Physical fitness, activity and training in children with juvenile idiopathic arthritis

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Physical activity and fitness are increasingly recognized as important outcomes in the follow-up and treatment of patients with juvenile idiopathic arthritis. In the past, major concerns were on the detrimental effects of physical exercise; now evidence is growing on the beneficial effects of exercise. The purpose of these exercise programs is to promote a more active lifestyle and/or enhance physical fitness. This article will review the findings of recent studies in juvenile idiopathic arthritis in the area of physical fitness, physical activity and training. It is advised that clinicians are discussing appropriate levels of physical activity (daily participation in >60 min of moderate-to-vigorous physical activity) with their patients in clinical consultations.

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Pediatric HEALTH

Nowadays, pediatric health professionals have acknowledged the use of exercise in the prevention, diagnosis and treatment of chronic childhood conditions and related health problems. Physical fitness is a principal element of clinical exercise physiology and is a multidimensional concept that has been defined as a set of attributes that people possess or achieve to perform physical activity [1]. In current pediatric research, physical fitness has become synonymous with cardiorespiratory or aerobic fitness. In general, aerobic fitness is expressed as the maximal oxygen uptake (VO_{2max}); and is widely recognized as the best single measure of a person's aerobic fitness [2].

As opposed to healthy children, children with a chronic condition often are constrained from participation in physical activities or sports 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 and to further hypoactivity [3]. Physical activity can be measured using different methods. All methods have their pros and cons. For example, doubly-labeled water can be used to estimate the activity energy expenditure with great precision over a 2 week period; however, the costs are high and ease of measurement is low. On the other hand, activity estimates from questionnaires and activity recalls are relatively easy to obtain but the precision of these methods are low. Activity monitoring, using small devices worn at the hip, wrist or ankle that record acceleration of a body segment, seems to be a promising method to objectively assess and profile physical activity [4–6], and seems to be more valid than indirect assessments (e.g., questionnaires and activity logs) [7].

Physical fitness can also be measured using different methods. For example there are several different exercise testing methods to directly measure peak oxygen uptake – the gold standard – of aerobic fitness, such as graded treadmill or cycle ergometer tests with respiratory gas analysis. In addition, there are also tests to estimate the aerobic fitness from, for example, endurance time (e.g., Bruce treadmill test [8]) or time to complete a task (e.g., 9-min run/walk [9]). For these tests there is also a trade-off between ease of measurement and precision. Direct measurement of oxygen uptake during peak exercise is more precise than estimates of aerobic fitness from field tests.

Sufficient levels of physical activity and physical fitness is just as important for the health status of children with juvenile idiopathic arthritis (JIA) as it is for healthy children.

Physical fitness is not only an important indicator for health, it is also an important determinant of functional capacity of a subject. Unfit and/or inactive children are at additional risk for a variety of health conditions associated with a hypoactive lifestyle (e.g., cardiovascular conditions, obesity and prediabetes). Furthermore, sufficient levels of physical activity is necessary for an optimal physical, psychological and emotional development of a child.

However, children with JIA might have a reduced physical fitness [10] and be less active than peers [11–13], which causes an unnecessary risk for the development of cardiovascular disease as well as a risk for reduced psychosocial and physical functioning. The link between physical activity, health-related fitness and health is described by Bouchard and coworkers in the model shown in Figure 1 [14].

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Physical fitness

Health-related fitness

Physical fitness can be divided in various components, namely health-related fitness (peak oxygen uptake; VO_{2peak}), and performance-related fitness (muscle strength, anaerobic capacity). VO_{2peak} is most frequently assessed using progressive graded exercise tests on a cycle ergometer with respiratory gas analysis in children with JIA [10], although some researchers have used treadmill testing in children with JIA [15,16].

