 30 seconds sprint.

Cardio-pulmonary exercise test (CPET)

Patients performed a cardio-pulmonary exercise test using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The test started with 1 minute of unloaded cycling, preceded to the application of resistance to the ergometer. After this minute, workload was increased with a constant increment of 10 or 20W every minute. The protocol was selected to elicit a maximal exercise response within ~6–12 minutes.[27] This protocol continued until the patient stopped because of exhaustion, despite verbal encouragement of the test-leader. The highest achieved workload (W_{max}) was recorded. During the cardiopulmonary exercise test, subjects breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Viasys, Bilthoven, the Netherlands). Expired gas was passed through a flow meter (Triple V volume transducer), an oxygen (O_2) analyser and a carbon dioxide (CO_2) analyser. The flow meter and gas analysers were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2) and the respiratory exchange ratio (RER= VCO_2/VO_2) from conventional equations. Heart rate (HR) was measured continuously during the maximal exercise test through a bipolar electrocardiogram. Maximal effort occurred when one of the two criteria were met: HR >180 beats per minute or RER >1.0. Peak oxygen consumption (VO_{2peak}) was taken as the average value over the last 30 seconds during the maximal exercise test. Relative VO_{2peak} was calculated as absolute VO_{2peak} divided by body mass. For both the anaerobic exercise test as well as the cardio-pulmonary exercise test, the patients were compared to recently obtained reference values from the laboratory using the same experimental procedures.[28]

Statistics

All data were entered and analysed in SPSS 12.0 for Windows. Due to the small number of patients and the individual variability in response, there were no statistically significant differences between the patients in the two treatment protocols with respect to any of the variables. Therefore, the data of both groups were pooled and used together in the statistical analysis. Independent samples T-tests were used to test differences between patients and reference values. Alpha level was set at $p<0.05$ for all analyses.

Results

The anthropometrical parameters of the patients indicated that none of 13 patients were obese and three patients were overweight, although mean scores did not differ from reference values. The results of the Movement ABC are shown in Table III and indicate that 7/13 of the patients had a score below the 15th percentile score in the 'ball skills' domain compared to healthy children. All patients scored above the 15th percentile in the manual dexterity domain. One patient scored between the 5th and 15th percentile on dynamic balance.

Table III. Frequencies of percentile scores of the Movement ABC test.

	Manual dexterity (number of patients)	Ball skills (number of patients)	Static and dynamic balance (number of patients)
> P15	13	6	12
P5 - P15*	0	3	1
≤ P5	0	4	0
Total	13	13	13

* Scores between the 5th and the 15th percentile indicate that the child is at risk for motor delay.

The strength measurement data (Table IV) indicated that only knee extension strength was significantly reduced from normal values. All other muscle tests were within normal ranges. The measurements of the anaerobic capacity indicate that all values were significant lower in the survivors of ALL compared to the control group (Table V). Table V also shows the data of the cardiopulmonary exercise test. VO_{2peak}, $VO_{2peak/kg,}$, W_{max} and VE_{max} were

significant lower in the survivors of childhood leukaemia compared to reference values.

Table IV. Muscle strength measurement values of six different muscle groups (mean, standard deviations (SD) and range, z-scores and p-values.

	Patients		Controls			
	Mean	**SD (and range)**	**Mean***	**SD (and range)***	**Z-score**	**P-value**
Grip strength	117.4	75.20 (36.0-290.0)	120.5	57.0 (57.4-192.0)	-0.32	0.35
Shoulder abductor	161.8	64.17 (75.0-298.0)	144.7	46.2 (93.7-226.3)	0.58	0.1
Knee extensor	252.1	81.13 (129.0-350.0)	299.7	98.9 (166.0-396.0)	-0.67	**0.001**
Foot dorsal flexor	206.6	81.77 (78.0-346.0)	185.7	50.9 (127.5-248.9)	0.41	0.25
Wrist extensor	142.3	68.46 (64.0-280.0)	153.2	66.0 (75.0-237.0)	-0.14	0.8
Hip flexor	212.0	78.31 (112.0-336.0)	206.6	65.6 (129.4-291.4)	0.14	0.6

*Control values obtained from references [23-25].

Table V. Anaerobic and aerobic exercise performance of the 13 ALL survivors

Variables	**Mean ± SD**	**Range**	**Mean predicted ± SD**	**P-value**
Wingate Anaerobic test				
Mean Power (Watt)	376.1 (171.9)	163–587	492.9 (276.9)	**0.000**
Peak Power (Watt)	538.6 (289.6)	218 -1094	867.32 (508.2)	**0.000**
Cardio-pulmonary exercise test				
VO_{2peak} ($L \cdot min^{-1}$)	1.99 (0.99)	0.93–3.398	2.69 (1.15)	**0.001**
$VO_{2peak/kg}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	36.64 (18.3)	17.15–62.65	49.58 (21.22)	**0.001**
W_{max} (Watt)	155 (82.41)	60–280	222.98 (97)	**0.000**
VE_{max} ($L \cdot min^{-1}$)	64.69 (36.1)	27.60–146.5	94.9 (37.9)	**0.001**

Abbreviations: VO_{2peak}: peak oxygen uptake; $VO_{2peak/kg}$: peak oxygen uptake related to body mass, W_{max}: maximal work load; VE_{max}: maximal ventilation.

Discussion

This study found that long-term survivors of childhood leukaemia had a lower level of physical function and fitness compared with healthy children. Although the disease in the present patient group is in remission, they may experience late effects from the anti-leukaemia therapy (chemotherapy) affecting multiple organ systems. Chemotherapeutic agents have known toxicities on different organ systems and can affect the function of lung, heart and muscle.[29–31] Corticosteroid therapy, in particular protocols with dexamethasone, is associated with obesity or overweight as an early and late side effect.[32]

Movement ABC

The Movement ABC I showed that there were a number of patients with problems in hand-eye co-ordination. The outcome values of the movement ABC are quite remarkably compared to earlier described values. Reinders-Messelink et al.[33] studied motor performance in 17 children during and after chemotherapy. They found balance problems to be most severe during treatment. The manual dexterity skills showed an opposite pattern. The percentage of patients with manual dexterity problems was higher after treatment compared at the start. In the study of Schoenmakers et al.[3] the percentage of patients with manual dexterity problems (11%) was somewhat lower compared to the percentage of patients reported by Reinders-Messelink et al.[33] (33.3%). The percentage of patients with manual dexterity problems in the study (7.7%) was also lower than the number of patients reported by Reinders-Messelink et al.[33] The patients in the study of Schoenmakers et al.[3] were the same patients (13 of the 18) tested in the current study. The outcome might be due to the small sample size in all these studies. Just like the study of Schoenmakers et al., gross motor disturbance was found more frequently occurring than fine motor problems.[3] Unlike the study of Reinders- Messeling et al. there were no balance problems with the patients of the present study. The greatest problems were seen with the ball skills (hand-eye co-ordination). A relationship between the motor problems and vincristine-induced neurotoxicity seemed plausible, but the effect of other neurotoxic drugs, like methotrexate and steroids, could not be ruled out.[33–35]

Strength measurement

The findings of the present study indicates that 5–6 years after treatment muscle strength of the knee extensors was still reduced compared to reference values, other muscle groups were within the normal range, however. This might be explained by the effect of chemotherapy on muscle fibres (especially type II fibres) and the neural drive. Harila-Saari et al.[1] showed in their study both demyelination and a loss of descending motor fibres or loss of muscle fibres in a population after treatment from childhood ALL, indicating impairment within both the central and peripheral motor nervous system. Atrophy of type II fibres of the proximal muscle, especially those in the lower limbs, are manifestations of corticosteroid-related myopathies.[36] Decreased muscle strength has been identified in young adults

surviving ALL in their childhood.[37] Lehtinen et al.[38] found decreased motor nerve conduction in the peripheral nerves even 5 years after treatment, while 33% of their population still had clinical neurological findings.[38]

The reason why only a reduced strength in the knee extensors was found might be explained by the fact that lower extremity strength appears more affected than upper extremity strength in deconditioning studies.[39] Especially weight-bearing muscles in the lower extremities are the most affected muscles during periods of under loading.[39]

Anaerobic exercise capacity

The anaerobic exercise capacity of the patients in the present study was significantly reduced compared to the control group. This finding is in accordance with the findings of McKenzie et al.[15] in childhood and adolescent survivors of solid tumour cancers. During short-term high intensity exercise such as the WAnT Type IIa and Type IIx muscle fibres are heavily recruited.[26] It is well known that during catabolic periods such as cachexia and corticosteroid treatment the major amount of muscle atrophy occurs in type II muscle fibres.[36] Presumably type I fibres are more resistant to atrophy in these conditions. Moreover, recent studies suggest that WAnT performance is also related to intra- and inter-muscular co-ordination.[40] Thus, the reduced anaerobic capacity might be a result of both an impaired motor co-ordination and a reduced active muscle mass during exercise. In these patients, deviant scores were also found on the Movement ABC which could confirm the hypothesis of impaired motor co-ordination.

CPET

The various parameters of the cardiopulmonary exercise test indicate a significant decrease of the aerobic exercise capacity. The VO_{2peak}, W_{max} and VE_{max} were significant reduced compared to reference values, in concordance with other studies.[5] The significantly lower VO_{2peak} indicates that the physical fitness of ALL survivors is reduced compared to healthy children. VO_{2peak} is the product of cardiac output and the arterio-mixed venous oxygen difference (the Fick equation). Abnormalities in cardiac output may indicate reduced cardiac function. The patients had a maximal heart rate between 169–201 beats per minute at maximal exercise with, respectively, a respiratory exchange ratio between 0.95–1.41. This indicates that ALL survivors can

achieve high heart rates in combination with a metabolic acidosis, as is usually found in healthy children. The fact that there was no decrease of the blood saturation indicates that there was no major impairment in pulmonary function. The significant lower aerobic exercise capacity could be due to a combination of metabolic and neuromuscular impairments.

There is some evidence that exercise training can improve physical fitness and health-related quality of life of leukaemia patients.[41,42] This improvement makes it a relevant issue in the care for survivors of ALL. Exercise physiologists and other professionals could assist in designing appropriate exercise training programmes for attenuating cancer-related fatigue and improving physical fitness[36] in order to help increase physical fitness in children surviving cancer.[43,44] Because of the small patient group with a heterogeneous age range from a single centre, it is difficult to determine the generalizability of the current findings. Moreover, the cross-sectional design of the study does not show the rate of recovery after the treatment phase. Longitudinal multi-centre studies should be initiated to study the effects of the disease, treatment and rehabilitation in this patient group.

Conclusion

In conclusion, it was found that even 5–6 years after cessation of therapy there still are clear late effects of chemotherapy in patients treated for childhood leukaemia. Aerobic and anaerobic physical fitness and motor performance were considerably lower compared to healthy children. Chemotherapy-induced muscle atrophy, myopathy and neuropathy might be the cause of the significantly reduced test scores. The results indicate that prescription of exercise in general by health-care professionals would be advisable so that these children are encouraged to be just as active as they were before treatment. If children are already active, but still have a reduced exercise capacity, a tailored exercise programme should be initiated.

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4
Chapter

Exercise therapy in juvenile idiopathic arthritis: A systematic Cochrane review

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Abstract

Background

Exercise therapy is considered an important component of the treatment of arthritis. The efficacy of exercise therapy has been reviewed in adults with rheumatoid arthritis but not in children with juvenile idiopathic arthritis (JIA).

Objectives

To assess the effects of exercise therapy on functional ability, quality of life and aerobic capacity in children with JIA.

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (The Cochrane Library), MEDLINE (January 1966 to October 2007), CINAHL (January 1982 to October 2007), EMBASE (January 1966 to October 2007), PEDro (January 1966 to October 2007), SportDiscus (January 1966 to October 2007), Google Scholar (to October 2007), AMED (Allied and Alternative Medicine) (January 1985 to October 2007), Health Technologies Assessment database (January 1988 to October 2007), ISI Web Science Index to Scientific and Technical Proceedings (January 1966 to October 2007) and the Chartered Society of Physiotherapy website (http://www.cps.uk.org) were searched and references tracked.

Selection criteria

Randomised controlled trials (RCTs) of exercise treatment in JIA.

Data collection & analysis

Potentially relevant references were evaluated and all data were extracted by two review authors working independently.

Main results

Three out of 16 identified studies met the inclusion criteria, with a total of 212 participants. All the included studies fulfilled at least seven of 10 methodological criteria. The outcome data of the following measures were homogenous and were pooled in a meta-analysis: functional ability (n=198; WMD: -0.07, 95% CI: -0.22 to 0.08), quality of life (CHQ-PhS: n=115; WMD:

-3.96, 95% CI: -8.91 to 1.00) and aerobic capacity (n=124; WMD: 0.04, 95% CI: -0.11 to 0.19). The results suggest that the outcome measures all favoured the exercise therapy but none were statistically significant. None of the studies reported negative effects of the exercise therapy.

Reviewers' conclusions

Overall, based on 'silver-level' evidence (www.cochranemsk.org) there was no clinically important or statistically significant evidence that exercise therapy can improve functional ability, quality of life, aerobic capacity or pain. The low number of available RCTs limits the generalisability. The included and excluded studies were all consistent about the adverse effects of exercise therapy; no short-term detrimental effects of exercise therapy were found in any study. Both included and excluded studies showed that exercise does not exacerbate arthritis. The large heterogeneity in outcome measures, as seen in this review, emphasises the need for a standardised assessment or a core set of functional and physical outcome measurements suited for health research to generate evidence about the possible benefits of exercise therapy for patients with JIA. Although the short-term effects look promising, the long-term effect of exercise therapy remains unclear.

Background

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and is an important cause of short-term and long-term disability. JIA is a disease of unknown aetiology that begins before the 16th birthday and persists for at least six weeks. A diagnosis is made when other known conditions are excluded.[1] Studies in developed countries have reported a prevalence that varies between 16 and 150 per 100,000[2]. Data from two cross-sectional studies indicate that children with arthritis are physically less active compared to healthy children.[3, 4] Moreover, it was found that physical activity was related to physical fitness[4] indicating that lower physical activity level leads to deconditioning and functional deterioration, which reinforces an inactive lifestyle.[5]

Exercise therapy (for example, a training program) might prevent the deconditioning due to hypoactivity and break the vicious circle. Exercise therapy is considered as an integral part of the treatment of children with JIA.[2] Several types of exercise therapy can be distinguished, for example, physical training programs such as strength training for improving muscle strength and endurance exercise for improving cardiorespiratory fitness. Studies in adult rheumatoid arthritis (RA) patients have shown that these exercise modalities, or a combination of both, can improve physical fitness (muscle strength or maximal oxygen uptake) and function.[6-9]

In both adult RA and JIA, the focus has shifted from inflammation parameters to more patient-centred outcomes. For RA this resulted in the development of the OMERACT (Outcome Measures in Rheumatology) core set for RA[10] and in JIA the PRINTO (Pediatric Rheumatology International Trial Organization) core set.[11] The OMERACT core set consists of patient and physician global assessment and measures of pain, disability and an acute-phase reactant. The PRINTO core set consists of physician global assessment of disease activity, parent or patient (as appropriate for age) global assessment of overall wellbeing, functional ability, number of joints with active arthritis, number of joints with limited range of motion, erythrocyte sedimentation rate and health-related quality of life (HRQoL) measurements.

A systematic review on the effects of dynamic exercise therapy for treating adult RA has shown that adults can benefit from exercise in terms of improved exercise capacity, muscle strength and range of motion.[12] There is

some evidence that children with JIA can benefit from exercise as well.[13,14] Other evidence showed that exercise does not exacerbate arthritis.[15,16] However, not all of these studies are controlled studies. A systematic review of randomised controlled studies can determine whether exercise therapy is effective for children with JIA. Therefore, we performed a systematic review on the effects of physical exercise therapy for children with JIA.

Objectives

The primary objective was to perform a systematic review on the effects of exercise therapy for children with JIA in terms of functional ability, range of motion, number of joints with swelling (active joint count), number of joints with pain, health-related quality of life, parent or patient global assessment of overall wellbeing, pain, aerobic capacity and muscle strength.

Criteria for considering studies for this review

Types of studies

All full-length randomised controlled trials were eligible for inclusion.

Types of participants

This review concerned children with juvenile idiopathic arthritis (juvenile rheumatoid arthritis (JRA), juvenile chronic arthritis (JCA), juvenile idiopathic arthritis (JIA)) under 18 years of age, including all subgroups ((extended) oligo (pauci) articular JIA, rheumatoid factor (RF) negative and RF positive polyarthritis, systemic onset JIA, psoriatic arthritis, enthesitis related arthritis and other arthritis) as diagnosed by a rheumatologist based on established criteria from national and international organizations (ILAR, ACR, EULAR). Studies of osteoarthritis were excluded as this is not relevant for children with JIA.

Types of interventions

- Physical exercise therapy existing of
- Endurance training
- Strength training
- A combination of strength and endurance training
- Physical exercise during summer camps

Comparators to these interventions were:
A) Placebo;
B) Therapy Y, where therapy Y is any therapy that can be considered as a placebo exercise therapy as attention is given that is not expected to improve physical function because of a very low exercise intensity, but which may also be beneficial to the participants;
C) Standard medical care; because it is very difficult to develop a real placebo for exercise therapy, children receiving assessment only will be considered as receiving placebo.
In order to meet the inclusion criteria for this review all interventions must include an adequate description of the intervention including intensity, frequency, duration of training, and mode of administration. Trial duration must be a minimum of two weeks.

Types of outcome measures

We included all the outcome measures recommended for use in clinical trials in the PRINTO-core set[11] as well as training effects on exercise capacity and muscle strength. When reported, side effects, total number of dropouts and compliance with exercise were also included in the review.

Primary outcomes

- Functional outcome measures
- Functional ability (as measured on functional tests and questionnaires (i.e. JAFAS[17], CHAQ[18] and JASI[19])
- Joint range of motion measures
- Number of joints with swelling (active joint count)
- Number of joints with pain
- Health-related quality of life (i.e. HR-QoL, CHQ[20])
- Parent or patient global assessment of overall wellbeing
- Pain

Adverse outcomes (safety of exercise therapy) and other outcomes:

- Any reported side effects (e.g. disease flares)
- Total number of dropouts
- Withdrawals due to inefficacy or negative effects

Secondary outcomes

- Measures to evaluate the effects of exercise training on exercise capacity and muscle strength
- Aerobic capacity (VO_{2peak}) determined on maximal ergometer test
- Aerobic capacity (VO_{2peak}) estimated from submaximal ergometer test
- Aerobic capacity estimated from field test measuring aerobic fitness
- Muscle strength
- Compliance with exercise

Search strategy for identification of studies

We searched (up to October 2007) the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, EMBASE, PEDRO, SportDiscus, Google Scholar, AMED (Allied and Alternative Medicine), Health Technologies Assessment database, ISI Web Science Index to scientific and technical proceedings, the Chartered Society of Physiotherapy website and reference tracking using the search terms randomized controlled trial(s), (controlled) clinical trial(s), random allocation, double blind method, single blind method, Juvenile Rheumatoid Arthritis, Juvenile Chronic Arthritis, child, adolescent, physical therapy, physical exercise, rehabilitation, strengthening, hydro-, balneo-, spa-, and thalasso therapy. The search strategy was developed in co-operation with the Cochrane Musculoskeletal Review Group and combines a search string for the population, trials, and intervention (see appendix for details of the search strategy). We also hand-searched the databases for meeting abstracts and conference proceedings and searched the reference lists of the identified studies.

Methods of the review

Selection of studies

The search strategy identified a set of potentially relevant references. Two authors (TT, MvB) screened search results for potentially eligible studies. When titles and abstracts suggested a study was potentially eligible for inclusion, a full paper copy of the report was obtained. Disagreements between the two authors regarding a study's eligibility were resolved by discussion until consensus was reached or, where necessary, a third person (RHHE) acted as adjudicator.

In addition to extracting data, the review authors independently allocated each included trial to one of three methodology quality categories, based on the Cochrane Handbook for Systematic Reviews of Interventions.[21]
Category A: low risk of bias - plausible that bias is unlikely to seriously alter the results, all of the criteria met.
Category B: moderate risk of bias - plausible that bias raises some doubt about the results, one or more criteria partly met.
Category C: high risk of bias - plausible that bias seriously weakens confidence in the results, one or more criteria not met.

Data extraction and management

Two independent observers (TT, MvB) independently extracted data using a standard extraction form. Agreements between observers were assessed using a weighted kappa statistic. Disagreements were discussed by the two review authors until a consensus was reached. If no consensus was reached, a third review author (RHHE) acted as adjudicator. Data were extracted at baseline and the end of the intervention period. If data were missing or further information was required, serious attempts were made to contact the first two study authors to request the required information.

Assessment of methodological quality of included studies

Methodological quality was assessed independently by two review authors (TT, MvB) using the PEDro scale. The PEDro scale is based on the Delphi list developed by Verhagen et al.[22] which is based on 'expert consensus' not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more

empirical data comes to hand it may become possible to weight scale items so that the PEDro score reflects the importance of individual scale items. The purpose of the PEDro scale is to help the users of the PEDro database to rapidly identify which RCT is likely to be internally valid (criteria 2 to 9) and could have sufficient statistical information to make the results interpretable (criteria 10 and 11). An additional criterion (criterion 1) that relates to the external validity (generalisability or applicability of the trial) has been retained so that the Delphi list is complete. However, this criterion is not used to calculate the PEDro score reported on the PEDro web site.

The 11 criteria are: specification of eligibility criteria, random allocation, concealment of allocation, similarity between groups at baseline regarding the most important prognostic indicators, subject blinding, blinding of therapist, blinding of assessor, subject follow up, intention-to-treat analysis, between-group statistical comparisons are reported for at least one key outcome, point measure and measure of variability for at least one key outcome. All selected methodological criteria were scored as yes or no, resulting in a range from 0 to 10. The PEDro Scale has shown moderate levels of interrater reliability (intraclass correlation coefficient 0.54, 95% confidence interval (CI) 0.39 to 0.71).[23] To improve the reliability of this scale, any disagreement between the review authors was resolved by discussion with an independent review author (RHHE) until a consensus was reached.

The scale assessed the following criteria:

- Specification of eligibility criteria.
- Random allocation.
- Concealment of allocation.
- Similarity between groups at baseline regarding the most important prognostic indicators.
- Participant blinding.
- Blinding of therapist.
- Blinding of assessor.
- Participants follow up.
- Intention-to-treat analysis.
- Between-group statistical comparisons reported for at least one key outcome.
- Point measure and measure of variability for at least one key outcome.

Grading of evidence

The grading system as described in the 2004 book 'Evidence-based Rheumatology' [24] and recommended by the Musculoskeletal Group was used.

Platinum: a published systematic review that has at least two individual controlled trials each satisfying the following.
• Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
• Blinding of patients and assessors for outcomes.
• Handling of withdrawals >80% follow up (imputations based on methods such as last observation carried forward (LOCF) are acceptable).
• Concealment of treatment allocation.

Gold: at least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported.
• Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
• Blinding of patients and assessors for outcomes.
• Handling of withdrawals >80% follow up (imputations based on methods such as LOCF are acceptable).
• Concealment of treatment allocation.

Silver: a randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomised trial with a 'head-to-head' comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: The bronze ranking is given to evidence if at least one high quality case series without controls (including simple before and after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

Measures of treatment effect

All the trials to be included in the systematic review were entered into Review Manager 4.2. For continuous outcomes (functional ability, range of motion, number of joints with swelling (active joint count), number of joints with pain, quality of life, parent or patient global assessment of overall wellbeing, pain, aerobic capacity and muscle strength), a weighted mean difference between treatment and control groups was calculated, if possible. Dichotomous outcomes (number of side effects, total number of dropouts from study, compliance with therapy, physician and parent global assessment) were described.

The results from the various studies were tested for heterogeneity using the chi-square statistic, with a significance level of P=0.05. Overall effects were only being estimated for groups of trials using the same intervention. As such, several individual meta-analyses were performed. Meta-analyses were conducted according to a fixed-effect model. Where heterogeneity was significant, a random-effects model was used. Potential publication bias was evaluated with the inverted funnel plot technique. A sensitivity analysis was conducted to evaluate the robustness of the meta-analyses. This analysis examined the effects of methodological quality and potential differences in exercise frequency, intensity and duration.

Clinical relevance tables were compiled for pooled outcome measures as additional tables to improve the readability of the review. Weighted absolute change was calculated from the weighted mean difference (WMD) statistic in RevMan when trials using the same scale were pooled. Relative per cent change from baseline was calculated as the absolute benefit divided by the baseline mean of the control group. Since there were no statistically significant outcome measures, the number needed to treat (NNT) was not calculated.

Description of studies

Review authors TT and MvB selected a total of 16 citations of full-length reports and abstracts describing seven controlled exercise therapy trials[25-31] In one case, an article in the German language was obtained; this study was considered for inclusion because the review authors were able to read this language as well. Authors of abstracts were asked for a full-length manuscript. Two authors of abstracts responded to our call.[26,32] However, they were not able to provide a full-length version. Nor could they provide any details because the full-length article was not submitted yet. The author of the third abstract did not reply.[29] Four studies reported in seven controlled trials were identified by the review authors as randomised controlled trials.[25-28] Three out of these four RCTs were included in this review; one was excluded because it was not a full-length article.[26] Following is a brief description of the three remaining studies.

Epps et al.[25] carried out a RCT in which 78 children (43 girls, 35 boys; aged 4 to 19 years) with JIA were randomly allocated to receive a combined (hydrotherapy and land-based physiotherapy) or a land-based (only land-based physiotherapy) training program. The children in both groups received 16 one-hour treatment sessions over two weeks followed by local physiotherapy attendances for two months. Thirty-nine children were allocated to the combined group. The primary outcome measures included improvement in disease status which was calculated from six core outcome measures: CHAQ, physician's global assessment of disease activity, parent's global assessment of overall wellbeing, number of joints with limited range of motion (ROM), number of active joints and erythrocyte sedimentation rate; the secondary outcome measures included health-related quality of life (CHQ-PF50), muscle strength (peak power), cardiovascular fitness (time and maximal heart rate), pain (VAS scale) and patient satisfaction. These parameters were measured at baseline, two-months follow up and six-months follow up. The authors found that: "Two months after intervention 47% patients in the combined group and 61% patients in the land group had improved disease activity with 11 and 5% worsened, respectively". All secondary outcome measures demonstrated a mean improvement in both groups, with the combined group showing greater improvements compared with the land-based group in physical aspects of HRQoL (improvement of 33 versus 28 in the land-based group) and physical fitness.

Singh-Grewal et al.[27] carried out a RCT in which 80 children (43 girls, 35 boys; aged 4 to 19 years) with JIA were randomly allocated to a high-intensity aerobic training program (experimental group) or low-intensity training program (control group). Both groups participated in a 12-week, three times weekly training program consisting of high-intensity aerobics in the experimental group and Qigong in the control group. Forty-one children were allocated to the experimental group. The outcome measures included submaximal oxygen uptake at 3 km/hour ($VO_{2submax}$), maximal oxygen uptake (VO_{2peak}), peak power and functional ability (CHAQ). These parameters were measured at baseline and after completing the training program. The authors found that the exercise program was well tolerated in both groups. There was no difference in $VO_{2submax}$ (P=0.43) or in any other exercise-testing measure between the groups throughout the study period and no indication of improvement. The functional ability (CHAQ) was similar between groups (P=0.80) although the within-group change was statistically significant (mean difference -0.12; P<0.0001) and clinically meaningful in magnitude.

Takken et al.[28] carried out a RCT in which 54 children (38 girls, 16 boys; aged 5 to 13 years) with JIA were randomly allocated to receive a training program consisting of a one hour per week supervised training program for approximately 20 sessions in a local pool or to a control group that received standard medical care assessment only. Twenty-seven children were allocated to the experimental group. The outcome measures included functional ability (CHAQ and JAFAS), health-related quality of life (CHQ), range of motion, joint status and physical fitness. These parameters were measured at baseline, three months after the start and immediately after the end of the training program. The authors found no significant effects on functional ability (P=0.35, P=0.55 for CHAQ and JAFAS, respectively), range of motion (P=0.06), health-related quality of life (P=0.19, P=0.09, P=0.13 for JAQQ, CHQ-PhS and CHQ-PsS, respectively) and physical fitness (P=0.46).

In summary, of the three studies none compared exercise therapy to a placebo, two studies compared exercise therapy to another therapy and one study compared exercise therapy to receiving standard medical care. The excluded studies are described in the 'Characteristics of excluded studies' table, which provides a summary of why studies were excluded from this review. The number of participating children varied from 54 to 80, with a median number of 78. The age range was between 4 years to 19 years of age.

Functional ability, health-related quality of life and aerobic capacity could be pooled for meta-analysis as the same outcome measures were used in the included studies. Heterogeneity in test protocol, test equipment, outcome or failure to report the measures for range of motion, number of joints with swelling, number of joints with pain, parent or patient global assessment of overall wellbeing and pain made pooling of these outcome measurements inappropriate. The exercise therapy programs of the included studies showed a great range in duration and exercise frequency (see table 'Characteristics of included studies'). Moreover, both land-based and pool-based modalities were used.

Methodological quality of included studies

The following PEDro scores were obtained (maximal score=10): Epps et al.[25]: 8, Singh-Grewal et al.[27]: 8, Takken et al.[28]: 7. None of the studies described blinding of the participants or therapists who administered the therapy. Based on the characteristics of the therapy, the included studies were categorised into one of three quality categories as described in the Cochrane Handbook for Systematic Reviews of Interventions version 4.2.5.[21]

The categories were as follows.
Epps et al.[25]: moderate risk of bias due to no blinding of participants or therapists; all other criteria were met.
Singh-Grewal et al.[27]: moderate risk of bias due to no blinding of participants or therapists; all other criteria were met.
Takken et al.[28]: moderate risk of bias due to no blinding of participants, therapists and assessors; all other criteria were met.

The evidence on the outcome measures from the studies of Epps et al.[25], Singh-Grewal et al.[27] and Takken et al.[28] were all graded as silver.

Results

Primary outcomes

Functional ability (pooled)

There was no statistically significant change in functional ability (CHAQ) between exercise and the control (n=198; WMD: -0.07, 95% CI: -0.22 to 0.08). Moreover, no significant differences were observed for studies which used exercise versus standard medical care assessment[33] (P=0.35) or when comparing two different exercise modes.[25, 27] This is expressed by I^2=0 % in the test for heterogeneity between studies. Takken et al.[28] measured functional ability using the JAFAS as well. The scores were very low (a mean score of 0.15 at baseline for the experimental group). The JAFAS scores range from 0 to 2 and a score of 0.15 is very close to the lowest possible score on this instrument. This so called 'floor effect' makes improvement on this instrument almost impossible. The JAFAS showed no significant differences between the groups (P=0.55) (see figure I)

Joint range of motion (descriptive)

There was no statistically significant improvement in joint range of motion between the exercise and control groups. Epps et al.[25] reported a decrease in the number of joints with loss of range of motion after two months follow up in the combined group and in the land group (decrease of five and four joints, respectively); however, this decrease was not statistically significant. Takken et al.[28] also reported no significant changes in range of motion from baseline measurement to immediately after the intervention (P=0.06).
Both groups showed a very small decrease over time (a decrease of 0.02 and 0.07 on the EPROM score in the intervention group and control group, respectively). Singh-Grewal et al.[27] reported that there was no worsening of range of motion (EPMROM) and also no differences between the groups (P=0.35).

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Table II: Characteristics of the included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Epps et al..[25]	CT comparing the effects of combined hydrotherapy programmes vs physiotherapy land techniques. Blinding: subjects and therapists were not blinded; assessors were blinded. Baseline: no significant differences, only difference the distribution of gender between the two groups. Dropouts: 4 dropouts after randomisation.	78 children with JIA (43 girls, 35 boys), aged 4-19 years. 7 children had oJIA, 15 children had extended oJIA, 33 children pJIA, 10 children sJIA, 12 children had enthesitis-related arthritis, and 1 child had psoriatic arthritis with psoriasis. Exclusion: severe systemic disease or any other condition that is unstable, suffering from quotidian fevers, inability to give informed consent or complete questionnaires owing to language barriers, musculoskeletal surgery within previous 6 months, neuromuscular condition which increases muscle tone, received intensive physiotherapy , no access to outpatient physiotherapy or hydrotherapy, and met general hydrotherapy exclusion criteria, such as chlorine allergy.	Patients in the combined and land groups received 16 1-hour sessions of treatment over two weeks followed by physiotherapy attendances for 2 months.	Improvement in disease status Measures: at baseline, after 2-month follow up, and after 6-month follow up.	PEDro-score: 8/10 Rank outcome measures: silver

Table II: Characteristics of the included studies (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Singh-Grewal et al..[27]	RCT comparing the effectiveness of high intensity aerobic training vs low intensity training. Blinding: subjects and therapists were not blinded; assessors were blinded. Baseline: no significant differences, only difference were evident in the distribution of JIA subgroups between the two groups. Dropouts: 10 dropouts after randomisation; 6 from the experimental and 4 from the control group	Patients in the combined and land groups received 16 1-hour sessions of treatment over two weeks followed by physiotherapy attendances for 2 months.	Individualized, prescribed exercise training: 10m walking warm-up; 10m general ROM exercise; 10m stretching; 30m aerobic interval training on treadmills etc.; 10m cooling down; 40-70% functional capacity; 8 weeks; twice a week, in hospital. C: Usual care: cardiac rehabilitation	Improvement in disease status Measures: at baseline, after 2-month follow up, and after 6-month follow up.	PEDro-score: 8/10 Rank outcome measures: silver

Table II: Characteristics of the included studies (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Takken et al.[28]	RCT comparing an aquatic training program vs controls. Blinding: subject, therapist and assessors were not blinded. Baseline: no significant differences. Dropouts: one dropout ; data not excluded from analysis.	54 children with JIA (38 girls, 16 boys), aged 5 -13 years. 23 children had oJIA, 29 children pJIA and 2 children sJIA. Exclusion: a systemic disease with fever, low haemoglobin level and a general feeling of malaise; exercise contraindication by a medical specialist; a recipient of a bone marrow transplant; and not feeling confident in water.	All patients received their usual care and medical treatment during the study. The patients in the experimental group received an aquatic group (2-4 children/ group) exercise program, 1 h a week, supervised by an instructed community physical therapist, for 6 months.	Included outcomes: function ability (CHAQ and JAFAS), Health-related quality of life (JAQQ and CHQ), joint status (pEPMROM), and aerobic capacity (VO_{2peak}, 6-min walking test). Measures: at baseline, 3 months, and 6 months	PEDro-score: 7/10 Rank outcome measures: silver

Number of joints with swelling (descriptive)

None of the included studies reported a statistically significant difference in the number of joints with swelling. Epps et al.[25] reported a decrease in the number of active joints after two-months follow up, in the combined group as well as the land group (a decrease of four and three active joints, respectively). Takken et al.[28] reported that the number of swollen and tender joints decreased in the intervention group (-55%) while the number of swollen and tender joints increased in the control group (+21%). These differences were almost statistically significant (P=0.07). Singh-Grewal et al.[27] reported no significant changes in active joint count between the groups (P=0.41).

Number of joints with pain (descriptive)

None of the included studies[25,27,28] measured the number of joints with pain.

Health-related quality of life (pooled)

All outcome measures of health-related quality of life indicated that there was no clinically important or statistically significant change in health-related quality of life between exercise and control groups (CHQ-PhS: n=115; WMD: -3.96, 95% CI: -8.91 to 1.00; CHQ-PsS: n=112; WMD: 2.57, 95% CI: -0.69 to 5.82; JAQQ: n=54; SMD: 0.33, 95% CI: -0.20 to 0.87; QoL: n=70; SMD: 0.17, 95% CI: -0.30 to 0.64). Moreover, no significant differences for both CHQ outcome measures (P=0.09, P=0.13 for CHQ-PhS and CHQ-PsS, respectively) were observed between studies which used exercise versus standard medical assessment as control[28] or when comparing two different exercise modes.[25] This is expressed with I^2=0% in the test for heterogeneity between the studies. Both JAQQ[28] and QoL[27] did not show any significant effects of the intervention over control or a different exercise mode (P=0.19 and P=0.47, respectively).

Parent or patient global assessment of overall wellbeing (descriptive)

None of the included studies measuring parent or patient global assessment of overall wellbeing reported a statistical significant difference. Epps et al.[25] reported a decrease in scores on the VAS-scale for parent global assessment of overall wellbeing after two months follow up in the combined group as well as in the land group (decrease of 6 mm and 7 mm, respectively). Singh-Grewal et al.[27] and Takken et al.[28] did not measure parent or patient global assessment in their studies.

Pain (descriptive)

None of the included studies measuring pain reported a significant decrease. Epps et al.[25] reported no significant decrease in pain, the change in pain was negligible. The pain score was decreased by 0.6 mm (on a 10 cm VAS scale) in the land group and increased by 7.3 mm in the combined exercise group. Singh-Grewal et al.[27] reported low levels of pain on a 10 cm VAS scale during training sessions. The differences were not different between the two groups (median 0, range 0 to 10 in both groups; P=0.09). Takken et al.[28] did not measure pain in their study.

Adverse outcomes

All included studies assessed possible adverse outcomes; however, none of these studies reported negative effects of the exercise therapy.

Dropouts

Epps et al.[25] reported a total of six dropouts after randomisation. Four patients did not complete a two-month assessment, two withdrew and two were lost to follow up. Two children could not be entered into the primary analysis because the preliminary definition of disease improvement was inconclusive. Therefore, 72 of 78 potential data sets were available for primary analysis. Singh-Grewal et al.[27] reported a total of 10 dropouts after randomisation: six children from the experimental group and four from the control group. In the experimental group, four dropped out before and two after baseline testing. In the control group, one dropped out before and three after baseline testing. All reported a lack of time as the reason for dropping out.

Takken et al.[28] reported one dropout during the training program; one boy stopped the training program after 15 sessions. Since he met the 75% criteria of 20 sessions, his data were not excluded from analysis.

Secondary outcomes

Aerobic capacity (pooled)

There was no statistically significant change in aerobic capacity (VO_{2peak}) between the exercise and control groups (n=124; WMD: 0.04, 95% CI: -0.11 to 0.19). Moreover, no significant differences were observed for studies which used exercise versus standard medical care assessment (P=0.46)[28] or when comparing two different exercise modes (P=0.35).[27] This is expressed with I^2= 0% in the test for heterogeneity between the studies. Epps et al.[25] did not measure VO_{2peak} in her study.

Muscle strength (descriptive)

Epps et al.[25] reported a small increase in the three muscle groups, in both groups, but none of the increases were statistically significant (P values were not provided). Singh-Grewal et al.[27] and Takken et al.[28] did not measure muscle strength in their studies.

Compliance with exercise (descriptive)

Epps et al.[25] reported that four patients did not complete a two-month assessment, two withdrew and two were lost to follow up. Singh-Grewal et al.[27] reported that completion of training sessions was 78% in the control group and 56% in the experimental group. An average of two sessions per week was completed by the experimental participants and 1.7 sessions by the control participants. The difference was most apparent in the number of home-based sessions. Takken et al.[28] reported that the children attended a mean number of 19.6 ± 3.9 out of 20 training sessions.

Pooled outcome measures were also given in clinical relevance tables, where possible (see Additional Table 01; Table 02; Table 03; Table 04).

Review: Exercise therapy in juvenile idiopathic arthritis
Comparison: Functional ability
Outcome: CHAQ

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Quality
Epps et al.[25]	38	-0.20(0.68)	36	-0.01(0.75)		21.30	-0.19 (-0.52, 0.14)	A
Singh-Grewal et al.[27]	35	-0.12(0.43)	35	-0.11(0.40)		60.08	-0.01 (-0.20, 0.18)	A
Takken et al.[28]	27	-0.18(0.50)	27	-0.05(0.78)		18.62	-0.13 (-0.48, 0.22)	A
Total (95% CI)	100		98			100.00	-0.07 (-0.22, 0.08)	

Test for hetrogeneity: Chi^2= 1.00, df= 2 (P=0.61), I^2=0%
Test for overall effect: Z= 0.92 (P=0.36)

-1.0 -0.5 0 0.5 1.0
Favours treatment Favours control

Figure I: Forrest plot functional ability (CHAQ).

Review: Exercise therapy in juvenile idiopathic arthritis
Comparison: Quality of life
Outcome: CHQ-PhS

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Quality
Epps et al.[25]	33	2.70(15.50)	28	4.00(14.70)		42.60	-1.30 (-8.89, 6.29)	A
Takken et al.[28]	27	-4.08(9.50)	27	1.85(14.50)		57.40	-5.93 (-12.47, 0.61)	A
Total (95% CI)	60		55			100.00	-3.96 (-8.91,1.00)	

Test for hetrogeneity: Chi^2= 0.82, df= 1 (P=0.37), I^2=0%
Test for overall effect: Z= 1.57 (P=0.12)

-100 -50 0 50 100
Favours treatment Favours control

Figure II: Forrest plot quality of life (CHQ-PhS).

Review: Exercise therapy in juvenile idiopathic arthritis
Comparison: Quality of life
Outcome: CHQ-PsS

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Quality
Epps et al.[25]	30	1.20(10.10)	28	-0.70(11.10)		35.30	1.90 (-3.57, 7.37)	A
Takken et al.[28]	27	3.34(6.40)	27	0.41(8.60)		64.70	2.93 (-1.11, 6.97)	A
Total (95% CI)	57		55			100.00	2.57 (-0.69, 5.82)	

Test for hetrogeneity: Chi^2= 0.09, df= 1 (P=0.77), I^2=0%
Test for overall effect: Z= 1.55 (P=0.12)

-10 -5 0 5 10
Favours contol Favours treatment

Figure III: Forrest plot quality of life (CHQ-PsS).

Review: Exercise therapy in juvenile idiopathic arthritis
Comparison: Quality of life
Outcome: JAQQ and QoL (VAS)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Quality
JAQQ								
Takken et al.[28]	27	1.80(5.40)	27	-0.04(5.50)		43.28	0.33 (-0.20, 0.87)	A
Subtotal (95%CI)	27		27			43.28	0.33 (-0.20, 0.87)	
Test for hetrogeneity: not applicable								
Test for overall effect: Z= 1.21 (P= 0.22)								
QoL								
Singh-Grewal et al.[27]	35	-0.20(1.50)	35	-0.50(1.90)		56.72	0.17(-0.30, 0.64)	A
Subtotal (95%CI)	35		35			56.72	0.17(-0.30, 0.64)	A
Test for hetrogeneity: not applicable								
Test for overall effect: Z= 0.72 (P= 047)								
Total (95% CI)	62		62			100.00	0.24 (-0.11,0.60)	
Test for hetrogeneity: Chi^2= 0.19, df= 1 (P=0.66), I^2=0%								
Test for overall effect: Z= 1.34 (P=0.18)								

-1.0 0.5 0 0.5 1.0
Favours control Favours treatment

Figure IV: Forrest plot quality of life (JAQQ and QoL).