There is a large body of evidence demonstrating that the VO_{2peak} of children and adolescents with JIA is lower compared with healthy peers. In the recent studies in JIA, between the ages 6.7–18 years, VO_{2peak} (L/min) and VO_{2peak} normalized for body mass (VO_{2peak}/kg in ml/kg/min) were respectively, 69.8 and 74.8% in children and 83 and 80% of predicted values for VO_{2peak} and VO_{2peak}/kg for healthy peers [17,18]. These observations confirm the results of a previous meta-analysis demonstrating that VO_{2peak} per kg body mass was on average 21.8% lower in children with JIA compared with healthy control subjects or reference values [10]. We recently studied the VO_{2peak} in a group of 12 young adults with JIA and observed a significantly reduced VO_{2peak} (Z-score for VO_{2peak}/kg was -1.0 ± 2.13), which was not significantly different from values observed in children and adolescents with JIA [19]. There is a need for longitudinal follow-up studies in physical fitness levels in JIA. The results of the previously mentioned study suggests that the physical fitness levels of JIA is not improving over time. This was also recently observed in a small group of patients with JIA who underwent autologous stem cell transplantation [20]. As shown in Figure 2, on average there is no improvement over time. In addition, several patients had an exacerbation of the JIA following autologous stem cell transplantation, which is observed in the sudden drops in VO_{2peak}/kg.

From these observations, it can be hypothesized that children and adolescents remain hypoactive when disease goes into remission with or without medication. The fact that young adults treated in a prebiologic treatment era and that younger children are currently being treated with newer biologicals are not scoring better on aerobic fitness suggests that there is hardly any positive effect of the developments in medical treatment over the last decade on physical fitness. Recent unpublished data from our group indicated that JIA patients with a history of anti-TNF biological use had a lower aerobic capacity compared to nonusers [Takken T, Unpublished Data]. This might be due to the fact that in the Netherlands anti-TNF is only prescribed for patients with a polyarticular disease-course who failed earlier treatment or had untreatable side effects on high-dose methotrexate [19].

It is probable that exercise therapy and physical activity promotion can further enhance aerobic fitness and exercise participation in patients with JIA, especially in the cases with severe disease [20].

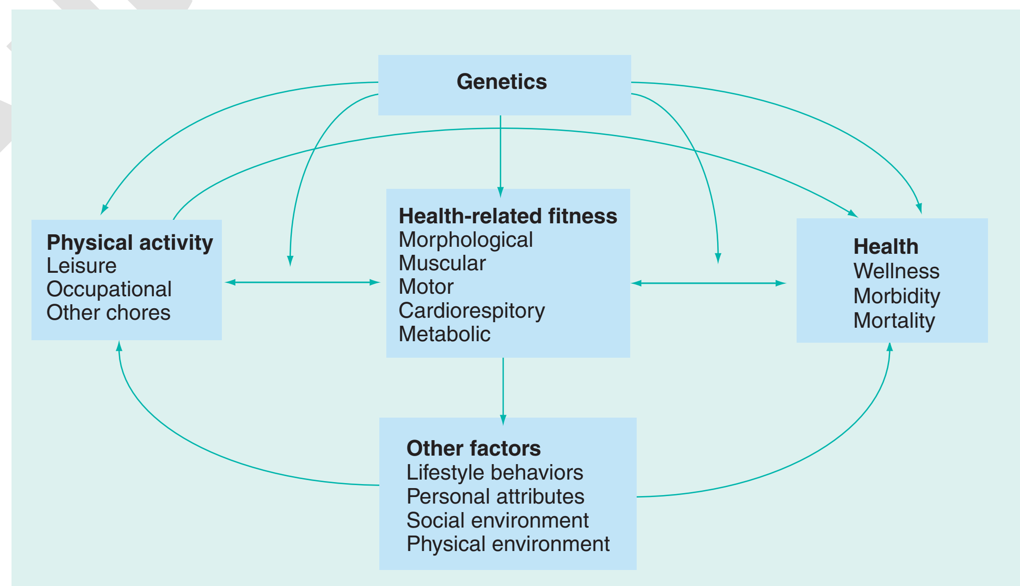

Figure 1. The model by Bouchard and coworkers linking physical activity, health-related fitness and health.
Reproduced with permission from [14].