Review: Exercise therapy in juvenile idiopathic arthritis
Comparison: Aerobic capacity
Outcome: VO_{2peak}

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Quality
Singh-Grewal et al.[27]	35	-0.10(0.45)	35	-0.10(0.50)		42.63	0.00(-0.22, 0.22)	A
Takken et al.[28]	27	0.00(0.37)	27	-0.07(0.35)		57.37	0.07(-0.12, 0.26)	A
Total (95% CI)	62		62			100.00	0.04(-0.11, 0.19)	
Test for hetrogeneity: Chi^2= 0.22, df= 1 (P=0.64), I^2=0%								
Test for overall effect: Z= 0.54 (P=0.59)								

-1.0 -0.5 0 0.5 1.0
Favours control Favours treatment

Figure V: Forrest plot aerobic capacity (VO_{2peak}).

Discussion

This review analysed the results of three randomised controlled trials (RCTs) for the effectiveness of exercise therapy in children with JIA. By applying strict selection criteria for inclusion, only full-length reports of randomised controlled trials were included. All three trials met at least seven criteria on the PEDro scale. Due to the nature of the interventions, the criteria 'patient blinded' and 'care provider blinded' could not be scored. Therefore, a score of eight might be considered as the best score possible in this kind of intervention studies. Evidence on the outcome measures in the included studies were all graded as 'silver' according to the grading system described by Tugwell et al.[21]

The trends for the outcome measures functional ability, joint range of motion, number of joints with swelling, health-related quality of life and aerobic capacity were similar. These outcome measures were all in favour of treatment changes but were not statistically significant. Functional ability, health-related quality of life and aerobic capacity were the only outcome measures which could be pooled into a meta-analysis and, therefore, could be used to provide stronger evidence compared to the other outcome measures. Importantly, all outcome measures reported no worsening with exercise therapy in the short term. The study of Takken et al.[28] showed a decrease in the number of joints with swelling after aquatic fitness training; this was the only study where improvements almost reached statistical significance. The randomised design also allowed controlling for maturation and developmental effect on the outcome measures such as functional ability, health-related quality of life, aerobic capacity and muscle strength.

The size of the improvement on functional ability (CHAQ) in the pooled data (n=231) is still clinically irrelevant when compared with the results of the study of Dempster et al.[34], who state that the minimal clinical important improvement on the CHAQ is a reduction in score of 0.13. Our meta-analysis showed an average reduction of 0.07 and can not be considered clinically relevant. The CHAQ has been demonstrated to suffer from a floor effect whereby scores are clustered at the normal end of the scale, or near 0.[35-37] This floor effect is also observed in this review and, therefore, might explain the missing significant improvement with exercise therapy.

Results for pain were contradictory. In the study of Epps et al.[25], the pain score was marginally decreased in the land-based group but increased in the combined group. Because these differences were small (7.9 mm on a VAS scale from 0 to 100 mm) it is hard to determine if these changes could be explained by the different types of training or by measurement errors of the outcome measure. The study of Singh-Grewal et al.[27] showed low levels of pain in both therapies. It is important to note that none of the participants of the included studies withdrew because of pain during exercise therapy. Parent or patient global assessment of overall wellbeing and muscle strength was only described in the study of Epps et al.[25] The evidence on this outcome measure is, therefore, inconclusive. The evidence in support of the effectiveness of exercise therapy on the number of joints with pain is also inconclusive as none of the included studies described this outcome measure in detail.

The excluded studies found comparable results for functional ability[33,38], health-related quality of life[33, 38] and aerobic capacity.[32, 38] However, none of the studies reported improvements. Pain scores reported in the excluded studies[16,32,38] did not show increases in pain. Furthermore, none of the excluded studies described the parent or patient global assessment of overall wellbeing or the number of joints with pain.

The following findings in the excluded non-RCT studies were in contrast with the findings in the included RCT studies: the number of joints with swelling[14, 16, 29], muscle strength[31, 32] and joint ROM.[13, 39] The study of Baldwin et al.[14] reported, despite the lack of data, that the changes in the number of joints with swelling were not statistically significant.

The studies of Moncur et al.[29] and Klepper et al.[16] both reported a significant decrease in the joint count after intervention. The studies of Fisher et al.[32] and Öberg et al.[31] reported muscle strength before and after intervention. Both studies reported significant increases in quadriceps strength; Fisher et al.[32] also reported a significant increase in hamstring strength. Both studies only studied two muscle groups. The studies of Bacon et al.[13] and Latzka et al.[39] both reported significant improvements in joint ROM but only described a few joints.

The strength of this review lies in its rigorous methods, which include thorough grading of evidence, systematic appraisal of study quality and, where possible, the use of meta-analysis. However, its main limitation is the

low number of available RCTs. There were only seven controlled trials of exercise therapy for JIA found, of which three with a total number of 212 participants could be included. Because there are few RCTs, indirect methods of identifying publication bias such as funnel plots are of limited value and were not conducted. The limited number of studies, participants, and the heterogeneity of interventions and outcome measures limits the precision of the results of this review. Consequently, it also means that a single unidentified trial, or further trials, could have a substantial effect on the results and conclusions.

Overall, exercise therapy did not result in significant effects on functional ability, health-related quality of life, aerobic capacity or pain. However, the low number of available RCTs limits the generalisability. The included and excluded studies are all consistent about adverse effects of exercise therapy; no short-term detrimental effects of exercise therapy were found in any of the studies. Both the included and excluded studies showed that exercise does not exacerbate the arthritis. The large heterogeneity in outcome measures, as seen in this review, emphasises the need for a standardised assessment or a core set of functional and physical outcome measurements suited for health research to generate evidence about the possible effects of physical exercise for children with JIA. Despite the short-term results of the intervention studies, the long-term effect of exercise therapy remains unclear and warrants further research.

Reviewers' conclusions

Implications for practice

Nowadays, exercise therapy is increasingly studied as treatment in childhood and juvenile arthritic conditions. This current review shows that the lack of statistically significant differences between intervention and control groups makes it difficult to conclude whether exercise therapy can be recommended as an effective treatment for JIA. Important to know is that both the included and the excluded studies were consistent about adverse effects of exercise therapy. None of the studies found short-term detrimental effects of exercise therapy.

Implications for research

The evidence regarding the efficacy of exercise therapy is drawn from a small number of randomised controlled trials. There was limited uniformity of outcome measures which limited the ability to pool data for a reliable meta-analysis. The large heterogeneity in outcome measures, as is seen in this review, emphasises the need for a standardised assessment or a core set of functional and physical outcome measurements suited for health research to generate evidence about the possible benefits of exercise therapy for children with JIA, and only then can the true importance of exercise therapy be stated.

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Appendix

The search strategy is developed in co-operation with the Cochrane Musculoskeletal Review Group and combines a search string for the population, trials, and intervention (this is the search strategy for the CENTRAL database, and is adapted to the other electronic databases).

Patients	23.Arthritis, Juvenile Rheumatoid.sh 24.Arthritis, Juvenile Chronic.tw 25.Arthrit$, Juvenile.tw 26.Arthrit$.tw 27.Child$.tw 28.Adolescence.tw 29.Child, Preschool.tw 30.Adult 31.or/23-26 32.31 not 30 33.or/27-29 34.32 and 33

Trials	1.randomized controlled trial.pt. 2.controlled clinical trial.pt. 3.randomized controlled trials.sh. 4.random allocation.sh. 5.double blind method.sh. 6.single blind method.sh. 7.1 or 2 or 3 or 4 or 5 or 6 8.(animal not (human and animal)).sh. 9.7 not 8 10.clinical trial.pt. 11.exp clinical trials/ 12.(clin$ adj25 trial$).ti,ab. 13.((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 14.placebos.sh. 15.placebo$.ti,ab. 16.random$.ti,ab. 17.research design.sh. 18.volunteer$.ti,ab. 19.10 or 11 or 12 or 12 or 13 or 14 or 15 or 16 or 17 or 18 20.19 not 8 21.20 not 9 22.9 or 21

Therapy	35.physical therapy.sh. 36.physical$.tw. 37.physio$.tw. 38.exercise.sh. 39.exercis$.tw. 40.rehabilitation.sh. 41.rehabilitation$.tw. 42.strengthening.tw. 43.hydro therapy.tw. 44.balneo therapy.tw. 45.spa therapy.tw. 46.water therapy.tw. 47.thalasso therapy.tw.

5
Chapter

Aerobic and anaerobic exercise capacity in children with juvenile idiopathic arthritis

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Abstract

Objective

To compare the aerobic and anaerobic exercise capacity of children with juvenile idiopathic arthritis (JIA) with healthy controls, to determine if there were differences based on disease onset type, and to examine the relationship between aerobic and anaerobic exercise capacity in children with JIA.

Methods

Sixty-two patients with JIA (mean ± SD age 11.9 ± 2.2 years, range 6.7–15.9) participated in this study. Aerobic exercise capacity was measured using a cardiopulmonary exercise test. Anaerobic exercise capacity was measured using the Wingate Anaerobic Exercise Test (WAnT).

Results

All patients were able to perform the cardiopulmonary exercise test and WAnT without adverse events. On average, the maximal oxygen uptake (VO_{2peak}) and $VO_{2peak/kg}$ were 69.8% and 74.8%, respectively, of that predicted compared with healthy controls. Mean ± SD power was 66.7% ± 37.2% of that predicted compared with healthy children. Mean ± SD peak power was 65.5% ± 43.1% of that predicted compared with healthy children. There were significant differences between subgroups of JIA; the oligoarticular-onset group values did not significantly differ from healthy control values; the polyarticular rheumatoid factor positive–onset subgroup had the greatest impairment in both aerobic and anaerobic exercise capacity. The correlations of mean power and peak power with VO_{2peak} were r=0.884 and r=0.697, respectively ($P<0.05$).

Conclusion

This study demonstrates that both the aerobic and anaerobic exercise capacity in children with JIA are significantly decreased. The WAnT might be a valuable adjunct to other assessment tools in the follow-up of patients with JIA.

Introduction

Children with juvenile idiopathic arthritis (JIA) are believed to have a lower aerobic capacity, anaerobic capacity, and functional ability, which means that they have more problems in performing daily activities compared with healthy children.[1] These lower parameters could lead to a more inactive lifestyle. Nonetheless, the manifestations of the disease such as chronic joint pain and stiffness, synovitis, and deformity are also thought to aggravate an inactive lifestyle.[2,3] The aerobic capacity in children with JIA has been studied extensively in recent years.[4–12] Most of these studies suggest that patients with JIA have impairment in aerobic fitness[13], but little is known about the anaerobic capacity of children with JIA.[10,14-17] Anaerobic capacity is important because most daily activities performed by children are anaerobic in nature. In a study by Takken et al.[15], a large association between anaerobic physical fitness and functional ability demonstrated the importance of anaerobic physical fitness for children with JIA. Malleson et al.[10] compared anaerobic fitness of a group of children with chronic arthritis with that of healthy controls and found no significant differences between mean peak anaerobic power for patients and controls; however, the mean values for both controls and patients were significantly lower than reported values for healthy children.[10] Fan et al.[16] and Wessel et al.[17] studied children with JIA during a 50-meter run and found reduced sprint ability compared with healthy peers. Fisher et al.[18] found that children with JIA could improve muscle strength significantly after an exercise training program, without increase in disease signs and symptoms.

The current evidence base for anaerobic exercise capacity is small and is derived from findings in small cohorts. In the current study, we aimed to increase the evidence basis for both aerobic and anaerobic exercise capacity and their interrelationship. We therefore studied 1) the aerobic and anaerobic exercise capacity of a large cohort of patients with JIA and compared these with healthy controls, 2) if there were differences in aerobic and anaerobic exercise capacity in children with JIA based on disease onset type, and 3) the relationship among aerobic and anaerobic exercise capacity in children with JIA.

Patients and Methods

Patients

Sixty-two patients with JIA participated in this study. The patients were recruited from the paediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital and were diagnosed with JIA according to the International League of Associations for rheumatology (ILAR) criteria.[19] Thirty-six patients had polyarticular-onset JIA (29 rheumatoid factor negative and 7 rheumatoid factor positive), 11 patients had oligoarticular-onset JIA, 8 patients were classified as having extended oligoarticular-onset JIA, and 7 patients were classified as having systemic-onset JIA. Fifteen patients in the cohort were off medication. Of the remaining patients, 41 patients were receiving nonsteroidal antiinflammatory drugs, 28 were receiving disease-modifying antirheumatic drugs, 6 were receiving corticosteroids, and 7 were receiving biologic agents (biologic response modifiers). Disease onset and duration were assessed by retrospective analysis of patients' files. During the tests, 35 patients had active disease, 12 patients were in clinical remission and taking medication, and 15 patients were in clinical remission and off medication, according to criteria developed by Ruperto and Martini.[20] All tests and measurements of the patients were performed on the same day, with enough resting time between the aerobic and anaerobic exercise tests. Informed consent was obtained from the parents and/or from the children if they were >12 years of age. The Medical Ethics Committee of the University Medical Center Utrecht approved all study procedures.

Anthropometry

The children's body mass and height were determined using an electronic scale and a stadiometer, respectively. Body mass index (BMI) was calculated as body mass (kg)/height (m^2). The BMI of the included children was compared with reference values of healthy Dutch children[21] and with international cut-off points for BMI for overweight and obese children.[22] Subcutaneous adiposity was determined from skinfold measurements using Harpenden skinfold calipers (British Indications, St. Albans, Hertfordshire, UK). Measurements were obtained in triplicate at 7 sites (at the right side of the body): triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf, and

thigh in accordance with the American College of Sports Medicine guidelines [23]. The sum of the 7 skin folds was used as an index for subcutaneous fat according to methods described by Pollack et al.[24]

Joint status

Joint status was assessed by the number of tender and swollen joints. Tenderness and swelling were scored for the following joints: temporomandibular, sternoclavicular, shoulder, elbow, wrist, metacarpophalangeal and fingers, knee, ankle, metatarsophalangeal, and toes. Joint mobility was scored on the Pediatric Escola Paulista de Medicina Range of Motion Scale (pEPMROM).[25] The pEPMROM measures mobility in children with JIA based on the evaluation of joint range of motion. Ten joint movements (cervical spine [rotation], shoulder [abduction], wrist [flexion and extension], thumb [flexion metacarpophalangeal], hip [internal and external rotation], knee [extension], and ankle [dorsiflexion and plantar flexion]) were examined using a goniometer and were classified on a 4-point Likert scale ranging from 0 to 3 (0 = no limitation and 3 = severe limitation). The final score was calculated as the sum of the joint score of each movement divided by 10, providing a final range of scores for joint movement from 0 to 3.

Functional ability

The Childhood Health Assessment Questionnaire (CHAQ) was adapted by Sing et al.[26] from the Stanford Health Assessment Questionnaire for use in patients' ages 1–19 years, and measures functional status. A Dutch version was translated and validated.[27] The CHAQ is a paediatric multidimensional questionnaire, which measures the child's ability in performing functions included in 8 areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) for a total item number of 30. Respondents are directed to note only those difficulties caused by arthritis. Each question is scored from 0 to 3 (0 = able to do with no difficulty, 1 = able to do with some difficulty, 2 = able to do with much difficulty, 3 = unable to do). The question with the highest score within each domain determined the score for that domain. Whenever aids or assistance were required, the score for that domain was increased to a minimum of 2. The mean of the scores on the 8 domains provided the CHAQ disability scale (range 0–3, with 0 denoting no disability and 3 denoting severe disability). The CHAQ also incorporates a

double-anchored, horizontal, 10-cm visual analog scale for the assessment of the child's overall well-being and a visual analog scale for the assessment of the intensity of the child's pain.

Cardiopulmonary exercise test

The maximal oxygen uptake (VO_{2peak}) attained during a graded exercise test to volitional exhaustion is considered the single best indicator of aerobic physical fitness. Cardiopulmonary exercise test was performed on an electronically braked cycle ergometer (Lode examiner; Lode BV, Groningen, The Netherlands). The seat height was adjusted to the patient's comfort. Cycling started at a workload of 0W and the workload was increased by 20W every minute until the patient stopped due to volitional exhaustion, despite strong verbal encouragement. Patients breathed through a mouth piece that was connected to a calibrated metabolic cart (Oxycon Champion; Jaeger, Viasys, Bilthoven, The Netherlands). Expired gas was passed through a flow meter, oxygen analyzer, and carbon dioxide analyzer. The flow meter and gas analyzer were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio from conventional equations. Heart rate was measured continuously during the maximal exercise test with a 3 lead electrocardiogram.

Wingate Anaerobic Exercise Test

The Wingate Anaerobic Test (WAnT), as described by Bar-Or[28], was performed on a calibrated electromagnetic braked cycle ergometer (Lode Examiner; Lode BV). The ergometer was upgraded and calibrated by the manufacturer to a maximum resistance of 800W instead of the standard 400W. External resistance was controlled, the power output was measured, and mean power and peak power were calculated from the exercise results using the Lode Wingate software package (Lode BV, Groningen, The Netherlands). The seat height was adjusted to patients' leg length (comfortable cycling height). The external load (torque; in Nm) was determined by body weight (at 0.53 x body weight and 0.55 x body weight for girls and boys, respectively, <14 years of age and 0.67 x body weight and 0.7 x body weight for older girls and boys, respectively) according to the user manual. The patients' feet were placed in the Velcro toe straps and the exercise protocol was explained. The patients

were instructed to exercise for 1 minute with the cycle ergometer with an external load of 15W at 50–60 revolutions per minute. Thereafter the sprint protocol started. The patients were instructed to cycle as fast as possible for 30 seconds. Power output during the WAnT was corrected for the inertia of the mass of the flywheel (23.11kg·m^{-2}). Measured variables were mean power and peak power. Mean power represents the average power output over the 30-second sprint. Peak power is the highest recorded power output achieved during the 30-second sprint and represents the explosive characteristics of a person's muscle power. Recent data indicated that the WAnT could be reliably assessed in children with JIA.[29] The anaerobic exercise capacity of the patients with JIA was compared with age-, weight-, and sex-matched reference values obtained from 50 healthy Dutch children and adolescents as has been reported previously.[30] The subjects were recruited from family members of staff at our hospital or were living in the neighborhood of our hospital. All controls were tested following the same protocol as the patients.

Statistical analysis

Statistical analyses were performed using the statistical Package for the Social Sciences for Windows (version 12.0; SPSS, Chicago, IL). Variables were expressed as the mean ± SD and range; statistical comparisons between measurements were made using the Student's T-test. The data were also expressed as the percentage of impairment compared with reference values, because of the large ranges in age. Spearman's correlations were used to calculate possible correlations between the aerobic and anaerobic capacity. The level of statistical significance was set at P=<0.05.

Results

Fifteen boys and 47 girls were included in this study. The mean ± SD age of the patients was 11.9 ± 2.2 years with a range of 6.7–15.9 years. Mean ± SD age at disease onset and duration were 6.6 ± 3.6 years (range 0.5–15.3 years) and 4.7 ± 3.2 years (range 0.4–11.8 years), respectively. The anthropometric values are shown in Table I.

Table I: Characteristics of patients with juvenile idiopathic arthritis and controls

Characteristics	**Patients**			**Controls**			
	Mean	SD	Range	Mean	SD	Range	P-value
Age (years)	11.9	2.2	6.7-15.9	12.3	2.5	7.9-16.8	0.469
Body Mass (kg)	44.5	14.4	22.0-81.0	45.1	13.4	24.1-81.7	0.748
Height (meters)	1.53	0.14	1.24-1.83	1.57	0.14	1.29-1.91	0.278
BMI (kg/m^{-2})	18.7	3.7	13.2-28.2	18.0	2.6	13.8-26.5	0.613
Σ7SF(mm)	103.2	46.5	41.3-240.3	85.3	35.0	44.2-175.0	< 0.0001
pEPMROM	0.3	0.3	0.0-1.3				
Swollen Joints	3.0	4.6	0.0-24.0				
CHAQ	0.7	0.7	0.0-2.5				
Disease onset (years)	6.6	3.6	0.5-15.3				
Disease duration (years)	4.7	3.2	0.4-11.8				

Values are the mean ± SD (range) unless otherwise indicated. Abbreviations: BMI: Body Mass Index; Σ7SF: sum of 7 skin folds; pEPMROM: Pediatric Escola Paulista de Medicina Range of Motion Scale; CHAQ: Childhood Health Assessment Questionnaire.

The mean body mass of the patients was 44.5 ± 14.4 kg (range 22.2–81.0 kg), the mean height was 1.53 ± 0.14 meters (range 1.24–1.83 meters), and mean BMI was 18.7 ± 3.7 kg/m^2 (range 13.2–28.2 kg/m^2). The mean sum of the 7 skinfold measurements was 103.2 ± 46.5 mm (range 41.3–240.3 mm). The sum of the 7 skinfold measurements of the children with JIA was significantly higher (P<0.0001) compared with healthy controls. The anthropometric parameters of the patients indicated that none of the patients were obese and 10 patients were overweight, although mean BMI and weight values did not differ from reference values. The results of joint status, joint mobility, and functional ability are shown in Table I. The patients had a mean ± SD of 3.0 ± 4.6 tender and swollen joints (range 0.0–24.0) and a mean pEPMROM

score of 0.3 ± 0.3 (range 0.0–1.3), indicating that the cohort had almost no limitation due to active synovitis. The mean ± SD CHAQ score of the patients was 0.7 ± 0.7 (range 0.0–2.5), indicating mild-to-moderate disability [31]. The results of aerobic and anaerobic exercise tests are depicted in Table II.

Table II: Aerobic and anaerobic exercise capacity of patients with JIA and controls*

	JIA	Controls	% of predicted	P value
VO_{2peak} (L·min)	1.5 ± 0.5	2.2 ± 0.7	69.8 ± 23.6	<0.0001
Boys	1.8 ± 0.7	2.3 ± 0.7	77.1 ± 30.6	0.01
Girls	1.4 ± 0.4	2.1 ± 0.8	67.6 ± 20.8	<0.0001
$VO_{2peak/kg}$($ml \cdot kg^{-1} \cdot min^{-1}$)	34.6 ± 8.0	49.1 ± 8.0	74.8 ± 16.6	<0.0001
Boys	39.2 ± 7.1	53.3 ± 7.0	73.6 ± 13.4	<0.0001
Girls	33.1 ± 7.7	44.1 ± 6.1	75.1 ± 17.6	<0.0001
Mean Power (Watt)	250.3 ± 137.1	370.4 ± 177.5	66.7 ± 37.2	<0.0001
Boys	286.1 ± 189.9	360.4 ± 173.8	79.4 ± 52.7	0.15
Girls	238.7 ± 115.3	381.7 ± 185.3	62.5 ± 30.2	<0.0001
Peak Power (Watt)	423.1 ± 275.3	635.0 ± 328.0	65.5 ± 43.1	<0.0001
Boys	464.5 ± 338.3	615.0 ± 327.7	75.5 ± 55.0	0.11
Girls	409.9 ± 254.8	657.7 ± 334.3	62.3 ± 38.7	<0.0001

* Values are the mean ± SD unless otherwise indicated. JIA=juvenile idiopathic arthritis; VO_{2peak}=maximal oxygen uptake; $VO_{2peak/kg}$=maximal oxygen uptake corrected for body mass.

All children were able to complete the aerobic and anaerobic exercise test without adverse effects, such as dizziness, fainting, or even vomiting. VO_{2peak} was on average 77.1% ± 30.6% and 67.6% ± 20.8% of that predicted for boys and girls, respectively. $VO_{2peak/kg}$ was on average 73.6% ± 13.4% and 75.1% ± 17.6% of that predicted for boys and girls, respectively. The anaerobic capacity was <67% of that predicted for both peak power and mean power compared with the healthy controls. Mean power was on average 79.4% ± 52.7% and 62.5% ± 30.3% of that predicted for boys and girls, respectively. Peak power was on average 75.5% ± 55.0% and 62.3% ± 38.7% of that predicted for boys and girls, respectively. The differences between boys and girls were statistically significant for VO_{2peak} (P=0.023) and for $VO_{2peak/kg}$ (P= 0.009). The children in remission (off medication) also had lower aerobic and anaerobic exercise capacity than controls. The VO_{2peak} and $VO_{2peak/kg}$ were 69.8% (P<0.0001) and 74.8% (P<0.0001) of that predicted, respectively. The mean power and peak power were 60.4% (P<0.0001) and 49.3% (P<0.0001) of that predicted, respectively. There was no difference in aerobic and

anaerobic exercise capacity between the children in remission and the children receiving medication. It is noteworthy to mention that 95% of all patients (n=59) had an impaired aerobic exercise capacity and 94% (n=58) had an impaired anaerobic capacity. The outcomes of the aerobic and anaerobic capacity for the different subtypes in this study are shown in Table III as additional findings. Table IV shows that there were significant correlations between the impairments of the mean power, peak power, and VO_{2peak}.

Tabel III. Outcome values (% of predicted) of aerobic and anaerobic capacity for the different subgroups of JIA*

Subgroup JIA	Mean Power	Peak Power	VO_{2peak}	$VO_{2peak/kg}$
Polyarticular RF^-	64.4 (29.5)†	64.7 (41.5) †	65.2 (19.9) †	70.2 (14.8) †
Polyarticular RF^+	52.5 (38.2) †	48.4 (41.1) †	52.8 (22.3) †	62.5 (8.4) †
Oligoarticular	94.8 (55.3)	94.4 (57.8)	89.3 (32.6)	78.8 (16.9) †
Oligoarticular extended	57.2 (23.4) †	52.7 (26.1) †	68.3 (14.6) †	75.7 (21.1) †
Systemic	64.7 (27.9) †	65.2 (30.7) †	64.5 (19.7) †	60.3 (1.8) †

* Values are the mean ± SD. RF^+=rheumatoid factor positive; RF^-=rheumatoid factor negative; see Table II for additional definitions. † Significant different ($p<0.05$) from reference values.

Table IV: Pearson's correlations (r) between VO_{2peak}, $VO_{2peak/kg}$, Mean Power and Peak Power*.

	VO_{2peak}	$VO_{2peak/kg}$	Mean Power	Peak Power
VO_{2peak}		0.422†	0.884†	0.697†
$VO_{2peak/kg}$			0.085	0.039
Mean Power				0.940†
Peak Power				

*See Table II for definitions.
† $P<0.01$.

Discussion

The goal of this study was to compare the aerobic and anaerobic exercise capacity of children with JIA with that of age-, weight-, and sex-matched healthy controls; to determine if there were differences in aerobic and anaerobic exercise capacity in children with JIA based on disease onset type; and to examine the relationship among aerobic and anaerobic exercise capacity in children with JIA. The results show a significantly decreased aerobic as well as anaerobic capacity in children with JIA compared with healthy controls. The decreased aerobic capacity is in line with earlier findings by our group[5] and by others[4,13] and has been discussed extensively. In the current study, anaerobic capacity was expressed by means of peak power and mean power, which demonstrated that most of the children with JIA had a significantly lower anaerobic capacity compared with healthy children. Our study is the first to assess anaerobic exercise capacity in a large cohort of children with JIA compared with a healthy control group. Lower anaerobic capacity was also found in the results of the study by Lelieveld et al.[32] in which the mean power in a group of adolescent patients with JIA was on average 88% and 74% of that predicted for adolescent boys and adolescent girls, respectively, compared with healthy controls. The peak power was on average 92% and 67% of that predicted for adolescent boys and adolescent girls, respectively. In both our study and that of Lelieveld et al.[32], distinctive sex differences were found; girls were more impaired than boys in anaerobic fitness.

Within the different subgroups of JIA it is noticeable that the oligoarticular-onset group values did not significantly differ from healthy control values, and that the polyarticular rheumatoid factor positive–onset subgroup had the greatest impairment in both aerobic and anaerobic exercise capacity. These findings indicate that it is important to also distinguish the different subgroups of JIA in relation to anaerobic outcome parameters because this parameter can show great differences within the entire JIA cohort. This severe impairment in the polyarticular rheumatoid factor positive subgroup in relation to both aerobic and anaerobic exercise capacity has never been described before and could be a subject for further research. The higher rate of joint impairment and joint destruction that is prevalent in polyarticular rheumatoid factor positive JIA according to most textbooks[33] could be a determining factor. The longer duration of joint disease in polyarticular cases

could be another factor of influence; these and other factors should be subject to further research.

During the WAnT, 80% of energy turnover is derived from anaerobic alactic and lactic acid metabolism dominated by glycolysis; therefore the WAnT is highly anaerobic[34] and is not primarily affected by aerobic fitness. Limitations in the WAnT are more peripheral in nature.

Chronically sick children often display a subnormal exercise capacity. This could be explained by 2 main causes: first by hypoactivity, which leads to detraining, and second by specific pathophysiologic factors that limit 1 or more exercise-related functions.[35]

Arthritis in childhood may result in significant muscular deficits.[36–40] Localized muscle weakness and atrophy around inflamed joints, secondary to disuse, are common in children with joint disease, and may persist long after the resolution of the arthritis.[11,38] Giannini and Protas[37] found significantly reduced isometric quadriceps strength in children with JIA compared with healthy controls. Lindehammar et al.[39,40] assumed that muscle weakness is in part caused by atrophy of the muscle, which is influenced by local arthritis. The presence and intensity of local arthritis is an important factor affecting muscle function in patients with JIA.[40] Muscle weakness may result from disuse, because a smaller or deconditioned muscle has a lower cross-sectional area to generate force.[41] The sum of skinfold measurements was significantly higher in the JIA group than in controls. A lack in muscle activity due to arthritis and the resulting muscle wasting can contribute to a decreasing free fat mass composition[42] and an increasing sum of skinfold measurements.

The impairment in anaerobic exercise capacity might have strong clinical implications because many activities of daily living, such as play, leisure, and sport activities, are initially short term and high intensity (anaerobic) in nature.[43] Impairment in anaerobic exercise capacity makes these activities difficult to perform or impossible to perform at all. Takken et al.[15] found a significant relationship between anaerobic exercise capacity and functional ability in patients with JIA. This illustrates a possible physiologic basis for activities of daily living in paediatric rheumatology patients.

The study by Hebestreit et al.[11] demonstrated that some patients with HLA–B27-positive juvenile spondylarthritis in whom disease is inactive or in remission had reduced aerobic fitness. In the current study, the children who were in remission (off medication) also showed a lower exercise capacity compared with healthy controls. The lower exercise capacity in the children in remission (off medication) did not differ significantly from the other patients. Therefore, we can say that children whose disease has been inactive for long

periods still have deficits in aerobic and anaerobic capacity. Malleson et al.[10] concluded that "disease severity may be related to fitness levels, but psychological factors may perhaps be more important determinants of fitness." This could also be true for our 15 children who were off medication.

Children with JIA seem to have realistic perceptions of their own physical capabilities, and even those children who are less fit and perceive themselves as having less athletic competence do not appear to have lower self-esteem [10]. Several studies have demonstrated that children with JIA can safely participate in physical activities.[14,44–47] Exercise may prevent cardiovascular disease, osteoporosis, and the decline of functional ability. A training program might prevent deconditioning due to hypoactivity and break the vicious circle, thus improving functional ability. Hypoactivity is not only caused by detraining, but indirect links such as fear, overprotection, ignorance, and social isolation could also play a significant role. Aerobic exercise has been shown to have beneficial health effects for this patient group.[36] It is yet to be determined if anaerobic exercise training should be performed in children with JIA. Because of the high impact on bones and cartilage, its safety should be studied carefully in patients with JIA before this training model can be recommended for use in the clinical setting. The relationship of anaerobic capacity with activities of daily living and functional outcome underlines the importance of further studies in the direction of exercise therapy in JIA. The different outcomes in (an)aerobic capacity between subgroups of JIA that were found in this study underline that exercise programs, to improve fitness, should be individualized or at least be modified according to different subgroups.[4]

Bar-Or and Rowland[48] suggested that children, prepubescents in particular, are metabolic nonspecialists. This means that children are less specialized as anaerobic or aerobic performers. This is in accordance with our study in which children showed similar impairment in anaerobic and aerobic performance. Despite our finding of a moderate to large relationship between the impairment in aerobic and anaerobic exercise capacity, we advise testing both, because they represent 2 different physiologic parameters. The WAnT might be a valuable adjunct next to other more commonly used assessment tools, such as the CHAQ, the Juvenile Arthritis Functional Assessment Scale, hand-held myometry, and aerobic exercise tests.

In conclusion, we found that both aerobic and anaerobic exercise capacity were significantly decreased in a large cohort of patients with JIA under 16 years of age. Moreover, distinct differences were observed between sexes

and disease subgroups. A moderate to large relationship was found between aerobic and anaerobic capacity measures.

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6
Chapter

Aerobic and anaerobic exercise capacity in adolescents with juvenile idiopathic arthritis

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Abstract

Objective

To examine the aerobic and anaerobic exercise capacity in adolescents with juvenile idiopathic arthritis (JIA) compared with age- and sex-matched healthy individuals, and to assess associations between disease-related variables and aerobic and anaerobic exercise capacity.

Methods

Of 25 patients enrolled in a JIA transition outpatient clinic, 22 patients with JIA were included in this study (mean ± SD age 17.1 ± 0.7 years, range 16–18 years). Aerobic capacity was examined using a Symptom Limited Bicycle Ergometry test. Anaerobic capacity was assessed with the Wingate Anaerobic Test. Functional ability was assessed with the Childhood Health Assessment Questionnaire. Pain and overall well-being were measured using a visual analog scale. Disease duration and disease activity were also assessed.

Results

Absolute and relative maximal oxygen consumption in the JIA group were significantly impaired (85% and 83% for boys, respectively; 81% and 78% for girls, respectively) compared with healthy controls. Mean power was also significantly impaired (88% for boys and 74% for girls), whereas peak power was significantly impaired for girls and just failed significance for boys (67% for girls and 92% for boys). A post hoc analysis correcting for underweight and overweight demonstrated that body composition did not influence the results substantially.

Conclusion

This study demonstrated that adolescents with JIA have an impaired aerobic and anaerobic exercise capacity compared with healthy age- and sex-matched peers. The likely cause for this significant impairment is multifactorial and needs to be revealed to improve treatment strategies.

Introduction

Although the outcome of juvenile idiopathic arthritis (JIA) is generally considered as good, with many children experiencing a spontaneous remission, long-term outcome studies show that between 39% and 65% of children with JIA have active disease into adulthood.[1–4] Adolescents with JIA and their parents call for developmentally appropriate care that addresses physical, social, psychological, and vocational issues.[5] One of the issues that need to be addressed is the physical fitness of the adolescents with JIA. It is now widely accepted that regular vigorous physical activity for children and youths has beneficial effects on growth and development and on achieving optimal adult health.[6] Physical activity guidelines for children and youths primarily advocate the accumulation of 1 hour of at least moderate-intensity physical activity per day. Secondly, children must take part in activities that help develop and maintain physical fitness on at least 2 occasions per week.[7]

There is growing evidence that children with JIA have moderate to severe impairment in physical fitness as represented by maximal oxygen consumption (VO_{2peak}) and perform less daily physical activities as compared with healthy children.[8,9] In the short term, decreased physical fitness and activity levels can lead to further functional deterioration.[10] In the longer term, decreased physical fitness and activity levels can lead to an increased risk for cardiovascular disease.[11–13]

Physical fitness is most often described in terms of cardiorespiratory or aerobic fitness, muscular endurance and strength, flexibility, and body composition.[14] However, physical fitness should also include anaerobic fitness because there is indication of a strong association between anaerobic physical fitness and daily functional ability.[15] The causality of impaired physical fitness in children and adolescents with JIA is unknown. Klepper et al.[16] suggested that physical fitness levels are less related to the degree of disease activity than often thought. Also, pain and disease activity are less related than often presumed. Malleson et al.[17] demonstrated in a large cohort of patients with JIA that disease activity accounted for only 6.5% of the variance in pain scores and stressed the importance of investigating the role of other factors, including psychosocial factors. It is likely that impaired physical fitness levels in adolescents with JIA are also caused by a variety of factors. The goal of this study was to examine the aerobic and anaerobic exercise capacity in adolescents with JIA compared with age- and sex-matched

healthy individuals, and to assess associations between disease-related variables and aerobic and anaerobic exercise capacity.

Patients and Methods

Patients

Patients attending the adolescent JIA transition outpatient clinic were eligible for the study. Patients were diagnosed by a paediatric rheumatologist according to the International League of Associations for Rheumatology (ILAR) criteria.[18] The adolescent JIA transition clinic is a combined outpatient clinic of the Beatrix Children Clinic and the adult rheumatology clinic of the University Medical Center Groningen with the aim of transferring children ages 16–18 with JIA from paediatric to adult care. This outpatient clinic was started in 2001 to improve transitional care with an approach that is adolescent focused and evidence based. One of the issues in transitional care that needs to be addressed is the physical fitness of the adolescents with JIA, and therefore a protocol was designed to measure their aerobic and anaerobic exercise capacity. All tests were performed on the same day with sufficient resting time in between the aerobic and anaerobic tests. In this study, the included patients were referred to as the JIA group. Reference data for aerobic exercise capacity collected from healthy Dutch controls were published by Binkhorst et al.[19] In the Binkhorst et al.[19] study, the same aerobic test protocol as in our study was used. Reference data for aerobic exercise capacity were matched for age and sex. Reference data for anaerobic exercise capacity were collected from healthy Dutch children attending a secondary school in the city of Assen, The Netherlands, because no published reference data for adolescents were available. Their anaerobic capacity was assessed with the same test protocol as in our study. These data were also matched for age and sex. This group was referred to as the Wingate group. Patients were fully informed about the test procedures and the possible risks involved and informed consent was obtained.

Anthropometry

Body mass and height were determined using an electronic scale and a stadiometer. Body mass index (BMI) was calculated as body mass(kg)/height (m^2). The BMI of the JIA group and Wingate group was compared with reference values of healthy Dutch children[20], with international cutoff points for overweight and obesity[21], and with Dutch cut-off points for underweight.[22]

Wingate Anaerobic Test

Anaerobic capacity was assessed with the Wingate Anaerobic Test (WAnT) as described by Bar-Or.[23] The test was performed on a calibrated electromagnetic braked cycle ergometer (Lode Examiner; Lode BV, Groningen, The Netherlands), which was upgraded by the manufacturer to a maximal resistance of 800W instead of the standard 400W. The external resistance was controlled and the power output was measured using the Lode Wingate software package.[24] The seat height was adjusted to the patient's leg length (comfortable cycling height). The external load (torque, in Nm) was determined at 0.6 times body weight according to the user manual.[24] The patient's feet were securely tied to the pedals. Patients were asked to exercise for 5 minutes with an external load of 50W at 60 revolutions per minute after the sprint protocol started. The patients were instructed to cycle as fast as possible for 30 seconds and were strongly verbally encouraged ("Go," "Come on," "Keep on going," "Faster"). Patients were informed about how much time was left. Measured variables were mean and peak power. Mean power represents the average power output during the 30-second sprint. Peak power is the highest recorded power output achieved during the 30-second sprint.

Symptom Limited Bicycle Ergometry test

Aerobic capacity was assessed using a Symptom Limited Bicycle Ergometry test (SLBE). SLBE was performed on an electronically braked cycle ergometer (Jaeger physis hc; Viasys, Bilthoven, The Netherlands). The seat height was adjusted to the patient's comfort. Patients rested until all measured variables were stable. Cycling started at a workload of 0W and the workload was increased by 20W every minute until the patient stopped due to volitional exhaustion, despite strong verbal encouragement from the investigators.

Patients breathed through a mouthpiece that was connected to a calibrated metabolic cart (Oxycon pro, Jaeger, Bilthoven, The Netherlands). Expired gas was passed through a flow meter, oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzer were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (= VCO_2/VO_2) from conventional equations. Heart rate was measured continuously during the maximal exercise test using an electrocardiogram.

Functional ability

Functional ability was assessed with the validated Dutch translation of the Childhood Health Assessment Questionnaire (CHAQ).[25,26] Using a paper version of the CHAQ, a number of questions were answered and scored (range 0–3; 0 = able to do with no difficulty, 1 = able to do with some difficulty, 2 = able to do with much difficulty, 3 = unable to do) in 8 domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities). When assistance or aids were required for a domain, the score for that domain was increased to a minimum of 2. The period for the self-assessment was a week. The mean of the 8 scores determined the CHAQ score (range 0–3).

Pain

Pain was measured using a Visual Analog Scale (VAS) that consisted of a 10-cm horizontal line with short vertical bars at each end. “No pain” was written at the left end (score 0) and “much pain” at the right (score 10). Patients were instructed to indicate their pain during the past week by drawing a vertical line. The higher the score, the higher the perceived pain.

Overall well-being

Overall well-being was measured using a VAS consisting of a 10-cm horizontal line with short vertical bars at each end. “Very well” was written at the left end (score 0) and “very bad” at the right (score 10). Patients were instructed to indicate their overall well-being during the past week with a vertical line. Higher values indicated worse overall well-being.

Disease duration

Disease onset was assessed by retrospective study of patients' charts. Disease duration was defined as the period between time of onset and time of assessment (equal to time since diagnosis).

Disease activity

Disease activity was assessed by an adult rheumatologist and a paediatric rheumatologist using Pediatric Rheumatology International Trials Organization (PRINTO) core set criteria.[27] Disease activity was accordingly classified as active disease, inactive disease, clinical remission on medication, and clinical remission off medication. Active disease was defined as active arthritis in $\geq$1 joint. Inactive disease was defined as no disease signs with medication. Six continuous months of inactive disease with medication was defined as clinical remission on medication, whereas 12 months off medication with inactive disease was defined as clinical remission off medication.

Statistical analysis

For statistical analysis, SPSS software, version 12 for Windows was used. Descriptive statistics were used for patient characteristics and for mean and peak power and VO_{2peak}. Independent sample t-tests were used to determine differences between the JIA group and the reference data. Analyses were performed for groups as a whole and for girls and boys separately. Pearson's and Spearman's correlation analyses were used to assess associations between disease-related variables and aerobic and anaerobic exercise capacity. Correlation coefficients between 0.26 and 0.49 reflect poor agreement, those between 0.50 and 0.69 reflect moderate agreement, and those $\geq$0.70 reflect high agreement.[28] P values <0.05 were considered statistically significant.

Results

Participants

In 2004 and the beginning of 2005, 25 adolescents with JIA were enrolled in the transition outpatient clinic. Twenty-two patients were included in this cross-sectional study, 9 boys and 13 girls. One patient was excluded because of Down syndrome and 2 patients refused participation. The population consisted of 5 patients with oligoarticular JIA, 2 patients with extended oligoarticular JIA, 8 patients with polyarticular rheumatoid factor (RF)–negative JIA, 3 patients with polyarticular RF-positive JIA, 2 patients with psoriatic arthritis, and 2 patients with enthesitis-related JIA. The mean (± SD) disease duration of the patients was 8.3 (± 4.8) years. Five adolescents had active disease, 13 patients had inactive disease, and 4 patients were in clinical remission without medication. Eight patients were receiving only nonsteroidal antiinflammatory drugs (NSAIDs); 1 patient was receiving only disease-modifying antirheumatic drugs (DMARDs); 7 patients were receiving both NSAIDs and DMARDs; 1 patient was receiving an NSAID, a DMARD, and a biologic agent; and 1 patient was receiving an NSAID and a biologic agent.