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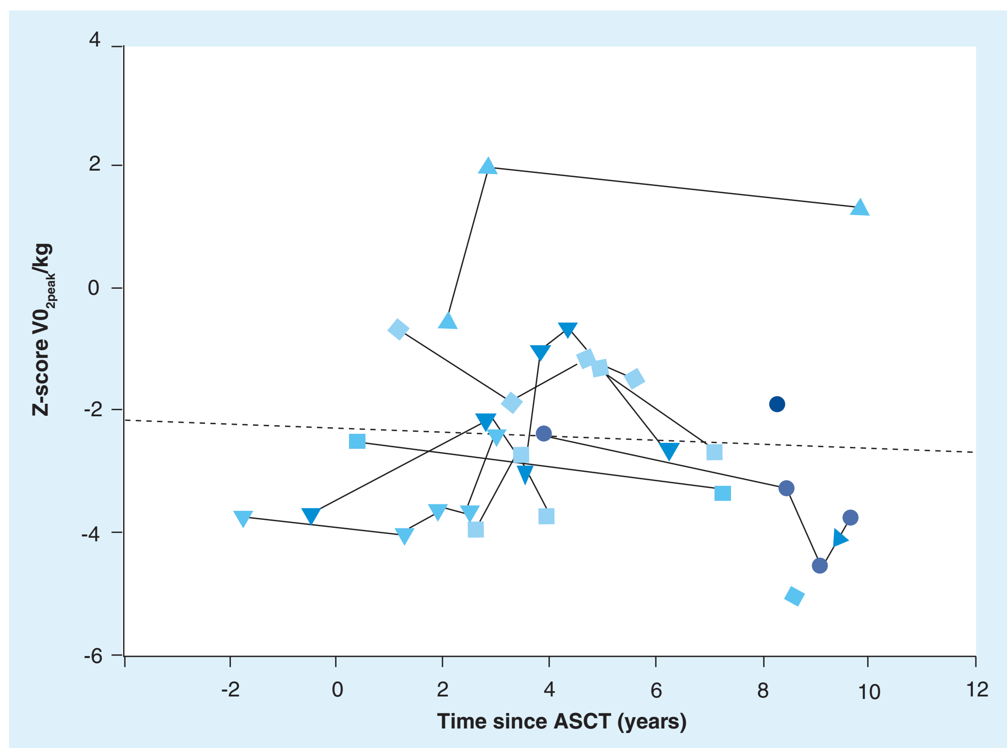

Figure 2. Changes overtime in VO$_{2peak}$/kg in children with juvenile idiopathic arthritis who underwent an autologous stem cell transplantation. The different symbols and lines indicate observations from individual patients. The dotted line indicates the trend line of the individual values over time.
ASCT: Autologous stem cell transplantation.
Data taken from [20].

Giannini and Protas also found that children with JIA had significantly lower peak work rate (amount of Watt that a subject can generate during a graded exercise test on a cycle ergometer), peak exercise heart rate (HR_{peak}) and exercise time than healthy control subjects matched for age, gender and body size [21,22]. Recently published observations in 91 children with JIA demonstrated that children with JIA had on average a HR_{peak} of 181 ± 14 bpm [23], while healthy children have on average a HR_{peak} 193 ± 7 bpm during cycle ergometry in our laboratory [24]. Some of the children with JIA stopped the exercise test because of fatigue and/or musculoskeletal complaints, and not because of a cardiopulmonary limitation during exercise. Owing to the range in HR_{peak}, it is important to measure the HR_{peak} of a subject during a graded exercise test and not to use a general prediction, such as 220-age.

Many centers do not have the equipment to perform respiratory gas analysis to measure VO_{2peak}. However, peak work load (W_{peak}) during a graded bicycle test can be used a surrogate measure for VO_{2peak}, since an excellent correlation between W_{peak} and VO_{2peak} ($r = 0.95$, $p < 0.0001$) has been observed in 91 children with JIA [23]. VO_{2peak} can be predicted from W_{peak}, weight and gender using the following equation [23]:

$$VO_{2peak}(L/\min)=0.308+0.146\times sex\ (0=female,1=male)+0.005\times weight\,(kg)+0.008\times W_{peak}\,(SEE=0.18\,L/\min)$$

This equation was established using a stepwise increased protocol with an increase of 20 W/min. In young children with a height less than 120 cm, increments of 10 W/min can be used and in children between 120–150 cm, 15 W increments per min can be used [25]. These rapid increasing protocols are to be preferred above slower increasing protocols, such as the Giannini protocol, with increases of 20 W per 3 min [21]. Slow incremental protocols often take quite long, approximately 20 min, and it is my experience that children will stop because of peripheral muscle fatigue and not because of cardiopulmonary limitation [26].