Preliminary group analysis

Independent-samples T-test for BMI demonstrated no significant difference between the JIA group and reference values of healthy Dutch children. Three of the 22 patients were overweight, 4 were underweight, and none were obese. A total of 27 adolescents were included in the Wingate control group, 14 boys and 13 girls. Two of these 27 were overweight, 3 were underweight, and none were obese. Independent-samples T-test for BMI demonstrated no significant difference between the Wingate group and reference values of healthy Dutch children. No significant differences between the JIA group and the Wingate control group were found with respect to age, weight, height, and BMI (Table I).

Table I: Characteristics of the patients with juvenile idiopathic arthritis (JIA) and the Wingate control group.*

Characteristics	JIA group (n=22)	Wingate group (n=27)	P†
Age (years)	17.1 ± 0.7 (16.0-18.2)	17.0 ± 0.6 (16.1-18.2)	0.60
Height (cm)	171.0 ± 8 (157-185)	176.0 ± 9 (159-189)	0.07
Weight (kg)	61.6 ± 12.0 (42.0-86.0)	65.2 ± 9.0 (48.9-86.0)	0.25
BMI (kg/m^2)	20.8 ± 2.7 (16.4- 26.8)	21.1 ± 2.3 (17.5 -26.5)	0.75
CHAQ score	0.5 ± 0.5 (0-1.8)		
VAS pain (0-10 cm)	2.8 ± 2.2 (0-6.9)		
VAS Overall well-being (0-10 cm)	2.2 ± 1.9 (0-6.3)		
Disease duration (years)	8.3 ± 4.8 (0.5 -16.7)		

* Values are the mean ± SD (range) unless otherwise indicated. BMI=body mass index; CHAQ= Childhood Health Assessment Questionnaire; VAS= visual analog scale.
† Based on independent-samples T-tests.

Preliminary aerobic exercise capacity

Independent-samples t-test demonstrated a significant lower absolute and relative VO_{2peak} in the JIA group as compared with the reference group for both boys and girls. On average, absolute VO_{2peak} in the JIA group was 85% of that predicted for boys and 81% of that predicted for girls. Relative VO_{2peak} in the JIA group was on average 83% of that predicted for boys and 78% of that predicted for girls (Table II).

Preliminary anaerobic exercise capacity

Independent-samples t-test showed a significant lower mean power in the JIA group compared with the reference group for boys and girls. On average, mean power in the JIA group was 88% of that predicted for boys and 74% of that predicted for girls. Girls in the JIA group showed a significant lower peak power compared with the reference group.
No significant difference in peak power between the JIA group and reference group was found for boys (P = 0.14). On average, peak power in the JIA group was 92% of that predicted for boys and 67% of that predicted for girls (Table II).

Table II: Aerobic and anaerobic exercise capacity of patients with juvenile idiopathic arthritis (JIA) and controls.*

	JIA	Controls	% predicted	P†
VO_{2peak} (Liters · min^{-1})	2.18 ± 0.68	2.62 ± 0.53	83 ± 19	<0.05
Boys	2.77 ± 0.44	3.24 ± 0.05	85 ± 13	<0.05
Girls	1.78 ± 0.49	2.20 ± 0.00	81 ± 22	<0.01
VO_{2peak} (ml · kg^{-1} · min^{-1})	35.36 ± 7.95	43.98 ± 5.85	80 ± 13	<0.01
Boys	41.97 ± 7.18	50.84 ± 0.05	83 ± 14	<0.01
Girls	30.78 ± 4.56	39.22 ± 0.07	78 ± 12	<0.01
Mean power (Watts)	410 ± 119	526 ± 92	80 ± 14	<0.01
Boys	531 ± 68	602 ± 48	88 ± 11	<0.05
Girls	327 ± 58	444 ± 44	74 ± 13	<0.01
Peak power (Watts)	605 ± 233	790 ± 180	80 ± 19	<0.05
Boys	847 ± 135	921 ± 134	92 ± 15	0.14
Girls	437 ± 91	648 ± 92	67 ± 14	<0.01

* Values are the mean ± SD unless otherwise indicated. VO_{2peak}= peak oxygen uptake; min= minute.

† Based on independent-samples T-tests.

Correlations

Pearson's correlation coefficient demonstrated a significant and high association between aerobic and anaerobic parameters (Table III). Spearman's correlation coefficient demonstrated a significant and low negative association between VAS pain and absolute VO_{2peak} and a significant moderate association between VAS pain and VAS well-being and CHAQ scores. Spearman's correlation coefficient also showed a significant low to moderate negative association between VAS well-being and aerobic and anaerobic parameters. A significant low to moderate association was found between disease activity and aerobic parameters. There was a significant low negative association between CHAQ scores and absolute VO_{2peak} and a significant moderate negative association between CHAQ scores and anaerobic parameters. There was no significant association between disease duration and any of the aerobic or anaerobic parameters, nor between disease duration, VAS pain, and VAS well-being scores. No significant association was found between disease activity and anaerobic parameters, VAS pain, and VAS well-being scores (Table IV).

Table III: Pearson's correlation (r) between absolute and relative VO_{2peak} and WAnT mean and peak power.*

	Absolute VO_{2peak}	Relative VO_{2peak}	WAnT mean power	WAnT peak power
Absolute VO_{2peak}		0.80†	0.92†	0.85†
Relative VO_{2peak}			0.74†	0.75†
WAnT mean power				0.96†

* VO_{2peak}= peak oxygen uptake; WAnT= Wingate Anaerobic Test.
† P< 0.01

Table IV: Spearman's correlation between VAS pain, VAS well-being, disease duration, disease activity, CHAQ, absolute and relative VO_{2peak}, and WAnT mean and peak power.*

	Absolute VO_{2peak}	Relative VO_{2peak}	WAnT mean power	WAnT peak power	VAS pain	VAS well-being
VAS pain	-0.47†	-0.30	-0.41	-0.38		
VAS well-being	-0.48†	-0.57‡	-0.45†	-0.50†	0.66‡	
Disease duration	0.37	0.21	0.37	0.35	0.06	-0.25
Disease activity	0.45†	0.58‡	0.33	0.30	-0.08	-0.03
CHAQ	-0.48†	-0.42	-0.51†	-0.55‡	0.50†	0.51†

* VAS= visual analog scale; CHAQ= Child Health Assessment Questionnaire; VO_{2peak}= peak oxygen uptake; WAnT= Wingate Anaerobic Test.
† P< 0.05
‡ P< 0.01

Post hoc analysis

Post hoc analysis was carried out to correct for abnormal body weight. In the JIA group and Wingate group, patients who were underweight or overweight were omitted in this analysis. In the JIA group 15 patients had normal body weight, 6 boys and 9 girls. In the Wingate group 22 patients had normal body weight, 12 boys and 10 girls.

Post hoc aerobic exercise capacity

Independent-samples t-test showed a significant lower relative VO_{2peak} for girls in the JIA group. Absolute VO_{2peak} for girls and absolute and relative VO_{2peak} for boys just failed significance. On average, absolute VO_{2peak} in the JIA group was 85% of that predicted for boys and 88% of that predicted for girls. Relative VO_{2peak} in the JIA group was on average 90% of that predicted for boys and 80% of that predicted for girls (Table V).

Post hoc anaerobic exercise capacity

Independent-samples t-test showed a significant lower mean power in the JIA group compared with the reference group for boys and girls. On average, mean power in the JIA group was 86% of that predicted for boys and 76% of that predicted for girls. Girls in the JIA group showed a significant lower peak power compared with the reference group. No significant difference in peak power between the JIA group and reference group was found for boys (P = 0.09). Peak power in the JIA group was on average 93% of that predicted for boys and 71% of that predicted for girls (Table V).

Table V: Aerobic and anaerobic exercise capacity of patients with juvenile idiopathic arthritis (JIA) and controls corrected for underweight and overweight*

	JIA	Controls	% predicted	P†
VO_{2peak} (Liters·min^{-1})	2.28 ± 0.62	2.62 ± 0.53	87 ± 18	0.12
Boys	2.78 ± 0.51	3.25 ± 0.05	85 ± 15	0.08
Girls	1.95 ± 0.44	2.20 ± 0.00	88 ± 20	0.12
VO_{2peak} (ml·kg^{-1}·min^{-1})	37.10 ± 8.42	43.88 ± 5.89	84 ± 11	<0.05
Boys	45.77 ± 5.01	50.85 ± 0.05	90 ± 10	0.06
Girls	31.33 ± 3.80	39.23 ± 0.07	80 ± 10	<0.01
Mean power (Watts)	411 ± 105	530 ± 94	80 ± 12	<0.05
Boys	519 ± 58	603 ± 48	86 ± 10	<0.05
Girls	339 ± 51	443 ± 49	76 ± 12	<0.01
Peak power (Watts)	616 ± 217	792 ± 188	80 ± 16	0.05
Boys	855 ± 75	920 ± 143	93 ± 8	0.09
Girls	456 ± 86	639 ± 98	71 ± 13	<0.01

* Values are the mean ± SD (range) unless otherwise indicated. VO_{2peak}= peak oxygen uptake; min= minute. † Based on independent-samples T-tests.

Discussion

The goal of this study was to examine the aerobic and anaerobic exercise capacity in adolescents with JIA attending a transition outpatient clinic compared with healthy individuals, and to assess associations between disease-related variables and aerobic and anaerobic exercise capacity. The results demonstrate a significant decrease in aerobic and in anaerobic fitness in adolescent boys and girls with JIA. This finding is worrying because fitness levels at the age of 18 are at their peak, tend to deteriorate during adulthood, and are a strong predictor of the work capacity of a person.[29] It is unlikely that adolescents with JIA, entering adulthood with diminished fitness levels, are able to bridge this gap. Therefore, we must create new strategies to reverse or even prevent this unwanted trend.

The study found distinctive sex differences in adolescents with JIA: girls were more impaired than boys in aerobic and anaerobic fitness. These findings are in line with the results found in the study by van Brussel et al.[30] in which 62 children with JIA ages 6–15 years were tested for aerobic and anaerobic exercise capacity.[30] Van Brussel et al.[30] also found a considerable significant decrease in aerobic as well as anaerobic fitness with the same sex differences. Because body composition can influence outcome, we performed a post hoc analysis to study the possible confounding effect of overweight and underweight. Body composition did not influence the results substantially.

The decrease in aerobic fitness is in line with findings of earlier studies in preadolescent children with JIA.[9] Several pathophysiologic factors specific to childhood JIA can limit aerobic capacity such as anaemia, muscle atrophy and weakness, impaired lung function, and joint stiffness.[31,32] This study demonstrates a significant low to moderate association between disease activity and aerobic exercise capacity. At the same time this study demonstrates a considerable decrease of aerobic capacity in adolescents with JIA who are under disease control and are in remission. It is likely that factors other than disease activity are involved in reducing aerobic exercise capacity. This needs further exploration.

This study is the first to assess anaerobic exercise capacity in adolescents with JIA in comparison with a healthy population, and it demonstrates a dramatic decrease of anaerobic exercise capacity, particularly in adolescent girls. This can have serious consequences for these patients' daily functioning because children are normally engaged in very short bursts of intense

physical activity that are anaerobic in nature.[33] Anaerobic fitness is needed in more intensive daily activities such as climbing stairs, playing outside, and cycling against a strong wind. Anaerobic fitness is also needed in sports with short intensive bursts of activity such as soccer, volleyball, and athletics. Adolescents with such a decreased anaerobic exercise capacity are prone to drop out of physical education classes at school. Girls are more prone than boys to develop sedentary lifestyle patterns, and sedentary patterns developed in youth and adolescence are likely to persist over time, resulting in a sedentary lifestyle.[34]

Decreased anaerobic capacity can therefore be responsible for low physical activity levels, poor exercise behaviour, and impairments in daily functioning. In our study, we found a significant inverse moderate association between CHAQ scores and anaerobic parameters. This is an indication that low anaerobic fitness indeed impairs daily functioning and confirms findings of an earlier report by Takken et al.[15]

The study demonstrated that disease duration (time since diagnosis) does not seem to be relevant for pain, well-being, and aerobic and anaerobic parameters. This study also demonstrated a low to moderate significant negative association between aerobic and anaerobic exercise capacity and VAS overall well-being scores. This finding indicates that adolescents with higher fitness levels feel better. In addition, a significant moderate association was found between VAS pain and VAS well-being scores. Pain and poor well-being are likely to reinforce each other.

This study also found a low to moderate significant association between VAS pain and well-being and CHAQ scores, indicating that pain and poor well-being are likely to lower functional ability. The study demonstrated no association between pain and disease duration and disease activity. We found a low and non-significant association between well-being and disease duration and disease activity. This enforces the idea that non-pathophysiologic factors may be responsible for a substantial reduction of aerobic and anaerobic exercise capacity. According to Bar-Or[35], chronic illness, by means of overprotection, fear, social isolation, and ignorance, can lead to hypoactivity, which is the trigger for further detraining and functional deterioration.

The study further demonstrates a strong and significant association between aerobic and anaerobic parameters, especially between WAnT mean power and absolute VO_{2peak}. Anaerobic exercise testing, which is safer and simpler than aerobic exercise testing, is therefore a possible valid instrument

to test exercise capacity and fitness. Further research is necessary to conclude if anaerobic testing can replace aerobic testing. This study has the limitation of including a small number of adolescents with JIA. It is therefore not possible to make strong assumptions over possible indicators of aerobic and anaerobic exercise capacity. A (multicenter) study with a larger sample size is needed.

In conclusion, we found that adolescents attending a transition outpatient clinic for patients with JIA have an impaired aerobic and anaerobic exercise capacity compared with healthy age- and sex-matched peers (girls more severely impaired than boys). The importance of improving aerobic and anaerobic exercise capacity in children and adolescents with JIA by means of exercise is widely accepted.[32] How this improvement can be achieved is still under debate. The likely cause for this significant impairment is multifactorial and needs to be revealed to improve treatment strategies.

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7
Chapter

Physical training in children with Osteogenesis Imperfecta

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Abstract

Objective

To study the effects of a physical training program on exercise capacity, muscle force and subjective fatigue levels in patients with mild to moderate forms of Osteogenesis Imperfecta (OI).

Study design

Thirty-four children with OI type I or IV were randomly assigned to either a 12 week graded exercise program or care as usual for 3 months. Exercise capacity and muscle force were studied; subjective fatigue, perceived competence and health-related quality of life were secondary outcomes. All outcomes were measured at baseline (T=0), after intervention (T=1), and after 6 and 9 months (T=2 and T=3, respectively).

Results

After intervention (T=1), peak oxygen uptake (VO_{2peak}), relative VO_{2peak} ($VO_{2peak/kg}$), maximal working capacity (W_{max}), and muscle force were significantly improved (17%, 18%, 10%, and 12%, respectively) compared to control values. Subjective fatigue decreased borderline statistically significantly. Follow-up at T=2 showed a significant decrease of the improvements measured at T=1 of VO_{2peak}, but $VO_{2peak/kg}$, W_{max}, and subjective fatigue showed no significant difference. At T=3, we found a further decrease of the gained improvements.

Conclusion

A supervised training program can improve aerobic capacity and muscle force and reduces levels of subjective fatigue in children with OI type I and IV in a safe and effective manner.

Introduction

Osteogenesis Imperfecta (OI) is a congenital connective tissue disorder characterized by increased bone fragility and osteopenia. The biochemical basis in most cases involves a quantitative abnormality, qualitative abnormality, or both in the biosynthesis of type I collagen, the principle organic component of the skeleton.[1] Severity varies over a wide range, reaching from intrauterine fractures and perinatal lethality to very mild forms with incidental fractures.[2] Although children with mild and moderate forms of OI are in general walkers (varying from household to community walkers [3]), fatigue, diminished exercise capacity, and exercise intolerance is frequently reported to limit these patients in their activities of daily living.[4]
Takken et al.[5] studied cardiopulmonary function in 17 children with OI type I. They found that heart and lung abnormalities in rest were absent. However, they also reported that exercise capacity and muscle force were significantly reduced compared with those of their healthy peers[5], whereas complaints of fatigue were related to proximal muscle weakness and a reduced peak oxygen uptake (VO_{2peak}). It was unclear whether the reduced VO_{2peak} and muscle force were a consequence of a hypoactive lifestyle or a specific consequence of the impaired muscle collagen synthesis. Takken et al. suggested that a physical intervention study in patients with OI might improve exercise capacity and muscle force.[5] In other chronic conditions in childhood such as cystic fibrosis[6] and leukaemia[7], exercise interventions have been reported to be beneficial in improving muscle force, exercise tolerance and activities in daily living.

To our knowledge, physical intervention studies have not been performed in children with OI. Exercise might have no effect on the disease itself; but may possibly improve the level of activities of daily living, self-esteem, and fitness in many of these children. Therefore, we designed a randomized controlled trial to study the effects of a physical training program on exercise capacity, muscle force and subjective fatigue in patients with the mild to moderate forms of OI.

Patients and Methods

Design and participants

Medical histories of children with skeletal dysplasias were obtained from the patient records of our hospital. The most widely used classification of OI is by Sillence et al. and distinguishes 4 clinical types.[8] Recently, this classification was expanded into 7 types.[9] The type of OI was diagnosed by a clinical geneticist in our hospital on the basis of the clinical features and a collagen biopsy of the patients. OI type I includes patients with mild disease and absence of major bone deformities, with typical vertebral fractures leading to mild scoliosis. Patients with OI type IV have mild to moderate bone deformities and variable short stature. Children were eligible for inclusion when they had documented OI type I or IV, were between 8 and 18 years old, had no fractures in the last 3 months before start of the study, and were at least household walkers according to the modified Bleck scale.[10] Forty children met our inclusion criteria (Figure I), and were invited to participate. Of these children, 1 child could not take part because of a fracture of the patella just before the start of the study. The parents of 2 children refused to participate for personal reasons, and the parents of 3 other children refused for logistical reasons. The remaining 34 children (12 boys and 22 girls) were enrolled in the study. Twenty-seven children had OI type I, and 7 children had OI type IV.

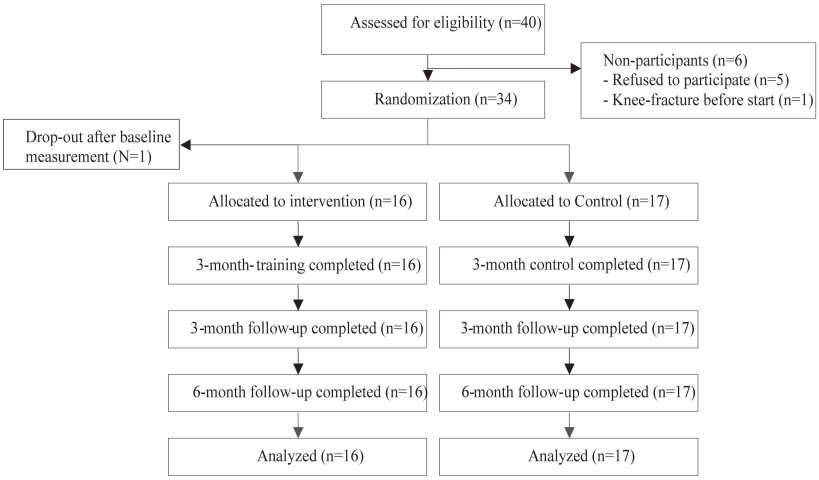

Figure I: Consort flowchart for intervention study in children with Osteogenesis Imperfecta.

Randomization was performed with a list of computer-generated numbers by an offsite data manager. Participants were randomly assigned to 1 of 2 groups (intervention and control) stratified for age, sex, and biphosphonates usage by using a block randomization procedure. In general, according to our hospital protocol, patients with OI were treated with medication (bisphosphonates [Olpadronate] at a dose of 10 mg/m^2 daily) when bone mineral density as measured with the DEXA Z-score was < -1.5 (measured at the lumbar spinal cord [L1-L4]) and platyspondyly or biconcave endplates are present. After randomization, and before the start of the intervention, 1 patient withdrew from the study because of personal reasons (Figure I). The observers (R.E. / T.T.) who assessed outcome variables were blinded to treatment allocation and were highly experienced in their assessments. Treatment allocation and the observers were kept blinded until the evaluation of the results. The study protocol was approved by the medical-ethics committee of the University Medical Center Utrecht, the Netherlands. Informed consent to participate was obtained from the parents, from the children when they were older than 12 years of age, or both.

Exercise training program

Patients allocated to the intervention group received a graded exercise program consisting of 12 weeks (30-sessions) aiming at improvement of exercise capacity and muscle force, whereas patients in the control group only received usual care. Patients allocated to the intervention group were instructed to attend exercise sessions twice a week held at a local physical therapy practice for 12 weeks consecutively and to perform home-based exercises once a week, starting after the sixth week of the intervention. The exercise sessions were supervised by local pediatric physical therapists, trained in our hospital to warrant the uniformity of the training program.

The 45-minute sessions included a 10-minute warm-up period. Ten minutes of aerobic training (on the basis of an intensity ranging from 60%-80% of their baseline peak heart rate) were followed by 15 minutes of free play and muscle training, and thereafter another 10 minutes of aerobic training were performed. The session ended with 10 minutes of cool-down exercises. The strength training consisted of exercises without heavy weights; the children learned the proper strength-training techniques and only used light weights as heavy as a maximum of 1 kg. This was performed to ensure a minimal risk of fracture. Attendance records were kept by the pediatric physical therapists. Patients in the intervention group maintained activity records for the home exercise sessions. Children (in both the intervention and control groups) were examined 4 times at our hospital in 9 months of follow-up (base-line [start of the intervention]: T=0), after intervention (3 months follow-up: T=1), and 6 months (T=2) and 9 months (T=3) after the start of the study. We primarily studied the exercise capacity and muscle force; secondary outcomes were subjective fatigue, perceived competence and Health-related Quality of Life (HRQoL).

Clinical characteristics

Weight (kg), arm span (cm), height (cm), and sitting height (cm) were determined by using an electronic scale and a stadiometer. Subcutaneous fat distribution was measured from skin fold measurement using Harpender skin fold calipers. The measurements were taken at seven sites (bilaterally); at the triceps, biceps, sub scapular, supra-iliacal, mid-abdominal, medial calf, and thigh, in accordance with the American College of Sports Medicine guidelines[11], and the sum of the 7 skin folds were used as an index for body fat.[12] Body Mass Index (BMI) was calculated as body weight (kg)/height (m)^2.

The fracture history (total number of fractures), presence of bowing of the long bones of the lower extremities and the presence of intramedullary rodding, presence of scoliosis (Cobbs angle >10 degrees), bone mineral density (with DEXA presented in Z-scores), and use of medication (Olpadronate, dose of 10 mg/m^2 daily) are described in the results section, presented in Table I, or both.

Cardio-Pulmonary Exercise Test

Patients performed a cardio-pulmonary exercise test (CPET) by using an electronically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands). The test started with 1 minute of unloaded cycling before the application of resistance to the ergometer. After this minute, workload was increased with a constant increment of 15 or 20 Watts every minute according to the Godfrey protocol.[13] This protocol continued until the patient stopped because of voluntary exhaustion, despite strong verbal encouragement of the test-leader. The highest achieved workload (W_{max}) was recorded. During the CPET, subjects breathed through a facemask (Hans Rudolph Inc, Kansas city, MO) connected to a calibrated respiratory gas analysis system (Cortex Metamax B^3, Cortex Medical, Leipzig, Germany). Expired gas was passed through a flowmeter (Triple V volume transducer), an oxygen (O_2) analyzer, and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2), and the respiratory exchange ratio (RER [=VCO_2/VO_2]) from conventional equations. The oxygen uptake eliciting the ventilatory anaerobic threshold (AT) was determined by using the criteria of an increase in both the ventilatory equivalent of oxygen (VE/VO_2) and end-tidal pressure of oxygen ($PETO_2$) with no increase in the ventilatory equivalent of carbon dioxide (VE/VCO_2).[14]

Heart rate was measured continuously during the maximal exercise test by using a heart rate monitor (Polar, Kempele, Finland). Maximal effort occurred when 1 of the 2 criteria were met: heart rate >180 beats per minute or RER >1.0. Peak oxygen consumption (VO_{2peak}) was taken as the average value for the last 30 seconds during the maximal exercise test. Relative VO_{2peak} was calculated as absolute VO_{2peak} divided by body mass.

Muscle force

Muscle force was measured with a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, the Netherlands) in 4 muscle groups (shoulder abductors, grip force, hip flexors and dorsiflexors of the ankle joint). Maximum muscle force was tested using the "break" method, in which the examiner gradually overcomes the muscle force of the patient and stops at the moment the extremity gives way. The tests were performed according to the Backman protocol.[15] Grip force was measured with the "make" method, in which the dynamometer was gripped as hard as possible for 3 seconds without pressing the instrument against the body and without touching the elbow to the body. Every muscle group was measured 3 times, and the highest score was recorded.

Fatigue

Fatigue was measured with the subscale subjective fatigue of the self-report questionnaire Checklist Individual Strength-20 (CIS-20).[16,17] The CIS-20 asks about fatigue in the 2 weeks before the assessment. There are 4 respective subscales, fatigue, concentration, motivation, and physical activity, consisting of items scored on a 7-point Likert-scale. A high total score indicated a high level of subjective fatigue and concentration problems and a low level of motivation and physical activity. The questionnaire has good reliability and discriminative validity.[17]

Perceived competence

The translated version of the Self-perception Profile for Children[18] (CBSK) was used to measure perceived competence.[19] The translated version has been cross-culturally validated for Dutch Children.[20] The test consists of 36 items, formulated as opposite pairs. Each answer was scored between 1 (most competent) and 4 (least competent). There are 6 subscales: scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct and global self-worth.

Health-Related Quality of Life

The Child Health Questionnaire Parent-Form 50 (CHQ) is a proxy report of assessing HRQoL.[21] A Dutch translation of the CHQ was used in this study[22], and was administered to the parents. The questionnaire consists of 50 items in 14 dimensions. From these dimensions a physical and psychosocial summary score can be calculated. A higher score reflects a better HRQoL of the child.

Statistical analysis

Descriptions of data by treatment allocation were expressed as mean plus or minus SD and range. The effects of the intervention were analyzed by using linear regression statistics with a group indicator (intervention: yes / no) as independent variable and the outcome variables as dependent separate variables. Results are presented as linear regression coefficients representing mean group differences with their corresponding 95% CIs. Statistical significance was considered to be reached when 95% CIs did not include the null value. Nominal variables were analyzed using χ^2 analysis. All results were analyzed by intention to treat. Statistical analyses were performed using SPSS software version 12.0 (SPSS, Chicago, IL).

Results

The baseline anthropometric values and clinical characteristics of both groups are shown in Table I. Forty percent of the children had a located collagen type I mutation. Thirteen children had $\geq$1 intramedullary rods, all in the lower extremities; 5 of these children were allocated in the intervention group. The reported intervention compliance, defined as the percentage of completed exercise sessions of the prescribed sessions, was 96.4%. All patients were able to complete the aerobic exercise test without adverse effects. No fractures occurred in the intervention group, whereas 3 children in the control group had a fracture during the study (Pearson's χ^2= 3.5; P= .061). The analysis of follow-up variables was adjusted for baseline differences in Vo_{2peak}, $Vo_{2peak/kg}$, W_{max}, AT, muscle force, subjective fatigue, perceived competence, and HRQoL.

Table I: Clinical characteristics of the intervention group and the control group at baseline (T=0).

	Intervention group (N=16)			Control group (N=17)		
Variables	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (years)	12.3	3.3	7.9-17.8	13.2	3.6	8.3-18.6
Weight (kg)	41.9	13.8	21.2-71.1	43.8	15.4	23.2-77.9
Height (cm)	150.0	20.0	120.0-180.0	150.0	20.0	120.0-170.0
BMI (kg/m^2)	19.0	3.3	15.1-24.4	20.5	5.5	14.4-31.4
∑7SF (mm)	335.0	113.2	162.4-522.6	359.6	130.0	193.8-568.6
Sitting height (cm)	76.5	6.9	66.0-92.0	77.1	7.9	64.0-88.0
Arm span (cm)	147.3	19.8	103.0-183.0	150.6	18.8	125.0-184.0
DEXA L1-L4 (Z-score)	-1.7	1.1	-3.1-1.0	-1.6	1.1	-4.8-0.0
Fracture history	5.1	1.5	3.0-8.0	5.1	4.3	3.0-21.0
Bowing		38%			41%	
Scoliosis		13%			35%	
Male:female ratio		6 : 10			5 : 12	
Bisphosphonates: yes / no		8 : 8			9 : 8	

Abbreviations: BMI: Body Mass Index; ∑7SF: sum of 7 skinfolds, DEXA: dual X-ray absorptiometry; L1-L4: lumbar spine, vertebra 1 to 4.

Table II shows that after 3 months of training (T=1), VO_{2peak}, $VO_{2peak/kg}$, W_{max}, and muscle force were significantly improved in the intervention group compared with the control group (17%, 18%, 10%, and 12%, respectively). After adjustment for baseline differences, the VO_{2peak} group difference increased statistically significantly with 0.192 L/min (95% CI -0.3; -0.1), the $VO_{2peak/kg}$ increased with 5.1 mL·kg^{-1}·min^{-1} (95% CI: -8.0; -2.2), W_{max} increased with 10.2 Watt (95% CI:-20.0; -0.5), and muscle force with 61 Newton (95% CI: -96.7; -26.2).

Table II. VO_{2peak}, VO_{2peak}/kg, W_{max}, AT, and muscle strength during the intervention and follow-up.

		Intervention group Mean (SD)	Control group Mean (SD)	Mean group difference (95% confidence interval)	Mean group difference (CI 95%) adjusted for baseline (T=0) measurements
VO_{2peak} (L/min)	T=0	1.25 (0.4)	1.50 (0.6)	0.25 (-0.1; 0.6)	
	T=1	1.49(0.4)	1.54(0.6)	0.05 (-0.3; 0.4)	**-0.19 (-0.3; -0.1)**
	T=2	1.41(0.4)	1.59(0.6)	0.18 (-0.2; 0.5)	-0.06 (-0.2; 0.1)
	T=3	1.42(0.4)	1.64(0.7)	0.21 (-0.2; 0.6)	-0.05 (-0.2; 0.1)
$VO_{2peak/kg}$ (ml/kg/min)	T=0	30.9 (5.8)	35.6 (10.4)	4.7 (-1.3; 10.7)	
	T=1	36.4(6.4)	35.5 (10.2)	-0.9 (-7.0; 5.3)	**-5.1 (-8.0; -2.2)**
	T=2	33.8 (6.8)	36.3 (11.1)	2.5 (-4.2; 9.1)	-1.6 (-6.0; 2.9)
	T=3	33.7 (9.3)	37.1 (12.0)	3.4 (-4.2; 11.0)	-1.5 (-6.1; 3.2)
W_{max}	T=0	107.3 (39.0)	128.6 (61.0)	21.3 (-15.3; 57.9)	
	T=1	122.7 (42.1)	134.0 (63.0)	11.3 (-27.0; 49.6)	**-10.3 (-20.0; -0.5)**
	T=2	117.6 (39.4)	135.3 (63.4)	17.7 (-20.1; 55.4)	-3.6 (-13.0; 5.8)
	T=3	114.9 (45.1)	135.6 (73.0)	20.7 (-22.7; 64.1)	-2.5 (20.2; 15.1)
AT	T=0	0.79 (0.25)	0.89 (0.33)	0.1 (-0.1; 0.3)	
	T=1	0.94 (0.18)	0.97 (0.43)	0.0 (-0.2; 0.3)	0.0 (-0.2; 0.1)
	T=2	1.0 (0.34)	0.90 (0.37)	-0.1 (-0.4; 0.2)	-0.2 (-0.4; 0.0)
	T=3	0.89 (0.34)	0.86 (0.24)	-0.0 (-0.2; 0.2)	-0.1 (-0.3; 0.1)
Muscle Force (Newton)	T=0	537.8 (183.7)	589.3 (187.7)	51.5 (-80.3; 183.4)	
	T=1	602.7 (182.6)	590.5 (184.5)	-12.2 (-142.6; 118.2)	**-61.4 (-96.7; -26.2)**
	T=2	616.2 (169.8)	657.9 (196.6)	36.3 (-94.5; 167.1)	-5.2 (-53.0; 42.5)
	T=3	621.3 (202.0)	680.1 (205.0)	58.8 (-85.8; 203.4)	6.5(-49.7; 62.8)

Legend: regression coefficients are presented in bold when p-value is lower than 0.05

Table III shows that subjective fatigue levels were decreased with borderline statistical significance in the intervention group (adjusted for baseline measures: 4.2 points; 95% CI: -0.3; 8.8, P= .068). AT, perceived competence (CBSK), and HRQoL (CHQ physical and psychosocial summaries) showed some improvements (10%, 2.4 %, 7.7%, and 6.2%, respectively), without being significant. Follow-up measurement 6 months after the start of the intervention (T=2) showed a significant decrease of the gained improvements in VO_{2peak} (6% decrease; adjusted ß= 0.131 L/min [95% CI: 0.0; 0.3]) at T=1. $VO_{2peak/kg}$, W_{max}, AT, perceived competence, subjective fatigue, and HRQoL showed, after adjustment, no significant difference as compared with T=1. In the control group, total muscle force increased significantly because of an

increase in muscle force in 1 girl (age 12 years) and 1 boy (age 18 years). Nine months after the start of the intervention (T=3), measurements again showed a decrease of the gained improvements compared with the results immediately after intervention (T=1). VO_{2peak}, $VO_{2peak/kg}$, and muscle force showed a significant decrease (ß= 0.16 L/ min [95% CI: 0.0; 0.3], ß= 4.4 mL/kg/min [95% CI: 1.5; 7.3], 71.1 Newton [95% CI: 7.2; 134.9], respectively). Subjective fatigue also decreased at T=3. W_{max}, AT, perceived competence and HRQoL showed no significant differences compared to T=1. No significant differences in exercise capacity, muscle force and subjective fatigue were found between the children who used bisphosphonates and the children who used no medication. No significant differences were observed between the measurements of perceived competence and HRQoL (data not presented).

Table III. Total score and fatigue during the intervention and follow-up

		Intervention group Mean (SD)	Control group Mean (SD)	Mean group difference (95% confidence interval)	Mean group difference (CI 95%) adjusted for baseline (T=0) measurements
Total score	T=0	48.6 (16.0)	42.4 (15.3)	-6.2 (-17.2; 4.9)	
	T=1	43.1 (17.9)	45.2 (16.8)	2.1 (-10.2; 14.4)	6.1 (-4.3; 16.5)
	T=2	48.2 (15.7)	46.1 (21.8)	-2.1 (-15.6; 11.5)	2.3 (-9.3;13.8)
	T=3	50.4 (15.7)	42.3 (17.4)	3.3 (-8.6; 15.2)	4.6 (-7.6;16.7)
Fatigue	T=0	20.7 (8.2)	17.9 (9.1)	-2.7 (-8.9; 3.4)	
	T=1	16.7 (6.3)	19.3 (9.4)	2.6 (-3.1; 8.3)	4.2 (-0.3;8.8)
	T=2	21.9 (7.7)	19.9 (8.7)	-2.1 (-7.9; 3.8)	-0.6 (-5.5;4.4)
	T=3	21.3 (7.8)	17.5 (10.0)	3.9 (-2.4; 10.2)	5.0 (-1.0;11.0)

Legend: regression coefficients are presented in bold when p-value is lower than 0.05

Discussion

In this study, a significant improvement in aerobic capacity and muscle force was found after 3 months of training in children with OI. However, the effects decreased with time after the intervention was stopped. The same pattern was also found for subjective fatigue. This clinically relevant improvement in aerobic capacity is greater than reported in healthy children, who after a comparable training period[23] in general improve approximately 8% in $VO_{2peak/kg}$. These large improvements can be explained by the lower initial levels of VO_{2peak} of children with OI.[5] Children with OI are relatively hypoactive and will improve to a greater extent during the first few months of training compared with healthy peers. Although the intervention consisted only of low-resistance strength training without heavy weights, there was a 12% improvement in muscle force in the children in the intervention group during the training period compared with the children in the control group. This improvement is less than has been reported for healthy children after an 8-week resistance training program, for which improvements in muscle force between 5% and 40% were reported.[24] The smaller progression in our study was expected because we only used very light resistance. However, the improvement in muscle force is clinically relevant for patients with OI because muscle force and the strength of bones are strongly associated.[25] In other chronic conditions, exercise interventions have been reported to be beneficial in improving exercise capacity and muscle force. The study of Klijn et al.[6] in children with cystic fibrosis showed that a 12-week exercise training program was effective in improving aerobic performance, anaerobic performance, and HRQoL. The study of San Juan et al.[7] showed in children with leukemia that a 16-week intra-hospital supervised conditioning program, including both strength and aerobic training, resulted in significant increases in aerobic capacity, muscle force, and functional ability.

In our study, 3 and 6 months (T=2 and T=3) after the completion of the intervention program, the children were not able to maintain the gained training effects. This is in contrast to findings in children with a congenital heart disease who maintained their exercise capacity 6 months after cardiac rehabilitation.[26] Elucidating the effects of detraining (reversibility) on children is confounded by the child's continued growth and development during the detrained period. As in adults, it seems that adaptations to training are transient and will steadily decay once training has stopped.[27]

This decay is also seen in this study. A long-term benefit depends upon the continuation of training sessions into adult life.[27]

Many of the included patients were not involved in regular exercise with sufficient intensity. Patients might avoid these exercises because of the risk of fractures or environmental concerns such as neighborhood safety.[28] This study indicates that children with mild to moderate OI can participate safely and effective in a supervised and individual tailored training program. This form of physical training can be an important way of increasing fitness in children with OI, because participation in regular sport activities is not an option for most children because of their reduced exercise capacity and their increased fracture risk. Supervised training and close monitoring of patients is also likely to improve patient compliance. Future studies should focus on the perceived barriers of these children to participate in physical exercise in their own neighborhood or in school, on children with type IV and III who are wheelchair-bound, and when unsupervised training can be as safe and effective as the current training regime. To maintain the improvement in exercise capacity and muscle force, the exercise regime need to be continued.

For some of our secondary outcome measures, we did not find any improvements during training or follow-up. On the physical summary of CHQ, for example, the children had a score of almost 50 at baseline, which indicates normal function compared with healthy children.[21] The subscales that contribute mostly to the physical summary score are physical functioning, (physical) role/social limitations, bodily pain/discomfort, and general health. On the CHQ psychosocial summary the patients scored >50, which is even higher than the healthy population.[21] The perceived competence of the patients did not change significantly. However, perceived competence seems not to be related to disease severity and impairment.[29] In the mildest form of OI (type I), a reduced athletic competence was previously reported.[29] In this study, no improvement on this subscale was observed after the intervention program. Individual supervised training can be advised as a safe and effective addition to current treatment methods in the short time. The long-term efficacy of this intervention requires further evaluation.

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8
Chapter

Summary and General Discussion

Marco van Brussel

Summary

Chapter 1 is a general introduction with background information about physical fitness and training in healthy children and children with a chronic condition.

Chapter 2 describes a systematic review on the physical fitness in survivors of acute lymphoblastic leukaemia (ALL). A systemic literature search was performed and identified 17 studies of which 3 studies were pooled in a meta-analysis. The analysis showed that the physical fitness in childhood leukaemia tends to be reduced, which suggests the need for engagement in regular physical activities to increase their functional capacity. In order to study whether these outcomes are also corresponding with Dutch survivors, we evaluated in **Chapter 3** the physical function and physical fitness in survivors of childhood leukaemia 5-6 years after cessation of chemotherapy. The evaluation showed that even after cessation of treatment, there were still clear late effects on motor performance and physical fitness. Chemotherapy-induced neuropathy and muscle atrophies are probably the prominent case for the reduced values. Physical training might be indicated in these patients to improve their physical fitness and muscle force.

In **Chapter 4**, we described the efficacy of exercise therapy on functional ability, quality of life, and aerobic exercise capacity in children with JIA by means of a systematic review. The analysis indicated that, overall, there is some evidence that exercise therapy can improve functional ability, health-related quality of life, physical fitness, and pain. However, the effects are not statistical significant. All studies (both, included and excluded) demonstrate that exercise therapy does not show detrimental effects on the short term and does not exacerbate arthritis. The large heterogeneity in outcome measures, as seen in our review, emphasise the need for a standardized assessment or a core set of functional and physical outcome measurements suited for health research to generate evidence about the possible effects of physical exercise for patients with JIA. With, among others, an example for a possible core set of physical outcome measurements in our mind we conducted the studies in **Chapter 5** and **6**.

Almost all physical fitness data are derived from findings in small cohorts and the current evidence base for anaerobic exercise capacity in JIA is small. Therefore, we compared in **Chapter 5** the aerobic and anaerobic exercise capacity of children with juvenile idiopathic arthritis (JIA) with healthy controls in a large cohort, to determine if there were differences based on

disease onset type, and to examine the relationship between aerobic and anaerobic exercise capacity in children with JIA. This study demonstrated that both the aerobic and anaerobic exercise capacity in children with JIA are significant decreased and that the WAnT, which measures the anaerobic exercise capacity, might be a valuable adjunct to other assessment tools in the follow-up of patients with JIA. In **Chapter 6**, we conducted a similar study in adolescents with JIA. In this study we examined the aerobic and anaerobic exercise capacity in adolescents with JIA compared with healthy peers, and to assess associations between disease-related variables and aerobic and anaerobic exercise capacity. The results demonstrated that also the adolescents have an impaired aerobic and anaerobic exercise capacity compared to their healthy peers. The likely cause for this significant impairment is multifactorial and needs to be revealed to improve treatment strategies. The combined sample of 87 subjects with JIA is a lager cohort than in any previous single study of exercise capacity.

In order to study the possibility of breaking through the descending spiral of deconditioning (as described in **Chapter 1**) we created an individual tailored training program for children with Osteogenesis Imperfecta (OI). To our knowledge, physical intervention studies have not been performed in children with OI. Therefore, we describe the findings of a randomized controlled trial on the effects of a physical training program on exercise capacity, muscle force and subjective fatigue levels in 33 patients with mild to moderate forms of Osteogenesis Imperfecta (OI) in **Chapter 7**. The patients in this study were randomly assigned to either a 12-week graded exercise program or care as usual for 3 months. After the exercise program, peak oxygen uptake (VO_{2peak}), relative VO_{2peak} ($VO_{2peak/kg}$), maximal working capacity (W_{max}), and muscle force were significant improved compared to control values. Follow-up measurements show a decrease of the gained improvements. These results show that a supervised training program can improve physical fitness and muscle force and reduces levels of subjective fatigue in a safe and effective manner.