Impaired VO_{2peak} does not appear to be significantly related to the severity of joint disease, but may be due to hypoactivity secondary to disease symptoms, especially in children with long-standing arthritis [4,9,10]. Physiologic factors, including

anemia, muscle atrophy, generalized weakness and stiffness, resulting in poor mechanical efficiency may also limit the child's performance.

Fitness in other rheumatic conditions

Of the other pediatric rheumatoid conditions, physical fitness levels in children with juvenile dermatomyositis, systemic lupus erythematosis and recently the fitness levels among children with mixed-connective tissue disease were reported. Their results are shown in Figure 3. As reference, the values as observed in children with chronic fatigue syndrome (significant overlap with fibromyalgia) is provided.

It is eminent that a rheumatic disease that primarily attacks the muscle will result in the lowest score in physical fitness, an overlap syndrome, such as mixed-connective tissue disease and JIA turns out to show almost equal outcomes in physical fitness. Interestingly, recently diagnosed children with chronic fatigue syndrome have on average a normal score in physical fitness compared with healthy peers Figure 3 [17,27–30].

Performance-related fitness

As previously mentioned, performance-related fitness includes components, such as muscle strength and anaerobic capacity. Impairments of muscle strength include weakness in hip extension and abduction, knee extension, plantar flexion, shoulder abduction and flexion, elbow flexion and extension, wrist extension and grip. Muscle bulk, strength and endurance should be examined at disease onset and monitored regularly. Bilateral measurements of circumference quantify asymmetries in muscle bulk. Functional muscle strength can be estimated in young children by observing their performance of age-appropriate motor tasks or activities of daily living. In older children, manual muscle testing can be done to measure isometric strength, especially if the child has pain while moving the limb against resistance. Instrumented measurements using a handheld or isokinetic dynamometer or modified sphygmomanometer [18,19] provide consistent and reliable information in patients with arthritis. Both isometric and isokinetic strength have been shown to be valid and reliable measures of muscle strength in normal children. In JIA the reliability of isometric strength measurement of the lower limb muscles has been assessed [31] and reported to have a sufficient intra- and inter-rater reliability [31]. Several studies have demonstrated that muscle strength is significantly reduced in children with JIA compared with healthy peers [32–36].

Lindehammar and Sandstedt reported in a longitudinal study that muscle strength diminishes rapidly near an inflamed joint [33]. This is