General Discussion

The paradigm shift

Hippocrates suggested that: "In every movement of the body, whenever one begins to endure pain, it will be relieved by rest".[1] Traditionally, bed rest and passive movements were, besides medications, indeed the predominant treatments for children with various chronic conditions. However, in the last decades there has been a dramatic shift towards physical activation. There is increasing evidence that physical activity and exercise treatment have no short term deleterious effects on various (chronic) conditions.

When focussed upon the chronic conditions described in this thesis, the aforementioned shift is certainly true for JIA.[2] The rationale for limiting patients` activity in JIA was the hypothesis that inflammatory conditions were best treated by rest. Conventionally, treatment for patients with JIA has been aimed at managing pain and inflammation, preserving range of motion, and maintaining muscle force through rest and limiting the strain on arthritic joints.[2,3] Furthermore, it was believed that intense exertion might induce pain, swelling, extreme fatigue and flare-ups. Nowadays evidence regarding the beneficial effects of regular physical exercise for arthritis patients is rapidly growing.[4,5] Several studies even have suggested that exercise programs could increase a patient's physical performance and well-being[6-8] with minimal, if any, deleterious effects. The latter is in line with the findings of our review about the efficacy of exercise treatment in children with JIA, described in Chapter 4. As for well-being, the findings in our review were not entirely in line with the aforementioned studies[6-8]; however, none of these studies were included in our review, because they were non-randomized controlled trials. The well-being, described as parent/ patient global assessment of overall well-being, showed no significant changes before and after exercise treatment. The physical fitness showed some positive increase after exercise treatment, but this increase was not statistically significant.

However, in children with childhood leukaemia, the primary focus of research is to increase the survival rate by optimising the medical treatment. For these children it is crucial to primarily deflect the life-threatening condition, before focussing upon the long term side-effects of the disease, the treatment of these side-effects, and the possible beneficial or harmful effects of physical activity and training. Fortunately, childhood leukaemia has an increasing number of survivors and more emphasis can (and should) be

focussed upon these long-term effects. Assessment of the damage from the anti-leukaemia treatment can be studied in several ways; one of them is by studying the physical activity and fitness in these children. In Chapters 2 and 3 we found that there are indeed long-term side-effects from the anti-leukaemia treatment upon the physical fitness and function of these children. However, the so-called paradigm shift towards physical activation and studying the possible benefits of physical training has not been well-established in childhood leukaemia. The first pilot studies of exercise therapy have only recently been published.

As in JIA, children (and adults) with OI were, until recently, also told to avoid movement and most recreational activities.[9] Up to now, therapy for children with OI consisted of rehabilitation (aiming at improvement of functional ability, adaptation of compensatory strategies, range of motion and muscle strength), orthopaedic surgery, and more recently, pharmacologic therapies aimed at improving bone quality. The attitude towards physical activity and training is slowly changing due to positive individual experiences with low intensity and non-contact activities. However, fear of injury still remains the main limitation towards physical activation. This fear was not unfounded, because the efficacy and safety of an exercise training program was not established in patients with OI. We are the first to show randomised controlled data (Chapter 7) about the efficacy of an individual tailored and supervised exercise training program in children with OI type I and IV. This study indicates that these children can participate effectively and safely in this exercise training program to improve physical fitness, muscle force and to decrease their subjective fatigue. This is an important finding suggesting that these children are able to perform better in physical activities than was thought before and that physical training could be an additional component in the treatment of these children.

Decreased physical fitness in childhood chronic conditions

In this thesis, all described childhood chronic conditions showed decreased levels of physical fitness (Figure 8.1). In Chapters 2 and 3 we showed that there are negative long-term side-effects from the anti-leukaemia treatment upon the physical fitness and function of these children. These findings are in line with earlier findings.[10-12] However, these findings were never pooled into a meta-analysis to make a general statement about the physical fitness as has been done in Chapter 2. Our review showed that physical fitness tends to be reduced in survivors of ALL during childhood, and suggests engagement in regular activities. Chapter 3 confirms these findings in Dutch survivors of childhood leukaemia. The physical fitness (both aerobic and anaerobic capacity) in these Dutch survivors was, even 5-6 years after cessation of childhood leukaemia treatment, impaired compared to the control group of healthy peers.

The combined sample of 87 subjects with JIA, described in Chapter 5 and 6, is a larger cohort than in any previous single study of exercise capacity. The results of both studies in children and adolescents with JIA demonstrated significant impairments in both aerobic and anaerobic capacity in most subjects with JIA compared with healthy controls. Chapter 5 reports that 95% of the children with JIA have impaired aerobic capacity and 94% have impaired anaerobic power, suggesting that that this is an almost universal problem in children with JIA. By reporting the exercise capacity in terms of percent of predicted values for healthy controls, the results also indicate that the magnitude of these impairments is large.

The study of Takken et al.[13] was the first study which described the physical fitness in children with OI. The physical fitness (expressed in VO_{2peak} and $VO_{2peak/kg}$) of the patients with OI type I was significantly lower compared with healthy subjects. The baseline measurements of the children, in both the training and in the control group, which are described in our training study (Chapter 7), also showed significant reduced values compared to healthy peers. The results of both studies suggest that children with mild to moderate forms of OI, as a group, have an impaired physical fitness. To our knowledge, these studies are the only 2 studies in which the physical fitness has been described in these children.

Since deconditioning can be defined as loss of physical fitness, measurements of alterations in aerobic capacity should provide an accurate assessment of the magnitude of deconditioning.[14] These low physical fitness levels indicate, therefore, the state of deconditioning in these children.

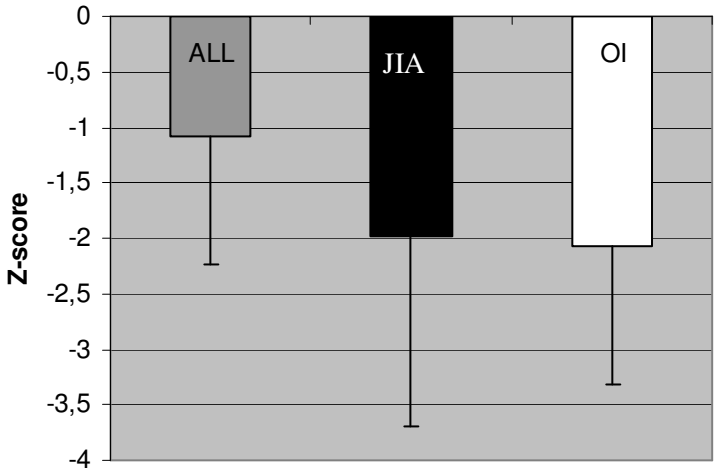

Figure 8.1: VO_{2peak} deviations (expressed as Z-scores) compared with control values.

Direct and indirect causes of decreased physical fitness

As said in the introduction, often the condition itself causes hypoactivity, which leads to a deconditioning effect, a reduction in the functional ability of the child, and further hypoactivity. However, in chronic conditions not only the effects of the condition itself are of influence upon the physical fitness, but also other indirect factors such as medication, fear, and a hypoactive life style could influence their physical fitness.[15]

Chemotherapy-induced muscle atrophy, myopathy and neuropathy might be the cause of the significantly reduced test scores in ALL. Muscle atrophy is a common problem in all cancer populations due to the catabolic effects of several chemotherapeutic agents such as vincristine and corticosteroids.[16-18] Muscle wasting implies decreased force capability of muscle and less muscle mass to consume oxygen during exercise.[19] Also the metabolic function of the muscle fibres can be impaired (due to decreased mitochondrial volume and/or mitochondrial myopathy) or reduced capillarisation induced by immunosuppressive therapy.[17] However, next to these effects, hypoactivity is also an unwanted effect of chemotherapy. Patients, often with complete remission of the basic disease, continue to be at risk of the consequences of systemic deconditioning resulting from restrained physical activity. In essence, chemotherapy invites a ''spectrum of disuse'' promoted by some parents and physicians for the sake of health protection after the life threatening disease.

This excessively protective approach, however, leads to an unnecessarily hypoactive life style with consequential obesity, skeletal muscle atrophy, and increased risk of cardiovascular disease.[20] As a result, early fatigue during low-to-moderate physical task becomes a self-perpetuating condition.[18]

In JIA, multiple pathophysiologic factors specific to the disease may limit the physical fitness in children with JIA.[21] A common finding in children with JIA is anaemia, which results in decreased oxygen supply towards the muscles; this anaemia in combination with the presence of muscle atrophy, results in poor utilization of oxygen by the exercising muscles, a higher mixed venous oxygen content, and low VO_{2peak}.[22] Furthermore, a lower quality and quantity of muscle mass probably cause primarily the reduced physical fitness of JIA patients.[23] Children with arthritis have been shown to participate in less physical activities and have a higher number of sleep hours than their peers.[24] These factors may also result in a descending spiral of deconditioning and disability resulting in an inactive lifestyle. Chapters 5 and 6 add information to the continuing discussion about the relationship between reduced fitness and disease status. In these chapters we found little difference in fitness levels between subjects who had active disease and were taking medications and those who were in clinical remission and not taking medications. This supports the current view that exercise capacity is not significant related to disease status in JIA.[25] Sex and disease type appear to be more important than either disease activity. In Chapter 5 we found the largest deficits in exercise capacity in children with positive rheumatoid factor polyarticular-onset JIA, and the smallest in those with persistent oligoarticular-onset JIA.
In both Chapter 5 and 6 we showed that aerobic and especially anaerobic exercise capacities are more impaired in girls than boys. While it mirrors the typical sex differences in healthy children, it is important to remember that girls with JIA in these studies were compared with an age-matched and sex-matched control group.

Next to the direct effects of the disease such as impaired bone development and impaired skeletal, cardiac and pulmonary muscle tissue, there are striking indirect factors influencing the physical fitness in children with mild to moderate forms of OI. In these children fear of fractures during exercise is the most frequent heard explanation for not participating in sport and leisure activities. This fear is often promoted by some parents and physicians for the sake of their health protection. This protective approach causes an unnecessary hypoactive lifestyle and therefore increased deconditioning. The fear of fractures during exercise is based on the lack of knowledge about the

effects of physical activity or training on the bones and other tissues. Fortunately, we have shown that these children can participate safely and effectively in exercise activities (Chapter 7). The subjective attitude towards physical activity was positively changed during the intervention in children and parents who participated in the study as described in Chapter 7.

As described above, the possible explanations for the decreased physical fitness in children with a chronic condition are multifactorial; therefore it is important to find these limitations per condition, so more specific treatment approaches can be formulated and executed in the future.

Physical activity, functional ability and health-related quality of life

Children with a chronic condition often have more problems in performing all kinds of daily activities (functional ability) compared with healthy peers. The performances of the activities of daily living require energy. Peak oxygen uptake (VO_{2peak}) determines the maximal quantity of energy which can be released by usage of oxygen, the aerobic metabolism.[26] Every litre of oxygen is about equal to 20 KJoules of energy. Patients with a reduced physical fitness perform the same activities at a higher intensive level compared with healthy individuals who have a higher physical fitness. In general, a minimal VO_{2peak} of 19 $ml \cdot kg^{-1} \cdot min^{-1}$ is necessary for normal daily activities.[27] Patients below this minimum are most likely not able to execute these activities. For example children who only can reach activities which require 5 METs [a], cannot participate in activities of 10 METs. The children are already performing at their maximum with light-moderate intensive activities; when stimulated to participate in activities of high intensity they are at risk of overtraining and extreme exhaustion. Already in 1983, Bar-Or[15] suggested a link between a low physical fitness and a low functional ability (see Chapter 1) in paediatric chronic conditions. Chapter 6 adds to our knowledge of the relationship between physical fitness, performance of daily activities, and health related quality of life by showing a significant and strong correlation among anaerobic capacity and functional ability, measured by CHAQ and

[a] A MET (or unit of metabolic equivalent), is defined as the ratio of a person's working metabolic rate relative to the resting metabolic rate. One MET is defined as 1 kilocalorie per kilogram per hour and is the caloric consumption of a person while at complete rest ($\approx$ 3,5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$). METs are commonly used in the context of aerobic exercise to gauge the intensity of the workout. A workout of 2-4 METs is considered light, while intensive activities can yield workouts of 12 or more METs.

disability index (DI). Simply put, subjects who were more physically fit reported feeling better and having less difficulty with daily activities.

Probably, the most important health-related benefit from high levels of physical activity is the improvement of physical fitness. Physical activity and physical fitness might be related; however they are not the same. Physical activity has important health benefits in youth. Physical activity is associated with more favourable biological cardiovascular disease risk-factor profiles in children and adolescents, such as lower blood pressure, more favourable serum lipid and lipoprotein levels, and decreased adiposity.[28] For children with a chronic condition it is thus also important to improve their physical activity and physical fitness levels to prevent these secondary risk-factors, to improve their health-related quality of life, and improvement of physical activity can add to an improvement of their self-esteem and enjoyment in sports and life.

The improvements in exercise capacity and VO_{2peak} brought about by physical training are related to improved health related quality of life, particularly in patients with exercise capacity limited by various disease processes.[29] However, up to now, there is no direct evidence that physical activity in children with a chronic condition is related to adult health related quality of life. In fact, there is little known about the relationship between increased physical fitness and improved health related quality of life in childhood and into adulthood.

Physical training

As described in Chapter 1, a training program might prevent the deconditioning due to hypoactivity and, therefore, could break the descending spiral of deconditioning. Although the physical fitness levels in the described chronic conditions are lower compared with healthy controls, we must focus upon the individuality of the child: can we increase the physical fitness or is the child already performing at his or her maximal capacity? Whenever the latter is true, we cannot increase his or her physical fitness and therefore we should be careful not to overtrain this child. However, in children who do not perform at their maximum, a training program might prevent the aforementioned deconditioning.

The role of exercise as therapy in children with a variety of chronic conditions is becoming increasingly recognized.[30] However, the clinician attempting to prescribe a physical training program for children with a chronic condition faces many difficulties. For these children, no clear recommendations exist concerning physical training programs. The mechanisms which are responsible for the loss of physical fitness in the child differ according to the condition; which is the reason for difficulty in proposing adapted programs of exercise.[31] Probably the most important issues in developing, and properly executing, physical training programs for children with a chronic condition is to consider the individual characteristics, the disease specific limitations of the locomotive apparatus, the short and long term side-effects of the treatment, nutritional status, and the (in)direct benefits or possible harms of a training program on the specific condition itself. The principle "one size fits all" does not apply for healthy children, and this principle is probably even less applicable for children with a chronic condition.

The question whether we should physically train children with ALL is debatable, because there are several arguments against physical training in this population. Anthracyclines (AC) are known to have both acute and late cardiotoxic side effects, especially in high doses.[32-36] Jarfelt et al. reported, in a longitudinal follow-up of ALL survivors, sub-clinical cardiac dysfunction with exercise stress echocardiography even after low doses of AC.[37] We do not know what the short and long-term effects of high intensity exercise upon the cardiac function are in children which are at risk for or show cardiotoxicity. Besides the possible cardiac impairments, other long-term side-effects are known which could endanger a safe and effective training, e.g. peripheral neuropathy and muscle atrophy as a result of catabolic effects of vincristine and corticosteroids. Before we should start with training in this population, there is a need for good RCTs which study the safety and efficacy of physical activation and training with regard to the cardiotoxicity and other side-effects of anti-leukaemia treatment; enabling us to make a more general statement about the safety and efficacy of physical training in this population. To our knowledge, there are only four small studies in which children with leukaemia were trained.[38-41] All showed improvements in physical fitness, however, none of these studies were controlled by randomization. These findings in combination with documented significant improvements of VO_{2peak} of adult cancer patients with endurance training[42], might be a good reason to explore the training capability in these children

after or even during the anti-leukaemia treatment. Moreover, repeated exercise may decrease the effects of muscle atrophy and cachexia due to both cancer and the toxicity of cancer therapy through suppressing inflammatory responses, enhancing immune function, rate of protein synthesis and antioxidant enzyme activities.[43] However, exercise interventions are expected to be especially successful in children with leukaemia because chronic deconditioning before the disease is not present in childhood leukaemia and the plasticity of body tissues and their adaptability to training is greater during childhood compared to adulthood.[18]

Few studies of physical training in children with arthritis are available. Most of them have a small study population, are not randomized, and rely on field testing rather than precise, standardized laboratory measurements of oxygen consumption and power output to assess fitness outcomes.[44] Increasing evidence shows that children with JIA can improve their physical fitness through a carefully constructed and supervised aquatic or land-based physical training program. Almost all studies, also those with little or no improvement, agree that children with JIA can safely participate in physical activities[45-49] with no detrimental or adverse effects. The latter was also found in Chapter 4 where we reviewed the efficacy of exercise therapy in children with JIA, however we must state that these studies only described that there were no short term detrimental and/ or adverse effects; whatever the long-term effects were, was not mentioned. In this review we only found 4 randomised controlled trials which could be pooled for several outcome measures in a meta-analysis. The results of this meta-analysis showed that the lack of statistically significant differences, between intervention and control groups, and heterogeneity in used outcome measures makes it difficult to conclude whether physical training can be recommended as an effective treatment for JIA, or what are the most effective guidelines for physical training in these children. Next to this, in Chapter 5 we raise the question whether anaerobic training is safe for children with arthritis, because these activities are typically faster, at a higher intensity, and have higher impact on the joints than those included in current general condition regimens (which are primarily aerobic regimens) for children with JIA. This may depend to a great extent on a child's disease type and status. While children with clinically active polyarticular-onset JIA are the most likely to have significantly impaired anaerobic capacity, their risk for injury with high-impact activities is high.[25] Those with clinically inactive disease may be able to safely participate in anaerobic training and improve their fitness and functional performance.

In Chapter 7 we described a training program and the results of this program in children with mild to moderate forms of OI. In this chapter a significant improvement in aerobic and muscle force was found after 3 months of training in these children. However, the effects decreased over time after the intervention was stopped. The same pattern was found for subjective fatigue. Since this was the first time anybody described the effects of a physical training program in these children, we can only make a statement according to this RCT and can conclude that these children are able to break through the spiral of deconditioning. The children improved their physical fitness, however the study did not show improvements in their physical functioning (assessed with the CHQ), due to a so-called ceiling effect measured at the baseline measurement. Therefore this questionnaire is not suited for the measurement of function in these children. The children themselves stated that they benefited from this kind of physical training.

After the completion of a training program, children (and adults) are often not able to maintain their gained improvements. How fast this decrease is depends on the training history, training duration of the program and the type of training. In order to maintain the improvements, the prescribed individual training regimens need to be continued, perhaps into adulthood. Most children with a chronic condition have an initial lower level of VO_{2peak} compared to healthy peers; they will improve to a greater extent during the first months; so training will be beneficial in most of the cases.

Participation and implementation

Although most health professionals now agree on the significance of keeping children with a chronic condition physically active and fit, when they are capable of participation and not already using their full potential, the realisation of this is not that easy. For the children who are able to increase their capability, we need to find ways to increase the daily activities in these children, such as increasing extra-curricular sports activities. In response of the findings in this thesis we currently are running a nationwide program to stimulate sports and physical activities and try to make the transition to peripheral sports clubs.

Clinical relevance

Determination of the physical fitness level in these children can be of clinical relevance, because this variable is a powerful predictor of mortality in both healthy and diseased adults.[50, 51] Whether the level of physical fitness during childhood also predicts the mortality can only be determined by longitudinal studies, which have not been finished up to now, because the population of these studies is still alive. It can only be assumed that the level of physical fitness in children can predict the mortality in adulthood. However, until results of longitudinal studies are unclear, it is still important to understand and distinguish the different direct and indirect causes for the decreased levels of fitness, for possible short term treatments. The studies in children with ALL and JIA showed that not only the aerobic capacity was decreased; but that the anaerobic exercise capacity was impaired as well. These impairments in anaerobic capacity might have strong clinical implications because many activities of daily living, such as play, leisure and sports activities, are initially short-term and high intensity (anaerobic) in nature.[52] Impairment in anaerobic capacity makes these activities difficult to perform or impossible to be performed at all.

This thesis also showed clinically relevant findings per chronic condition. For example, Chapter 7 showed an improvement in muscle force in children with OI. This improvement is clinically relevant for these patients, because muscle force and the strength of bones are strongly associated.[53] Moreover, we found that these children could participate safely and effectively in physical activities and training; this is of high clinical relevance since the current general way of thinking still is to keep these children away from physical activities. This current way of thinking is caused by fear of fractures and ignorance concerning the effects of physical activities and training.

The findings of significant impairments in exercise capacity in adolescents with JIA (Chapter 6) challenge any notion that children may "outgrow" their arthritis or recover their functional capacity simply by getting older. Adolescents with JIA who have impaired fitness, due to a sedentary lifestyle, may be at enlarged risk for reduced fitness in the middle and later adult years, when muscle mass and strength naturally decline.

Directions for future research

We must think across the existing line of thinking to understand the impact of each chronic condition on specific components of exercise capacity and, in turn, the effects of these impairments on children's functional performance/ ability. Furthermore, next to the short term effects more emphasis should be put on the long-term effects of well-structured exercise and training programs in children with leukaemia, juvenile arthritis, and Osteogenesis Imperfecta should be studied, so that we can increase our knowledge about the underlying physiological (and psychological) determinants in these conditions.

The review article in Chapter 4 showed the disturbing fact that many studies cannot be compared with each other due to different outcome measures. This finding is not only limited to studies in childhood arthritis, but almost all studies, regarding physical fitness and physical training, in children with a chronic condition are not analogous in their outcome measures. This emphasises the need for a standardized assessment or a core set of functional and physical outcome measures suited for health research to generate evidence about the level of physical fitness and possible effects of physical exercise training in individual chronic conditions. Next to these functional and physical outcome measures there is also a need for core sets of instruments for measuring activity and, maybe even more important, the participation in individual chronic childhood conditions.