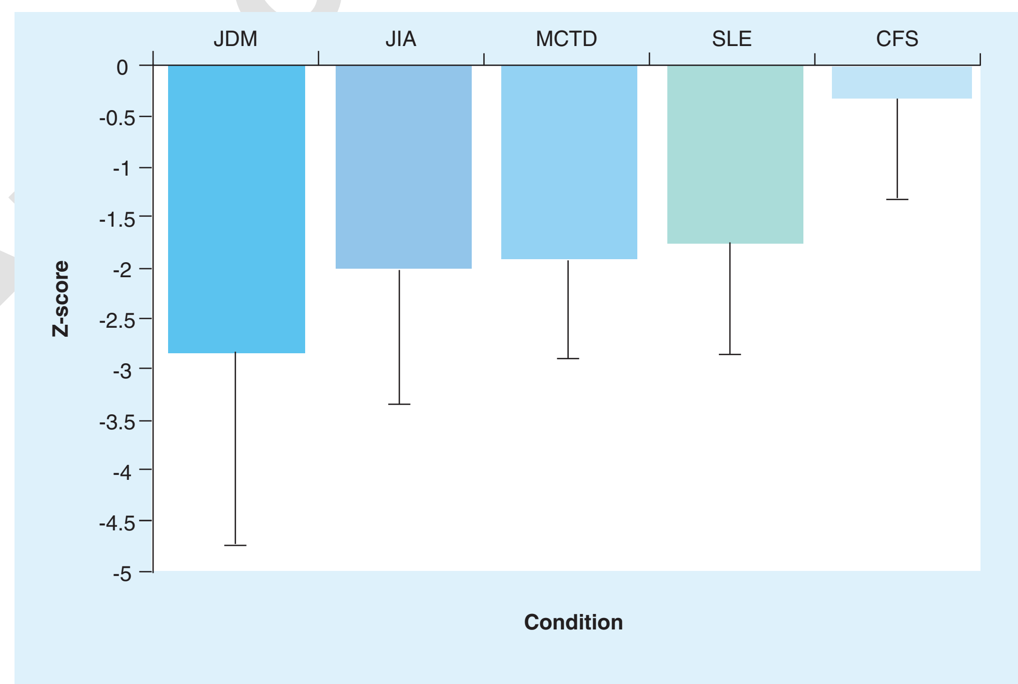

Figure 3. The Z-score for VO_{2peak}/kg of patients with juvenile dermatomyositis, systemic lupus erythematosis, mixed-connective tissue disease and chronic fatigue syndrome.
CFS: Chronic fatigue syndrome; JDM: Juvenile Dermatomyositis; JIA: Juvenile idiopathic arthritis
MCTD: Mixed-connective tissue disease; SLE: Systemic lupus erythematosis.
Data taken from [17,27–30].

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probably caused by atrophy of the muscle, which is influenced by local arthritis. One study suggested that muscle weakness may contribute to activity restrictions in children with arthritis. Fan and colleagues found a significant relationship between 50 m run times and lower extremity Childhood Health Assessment Questionnaire (CHAQ) scores in girls with JIA [37].

However, muscle strength testing in children with JIA, especially hand-held dynamometry using the 'break' technique, might be problematic in some cases, because children might give way due to pain instead of the limits in muscle strength. Moreover, in some case children can experience increased knee pain and swelling [35].

Anaerobic capacity can be assessed using short-term exercise tests. Usually anaerobic capacity is measured using a 30 s all-out cycle ergometer test, the Wingate Anaerobic Test [38]. Children have to cycle as fast as they can against a fixed resistance, and based on the number of revolutions per second, the power output is recorded [38].

Two recent studies investigating the anaerobic capacity in children and adolescents with JIA reported significantly lower values of anaerobic capacity in subjects with JIA [6,7]. Anaerobic capacity was reduced to the same extent compared with aerobic fitness (VO_{2peak}). Previously it has been found that the reduced anaerobic capacity was significantly correlated to CHAQ scores in 18 children with JIA, ages 7–14 years [39]. This is not surprising, since the typical physical activity behavior of children – short bursts of intense activities separated by periods of rest – is anaerobic in nature [40]. Given the apparently similar deficits in anaerobic capacity of youth with JIA, exercise training of the anaerobic energy system (e.g., high-intensity interval training) might be equally valuable as training of the aerobic system and, therefore, warranted in children with arthritis. However, this training modality has not yet been studied.

Another widely used performance-related fitness test is the 6-min walk test (6MWT). In this test children have to cover as much distance as they can in 6 min while walking (not running). This test is used in different patient groups, such as JIA, spina bifida, cerebral palsy and hemophilia [41–43]. Lelieveld *et al.* found a low correlation between walking distance and VO_{2peak} in children with JIA [44]. In addition, Paap *et al.* found that children with JIA were exercising at 80–85% of their HR_{peak} and VO_{2peak} during the 6MWT, indicating that it is an intensive, submaximal exercise test to measure functional exercise capacity in children with JIA [45]. Furthermore, these data indicate the exercise intensity at the end of the 6MWT can be used for the programming of exercise intensity during aerobic exercise training in children with JIA, because this exercise intensity is sufficient to improve fitness levels. The HR at the end of a 6MWT can thus be used for exercise programming. However, the 6MWT distance cannot be used as a measure of VO_{2peak} in children with JIA [46].

Fitness training

Aerobic capacity

In a recent Cochrane review it was identified that only three published randomized-controlled studies investigated the effects of exercise training for children with JIA [47]. However, none of these studies found improvements in VO_{2peak} following the aerobic training program. This lack of effect can be can be due to a low exercise frequency (for example once a week), low exercise intensity (intensity of exercise has to be above the intensity of daily activities), a low exercise adherence (children would often skip exercise sessions), or they did not perform the prescribed home exercises. These factors are essential for improving physical fitness.

However, aerobic fitness is important to improve the child's endurance for daily physical activities and play. In addition, aerobic fitness aids the recovery following intensive exercise. Based on the available literature, it is recommended that children with JIA and a deficit in aerobic fitness should train at least twice a week, with a moderate-to-vigorous intensity (60–85% HR_{peak}), for 45–60 min per session for at least 6–12 weeks [12,13]. The specific mode of exercise appears to be less important than the intensity, duration and frequency. However, weight-bearing exercise is necessary to maintain optimal bone growth and density. Low impact activities to improve proprioceptive function, balance and coordination can be incorporated into aerobic conditioning programs. Furthermore, large muscle groups should be used for improving VO_{2peak} as the exercise mode of testing should be comparable with the training mode (e.g., a walking/jogging exercise program should be evaluated using treadmill testing and not using cycle ergometry testing).

For children with active disease it is advised to refrain from any formal exercise training when they have fever (rectal core temperature >38.3°C). In addition, when they have active joints in the lower extremities, it is advised to do only low-to-moderate intensity exercise without

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intensive loading of the joints (e.g., running or jumping) [48]. For children with active disease in the wrist for example, it is recommended to wear a (dynamic) splint during exercise to protect the joint from high impact forces. Activities that cause pain and increase swelling in joints with active arthritis should be stopped or modified to lessen stress to the joint [48].

Anaerobic capacity

In a recent study van Brussel *et al.* [30], they hypothesized that training of the anaerobic energy system (e.g., high-intensity interval training) might be equally valuable as training of the aerobic system and, therefore, warranted in children with JIA. Although, this training modality has not yet been studied in children with JIA, improvements have been observed in function and fitness with anaerobic exercise training in children with other chronic conditions (e.g., cystic fibrosis and cerebral palsy) [49,50]. Particularly in children with a larger reduction in anaerobic capacity compared with aerobic capacity, this training modality might be effective. In addition, children prefer this anaerobic type of exercise, compared with the adult type of continuous endurance exercise. Suggested exercise sets consist of several (five) 15-bouts of high-intensity (or all out) 15–30 s sprint interchanges with 1–2 min of active rest (cycling with low resistance). A training session could consist of three of these exercise sets, with 5 min of active rest for recovery between the three sets of interval training.

Muscle strength

There is little evidence concerning the effectiveness of strength training for children with JIA. There is only one study, which is only published in an abstract form that studied muscle strength training in children with JIA. Fisher and colleagues examined the effects of resistance exercise using isokinetic equipment in 19 children with JIA of ages 6–14 years, who trained as a group three times a week for 8 weeks [51]. Each child's program was individualized and progressed based on their initial test results and response to training. Subjects demonstrated significant improvements in quadriceps and hamstring strength and endurance, contraction speed of the hamstrings, functional status, disability and performance of timed tasks. Control subjects with JIA who did not exercise had relatively no change to a slight decrease in muscle function during the same time period [51].

To date, there are no other published reports investigating the effects of strength training in children with JIA. However, recommendations for healthy children can be followed for use in children with JIA. For improving muscle strength children should perform resistance exercises for 2–3 times per week at an intensity of 60–75% of their one repetition maximum. The latter will be approximately 13–15 repetitions of an exercise until fatigue. The time per session will be 30–45 min. It is advised to use the entire range of motion of a patient (or within pain limits). The program should increase in intensity from 60% of the one repetition maximum with 1–3 sets, to a higher intensity of 75% with 3–4 sets. It is recommended that the resistance is only increased when 15 or more repetitions can be made with a sufficient technique, and resistance will only be increased with 5 to 10% per 3 weeks. A warm-up period of light activity, such as cycling should precede strength testing.

Encouraging active-healthy living

Several studies have identified a hypoactive lifestyle of children with JIA [16–18]. A significant association has been reported between accelerometry-measured physical activity and health-related fitness (VO_{2peak}) in children with JIA [12], suggesting a cause–effect relationship. In addition, no adverse effects of regular sport activity have been observed on joint scores in children with JIA [52]. However, the most frequently participated sports activity in that study was cycling and swimming (nonweight-bearing activities) [52]. On the other hand, a controlled weight-bearing exercise intervention study found improvements in joint status following 8 weeks of training in children with JIA [9]. Adult data indicate that exercise can have an anti-inflammatory effect in arthritis patients [53] as well as in other inflammatory diseases [54].