To accomplish this, more large multi-centred randomized controlled exercise trials should be executed for providing more conclusive information about the benefits and possible risks associated with aerobic, anaerobic and strength training in children with various chronic conditions. However, in order to compare study results, it is crucial to develop these aforementioned standardized core sets of physical-, functional-, activity, and participation outcome measures. In this thesis (Chapters 5 and 6) we provide a core set that should allow comparison of outcomes across studies in children with JIA, something that previously has been difficult. Such models should be created for every individual (chronic) condition, so that we can create clearer insights in the exercise physiology of these populations.

As we gain experience with many different patient populations, we will gradually be able to move beyond routine medical care issues to meeting the goals of optimising physical functioning and overall health and well-being for a wide variety of individuals with chronic conditions.[54]

Exercise testing and exercise physiologists

Exercise is often overlooked as a valuable component in the diagnosis and management of diseases in the paediatric and adolescent population; moreover, exercise testing can contribute significantly to the clinical assessment. There are numerous rationale for the use of exercise testing in paediatric diagnoses.[55] In fact, there are more paediatric than adult disorders in which exercise testing is of clinical relevance.[15] Rationale for exercise testing in the paediatric population have been listed by several authors[15, 56] and can been seen in Table 8.1.

Table 8.1: rationale for exercise testing adapted from Bar-Or[57]

Measure Physical Working Capacity - Assess function: establish whether a child's daily activities are within the child's physiologic functioning level. - Identify deficiency in specific fitness component: muscular endurance and force may limit daily performance rather than aerobic capacity (e.g. muscular dystrophy). - Establish a baseline before the onset of an intervention program. - Assess the effectiveness of an exercise prescription. - Chart the course of a progressive disease.
Exercise as a provocation test - Amplify pathophysiologic changes - Trigger changes otherwise not seen in the resting child
Exercise as an adjunct diagnostic test - Non-invasive exercise test can be used for screening to determine the need for an invasive test - Assessing the severity of dysrhythmias - Assessing the success of surgical correction - Assessing the adequacy of drug regimens at varying exercise intensities
Assessment and differentiation of symptoms: chest pains, breathlessness coughing, easy fatigability
Instil confidence in child and parent
Motivation or compliance in intervention program

The studies in this thesis also emphasize the importance of clinical paediatric exercise physiologists for their role in the health care. Paediatric exercise physiologists are important to the clinical setting of the healthcare, besides determining the physical fitness in a child (for prescribing activity programs and progression); they can identify a specific pathophysiological pattern in a given disease. The rationale is based on the increase in metabolic demands during exercise that stresses, sometimes to the limit, metabolic, ventilatory, gas exchange, cardiac, vascular, neuromuscular, and thermoregulatory functions.[58] A malfunction in a system is more likely to be discovered during stress than during rest, when functional demands are lower.[58]

Dilemma

Clinicians attempting to prescribe a program of exercise training in children with chronic conditions face a dilemma. In various chronic conditions, exercise may encourage health in part by stimulating growth factors and tissue anabolism. In contrast it is known that the same process of exercise, if sufficiently intense, can stimulate inflammatory cytokines and lead to a catabolic state.[59-62] Finding the optimal level of physical activity in children and adolescents with a chronic condition can be difficult because the underlying disease can be associated with increased basal energy, malnutrition and inflammation, all of which promote tissue catabolism even at rest.[30] This dilemma typifies the problem that exists in implementing exercise therapy for children with a variety of inflammatory/ catabolic conditions like childhood arthritis and cancer in which there is increasing interest in developing truly beneficial and safe exercise interventions.[22, 63]

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Dutch summary

(Nederlandse Samenvatting)

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(Nederlandse Samenvatting)

Onderzoek bij kinderen gaat gepaard met veel uitdagingen en er is nog veel onduidelijk over de fysiologische reacties op fysieke inspanning en training in relatie tot leeftijd, groei, maturatie en geslacht, vooral bij kinderen met een chronische aandoening. Morfologische parameters en fysiologische functies, zoals het hartvolume, longfunctie, aërobe capaciteit en spierkracht ontwikkelen zich met toenemende leeftijd en lichaamsgrootte; hierdoor kunnen kinderen niet zomaar gezien worden als een miniatuur versie van volwassenen. Hiernaast verandert de fysieke fitheid en de trainbaarheid ook tijdens de groei en maturatie. Variaties in groei en maturatie van een kind kunnen diepgaande effecten hebben op de aspecten van fysieke activiteit, fysieke fitheid en fysieke mogelijkheden.

Ondanks de grote toename van het aantal gepubliceerde onderzoeken over de inspanningsfysiologie bij kinderen in de laatste decennia, is deze hoeveelheid data schaars ten opzichte van de inspanningsfysiologische data bij volwassenen. Begrip van de fysiologie van het kind met een chronische aandoening tijdens inspanning is zelfs nog veel schaarser; in dit proefschrift hebben we geprobeerd om relevante studies toe te voegen aan deze schare data om hierdoor tot een beter inzicht te komen over de fysiologie van de fysieke fitheid en training bij deze kinderen. In de wetenschappelijke literatuur wordt de fysieke fitheid als synoniem gezien van de cardio-respiratoire (of aërobe) fitheid. Anaërobe fitheid heeft minder aandacht gekregen in vergelijking tot de aërobe fitheid, terwijl het meten van de anaërobe fitheid zeker belangrijk is aangezien de dagelijkse activiteiten van kinderen zowel uit aërobe als anaërobe activiteiten bestaan. In dit proefschrift hebben we naast de aërobe capaciteit ook de anaërobe capaciteit beschreven in de interventie studies (**Hoofdstuk 3, 5 en 6**). Na het bepalen van het huidige fitheidniveau per chronische aandoening en per kind, is het belangrijk om te onderzoeken óf deze kinderen fysiek trainbaar zijn, en hierdoor in staat zijn om de neergaande spiraal van deconditionering (zie ook **Hoofdstuk 1**) tegen te gaan óf dat deze kinderen al presteren op hun maximale kunnen en een grote kans bestaat op overtraining, wanneer zij gaan trainen. Wanneer de kinderen trainbaar zijn, is het aanbieden van de mogelijkheid om deel te gaan nemen aan sport en vrijetijdsactiviteiten misschien wel de belangrijkste en de meest logische causaliteit.

Dit proefschrift beschrijft drie verschillende typen chronische aandoeningen, namelijk acute lymfatische leukemie (ALL), juveniele idiopatische artritis (JIA) en Osteogenesis Imperfecta (OI). ALL is een verkregen acute aandoening met chronische gevolgen, JIA is een verkregen chronische aandoening en OI is een aangeboren en genetische chronische aandoening.

In **hoofdstuk 1** wordt een algemene inleiding gegeven over de fysieke fitheid en training bij gezonde kinderen en kinderen met een chronische aandoening, waaruit blijkt dat we kinderen niet zomaar kunnen beschouwen als miniatuur uitvoeringen van volwassen. **Hoofdstuk 2** beschrijft een systematische review over de fysieke fitheid (VO_{2piek}) bij overlevenden van acute lymfatische leukemie (ALL). Een systematische literatuur zoekopdracht werd uitgevoerd in de volgende databasen: MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PEDRO en SportDiscus. Uit deze zoekopdracht werden 17 wetenschappelijke studies geïdentificeerd. Uiteindelijk zijn drie studies geïncludeerd met in totaal 102 patiënten. De uitkomstmaten van deze studies werden, indien mogelijk, geanalyseerd door middel van een meta-analyse. Deze analyse geeft aan dat de fysieke fitheid bij kinderen met ALL verlaagd blijkt te zijn, wat aangeeft dat deze kinderen waarschijnlijk baat zullen hebben van deelname aan regelmatige fysieke activiteiten om hun functionele capaciteit te kunnen vergroten.

Om te bepalen of deze uitkomst ook geldt voor de Nederlandse overlevenden, hebben we in **Hoofdstuk 3** de fysieke functie en fysieke fitheid bij overlevenden van acute lymfatische leukemie 5 tot 6 jaar na het beëindigen van hun chemotherapie geëvalueerd. Dertien kinderen die de ziekte overleefd hadden participeerden in deze studie (gemiddelde leeftijd was 15,5 jaar). De evaluatie laat zien dat zelfs lang na het stopzetten van de chemotherapie er nog duidelijke (lange termijn) effecten te zien zijn op de motoriek en fysieke fitheid bij deze Nederlandse kinderen. Chemotherapie geïnduceerde neuropathie en spier atrofie zijn waarschijnlijk de meest prominente oorzaken voor deze verminderde uitkomstwaarden. Fysieke training kan geïndiceerd worden bij deze kinderen om hun fysieke fitheid en spierkracht te laten toenemen.

In **hoofdstuk 4** hebben we de effectiviteit van bewegingstherapie ("exercise therapy") op functionele vaardigheden, gezondheidsgerelateerde kwaliteit van leven en aërobe capaciteit bij kinderen met Juveniele Idiopatische Artritis (JIA) beschreven in de vorm van een systematische review (volgens de methodiek van de Cochrane Collaboration). De effectiviteit van bewegingtherapie bij kinderen met reuma was nog nooit eerder beschreven in de vorm van een Cochrane review; hetgeen bij volwassen wel het geval is. In de volgende elektronische databestanden is, tot november 2007, gezocht naar geschikte gerandomiseerde en gecontroleerde studies: MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PEDRO, SportDiscus, Google Scholar, AMED, Health Technologies Assessment database, ISI Web Science Index to Scientific and Technical Proceedings, and the Chartered Society of Physiotherapy website. Uiteindelijk zijn 3 studies met in totaal 212 patiënten in dit onderzoek opgenomen.

De methodologische kwaliteit van de geïncludeerde studies is gescoord met behulp van de PEDro-scorelijst. Dit is een lijst bestaande uit 10 onderdelen waarbij elk onderdeel dat aanwezig of beschreven is in een studie, gescoord wordt met een punt. Het aantal punten loopt op van 0 punten (slechte methodologische kwaliteit) punten tot 10 punten (uitstekende methodologische kwaliteit) punten. De methodologische kwaliteit van de gevonden studies was zeer goed (mediane PEDro-score van 8; range van 7 tot 8). De uitkomstmaten van de studies die met elkaar vergeleken konden worden, zijn geanalyseerd met behulp van een meta-analyse.

Deze analyse gaf aan dat er, in het algemeen, weinig bewijs is dat bewegingstherapie de functionele vaardigheid, de gezondheidsgerelateerde kwaliteit van leven, de fysieke fitheid kan verbeteren en de pijn kan laten afnemen; de gevonden positieve effecten waren niet statistisch significant. Alle studies (zowel de geïncludeerde als de geëxcludeerde) gaven aan dat bewegingstherapie geen nadelige effecten laat zien op de korte termijn en niet zorgt voor een exacerbatie van de ziekte. De grote heterogeniteit van de uitkomstmaten, zoals beschreven in onze review, benadrukt de noodzaak voor een gestandaardiseerde vaste set van functionele en fysieke uitkomstmaten die geschikt zijn voor gezondheidsonderzoek, om op deze wijze bewijs te verzamelen over de mogelijke positieve effecten van bewegingstherapie bij patiënten met JIA. Met onder andere een voorbeeld van een dergelijk vaste set van fysieke uitkomstmaten in onze gedachten hebben we **Hoofdstuk 5 en 6** opgezet.

Bijna alle data over de fysieke fitheid bij kinderen met JIA wordt verkregen uit studies met kleine cohorten en de huidige bewijskracht van anaërobe capaciteit bij deze populatie is zeer laag. In **Hoofdstuk 5** vergelijken we 1) de aërobe én anaërobe capaciteit van kinderen met JIA met die van gezonde controles in een grote cohort, 2) bepalen we of er verschillen bestaan die gebaseerd zijn op verschillende debuuttypen binnen deze ziekte, en 3) bekijken we of er een relatie bestaat tussen de aërobe en anaërobe capaciteit bij kinderen met JIA. Tweeënzestig kinderen met JIA (gemiddelde leeftijd 11,9 jaar) participeerden in dit onderzoek. De aërobe capaciteit werd gemeten met behulp van een maximale inspanningstest en gas-analyse. De anaërobe capaciteit werd gemeten met behulp van de WAnT (Wingate Anaerobic Test). De resultaten van deze studie geven aan dat zowel de aërobe als de anaërobe capaciteit significant verlaagd zijn ten opzichte van normaal waarden en dat de WAnT een waardevolle toevoeging kan zijn op andere meetinstrumenten in de follow-up van patiënten met JIA. Hiernaast bestaat er een verschil in de resultaten tussen de verschillende debuuttypen; hiermee dient rekening gehouden te worden in toekomstige studies. Tenslotte hebben we aangetoond dat er statistisch significante correlaties bestaan tussen de verlaagde aërobe en anaërobe capaciteit van kinderen met JIA.

In **Hoofdstuk 6** hebben we een gelijksoortig onderzoek verricht bij adolescenten met JIA. In deze studie hebben we de aërobe en anaërobe capaciteit van adolescenten met JIA vergeleken met gezonde leeftijdgenoten, hiernaast hebben we ook gekeken naar associaties tussen ziekte-gerelateerde variabelen en de aërobe en anaërobe capaciteit. Vijfentwintig adolescenten participeerden in dit onderzoek (gemiddelde leeftijd 17,1 jaar). De aërobe en anaërobe capaciteit werd op dezelfde manier bepaald als in **Hoofdstuk 5.** De resultaten van dit onderzoek geven aan dat de adolescenten, net als de kinderen in **Hoofdstuk 5**, een significant verminderde aërobe en anaërobe capaciteit hebben in vergelijking tot gezonde leeftijdsgenoten. De mogelijke oorzaak voor deze significante verlaging is multi-factorieel en moet onthuld worden om huidige behandelstrategieën te verbeteren. De bevindingen van een statistisch significante verlaging van de inspanningscapaciteit, bij adolescenten met JIA, tart elke idee dat kinderen over dit ziektebeeld heen kunnen groeien of dat hun functionele vaardigheden zullen herstellen naar mate zij ouder worden. De gecombineerde groep van 87 patiënten (uit **Hoofdstuk 5** en **6**) met JIA is de grootste cohort ooit beschreven in een studie naar inspanningscapaciteit.

Hoofdstuk 5 geeft hiernaast aan dat 95% van de kinderen met JIA een verminderde aërobe capaciteit hebben en dat 94% van de kinderen een verminderde anaërobe capaciteit hebben wat de suggestie wekt dat dit een bijna universeel probleem is bij kinderen met JIA.

Voor het bestuderen of het mogelijk is om de neergaande spiraal van deconditioning te doorbreken door middel van fysieke training, hebben we een individueel op maat gemaakt trainingsprogramma voor kinderen met Osteogenesis Imperfecta (OI) gecreëerd. Voor zo ver wij weten zijn er geen eerdere fysieke interventie studies bekend bij deze populatie en zijn wij de eersten die een dergelijk programma opzetten, uitvoeren en analyseren. In **Hoofdstuk 7** beschrijven we de bevindingen van een gerandomiseerde en gecontroleerde studie over de effecten van een fysiek trainingsprogramma op de inspanningscapaciteit, spierkracht en subjectieve vermoeidheid bij 33 patiënten met een milde tot gematigde vorm van Osteogenesis Imperfecta. De patiënten in deze studie werden gerandomiseerd in een trainingsgroep of in een controle groep voor 12 achtereenvolgende weken. De trainingsgroep kreeg een individueel op maat gemaakt trainingsprogramma en de controle groep kreeg alleen zorg zoals gebruikelijk. Direct ná het trainingsprogramma was de piek zuurstof opname (VO_{2piek}), de relatieve VO_{2piek}, het maximale vermogen (W_{max}) en spierkracht significant verbetert ten opzichte van de controle waarden. De follow-up metingen (6 en 9 maanden na de start van het trainingsprogramma) laten een afname zien van de verkregen verbeteringen. Deze resultaten geven weer dat een gesuperviseerd en individueel trainingsprogramma de fysieke fitheid en spierkracht kan laten toenemen en de subjectieve vermoeidheid kan verminderen op een veilige en effectieve manier; maar ook dat deze kinderen moeten blijven trainen om de verkregen resultaten te behouden.

Dankwoord

Dankwoord

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Marco

List of Publications

List of Publications

Peer reviewed (international)

Takken T, Van Brussel M, Engelbert RHH, Van der Net J, Kuis W, Helders PJM. Exercise Therapy in Juvenile Idiopathic Arthritis. Cochrane Library April 2008 [In Press]

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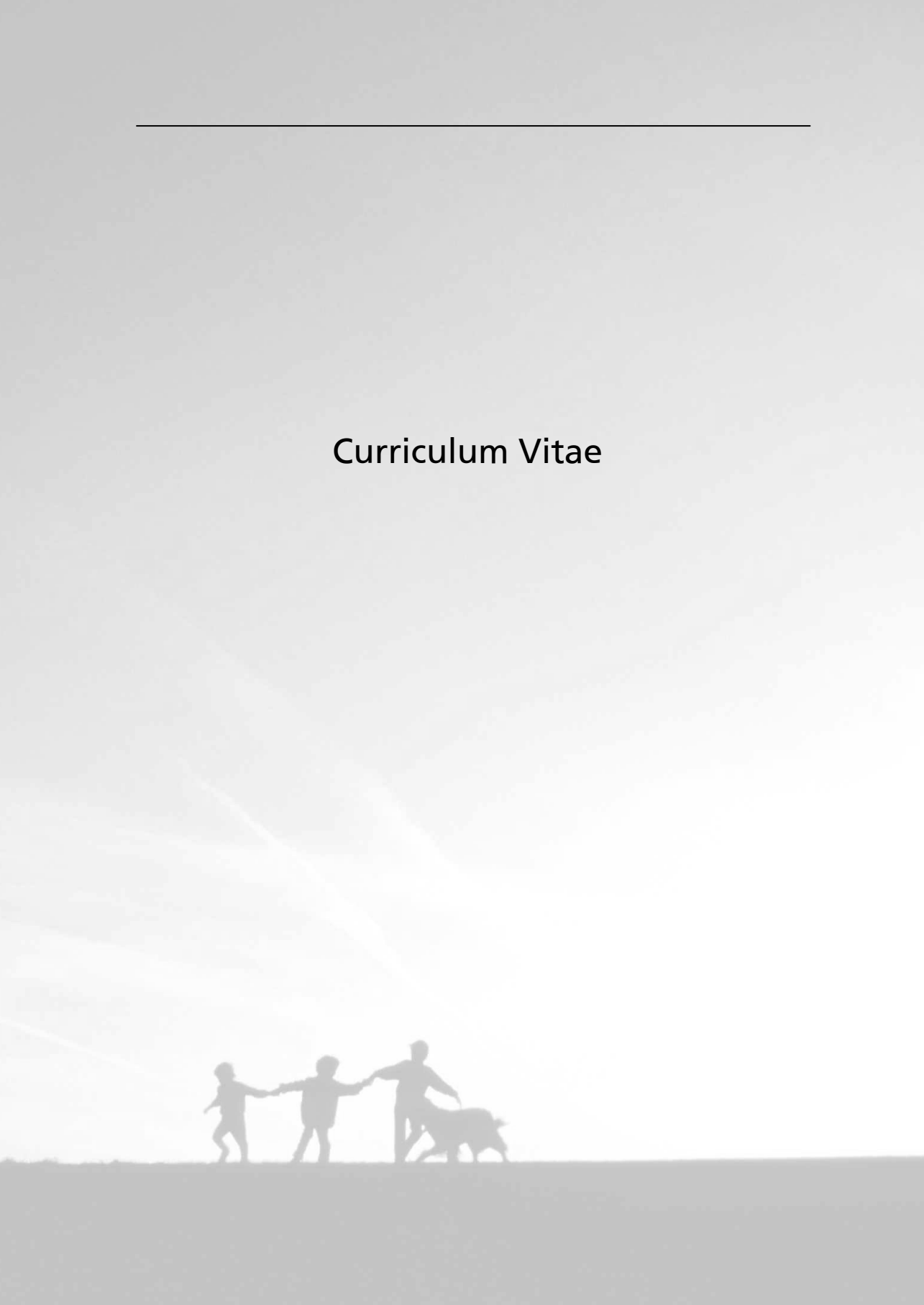

Curriculum Vitae

Marco van Brussel werd op 7 juni 1979 geboren in Zwolle. In 1999 behaalde hij het Atheneumdiploma aan de Van der Capellen scholengemeenschap te Zwolle. In aansluiting daarop startte hij met de opleiding Gezondheidswetenschappen aan de Universiteit Maastricht. In het 2e jaar koos hij voor de afstudeerrichting Bewegingswetenschappen.

In 2004 behaalde hij het doctoraaldiploma voor deze afstudeerrichting. De studie werd afgesloten door afronding van zijn afstudeerscriptie "*Acute Lymphoblastic Leukemia*". Zijn scriptie beschreef het onderzoek dat hij verricht had op de afdeling kinderfysiotherapie en pediatrische inspanningsfysiologie van het Wilhelmina Kinderziekenhuis (UMC) te Utrecht, onder begeleiding van Dr. T. Takken, waarin naar inspanningsfysiologische parameters werd gekeken bij overlevenden van acute lymfatische leukemie. In aansluiting op dit stage onderzoek kreeg hij van 2005 tot heden een aanstelling als promovendus aan deze zelfde afdeling onder leiding van Prof. Dr. P.J.M. Helders. Het resultaat van zijn promotietraject ligt nu voor u in de vorm van een proefschrift. De auteur hoopt dat u met het lezen van dit proefschrift evenveel plezier beleeft als hij zijn onderzoek verricht en uitgewerkt heeft.