The link between the physical activity levels of children and motor performance [55] suggests that the physical activity levels of children with JIA might be enhanced through the improvement of the reduced motor proficiency observed in children with JIA [56]. Furthermore, given the fact that adult physical activity levels are established in youth, it is important to encourage children and families of children with JIA to participate in regular physical activity. Regular physical activity can help in the prevention of cardio-vascular risk factors, obesity, reduced bone-health and reduced health-related quality of life in youths with JIA.

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Recently Lelieveld *et al.* performed a randomized-controlled study to investigate an internet-based activity promotion program among 33 JIA patient (10.8 ± 1.5 years old) [8]. This 17-week web-based e-learning program was combined with four group sessions. The following strategies were used to promote physical activity: health education; explanation of benefits of physical activity; reinforcement of self-efficacy; influence of family and school is recognized and used to promote physical activity; physical activity options in daily life are explored and encouraged; and smart goals are set (e.g., 'I am going to cycle to school three times a week instead of going by car, for the coming 2 months'). They observed the following changes in physical activity: energy expenditure from physcical activity was improved by +1.24 MJ/day, the amount of moderate-to-vigorous physical activity improved with 1 h per day and the number of days with more than 1 h of moderate-to-vigorous physical activity increased with 1.2 day per week. They observed the largest effects in children with low physical activity levels at baseline.

Although exercise capacity, as measured using the endurance time on the Bruce treadmill test, improved significantly this improvement was only 26 s, which could be hardly recognized as clinically relevant (effect size of 0.33). This is not surprising, since the relationship between physical activity and physical fitness is low in JIA [12] as well as in other childhood conditions, such as congenital heart disease for example [57]. It might be more effective to combine formal exercise training with a physical activity promotion program to increase activity as well as physical fitness in children with JIA.

Recommendations

Clinicians should stimulate an active healthy lifestyle as soon as possible after diagnosis.

In general, children with JIA should be advised to comply with public-health recommendations of daily participation in 60 min or more of moderate-to-vigorous physical activity that is developmentally appropriate, enjoyable and involves a variety of activities [58]. Moreover, children with JIA are advised to perform less than 2 h of sedentary activities during their leisure time (TV watching, browsing the internet and computer games among others) per day [58].

Clinicians should be aware of the detrimental effects of inactivity and sedentary behavior and stimulate physical activity in children with JIA. Advice regarding appropriate levels of physical activity should be implemented in clinical consultations.

In addition, clinicians are advised to provide written advices (including restrictions and permissions) to both primary-care providers as well as parents regarding appropriate levels of physical activity. Future studies should determine the most effective approach to promote physical activity and increase physical fitness in children with JIA.

Conclusion

Children with JIA are often restricted in their activities of daily living, have lower physically activity levels compared with their healthy peers, and have a reduced physical fitness. None of the currently performed randomized studies regarding exercise training in children with JIA have observed clinically significant improvements in physical fitness, and only one study has observed significant and clinically relevant improvements in physical activity. It is advised that clinicians discuss appropriate levels of physical activity with their patients in clinical consultations. Further children with JIA should adhere with public-health recommendations of daily participation in 60 min or more of moderate-to-vigorous physical activity.

Future perspective

One of the major needs in this field is a specific core-set of outcome measures for rehabilitation research in children with a rheumatic condition. Current studies are using a large variety of outcome measures that impedes comparability of the findings. The development of such a core set is needed in the next decade. Furthermore, the use of internet-based exercise interventions

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Executive summary

- A large body of evidence indicates that children with juvenile idiopathic arthritis (JIA) are less physically fit compared with healthy peers
- Children with JIA are also less active and are often not meeting public-health guidelines for physical activity participation.
- Effects of formal exercise training programs seems promising; however, adherence is often limiting the effectiveness.
- Physical activity-promotion programs seems promising and feasible; however, long-term effectiveness should be established.
- Cost–effectiveness of exercise and physical activity promotion programs should be established in JIA.

will become more wide spread as well as behavioral interventions to stimulate physical activity participation in this patient group. Moreover, there will be more attention for the physical fitness, activity and risk factors for cardiovascular disease in young adults with JIA. Finally, implementation of exercise training and physical activity promotion programs in clinical care should be established.

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