

Therapeutic effects of exercise training in patients with pediatric rheumatic diseases

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ABSTRACT

Over the past decades, the role of exercise training in rheumatic diseases has been largely explored. Currently, physical activity is well known to benefit patients with osteoporosis, osteoarthritis, systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathy, fibromyalgia and rheumatoid arthritis. Therefore, exercise training has been considered a valuable tool for treating rheumatic patients. The therapeutic effects of exercise training have also been investigated in pediatric rheumatic diseases. Collectively, studies have revealed the therapeutic potential of exercise in juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile dermatomyositis, juvenile fibromyalgia and other causes of chronic pain. The aim of this review is to familiarize the pediatric rheumatologist with the exercise science field; discuss the potential benefits of exercise training in pediatric rheumatic diseases, emphasize both research and clinical perspectives of this promising field; and propose practical models of pre-participation examinations and contraindications to exercise.

Keywords: physical fitness, motor activity, rheumatology, child.

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INTRODUCTION

Hippocrates, 2,400 years ago, stated: “That which is used develops; that which is not used wastes away... If there is any deficiency in food or exercise, the body will fall sick”. The prophetic words of the “father of Medicine” have gained increasing scientific support. Epidemiological studies have shown that physical inactivity substantially increases the relative incidence of coronary artery disease (45%), acute myocardial infarction (60%), arterial hypertension (30%), colon cancer (41%), breast cancer (31%), type II diabetes mellitus (50%), and osteoporosis (59%).¹ There is evidence that physical inactivity is independently associated with mortality, obesity, higher incidence of falls

and physical weakness in the elderly, dyslipidemia, depression, dementia, anxiety, and mood swings.²⁻⁶

In the pediatric population, sedentary lifestyle is also considered the major factor responsible for the pandemic increase in the incidence of juvenile obesity. In addition, recent findings have suggested that physical inactivity worsens the general health status of children and adolescents affected by several diseases, such as cardiovascular, renal, endocrine, neuromuscular, and osteoarticular diseases.⁷

Thus, it is evident that physical exercise practice is an extremely important therapeutic measure, considered the first-choice treatment in several chronic disorders, such as type II diabetes mellitus and arterial hypertension.

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The role played by physical exercise in adults with rheumatic diseases has also been studied. It is currently known that physical activity promotes innumerable benefits to patients with osteoporosis,⁸ osteoarthritis,⁹ systemic lupus erythematosus,¹⁰ systemic sclerosis,¹¹ inflammatory idiopathic myopathies,¹² fibromyalgia,¹³ and rheumatoid arthritis,¹⁴ with rare reports of adverse effects. Thus, physical exercise has been considered a valuable and safe therapeutic tool for treating patients with rheumatic diseases.

The therapeutic effects of physical training on pediatric rheumatic diseases have also been recently investigated.¹⁵ Studies have shown the great therapeutic potential of exercise for patients with juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM), juvenile fibromyalgia (JF), and juvenile idiopathic arthritis (JIA).^{7,15} However, the number of controlled studies with large samples is still limited. In addition, questions such as “What is the best type of training?” or “Does exercise affect the natural course of the disease?” are yet to be properly answered.

This brief review aimed at discussing the potential benefits of physical exercise in pediatric rheumatology, with emphasis on the future of this promising clinical and scientific field. In addition, classical concepts of physical training were introduced aiming at making the pediatric rheumatologist acquainted with the terminology of the exercise science.

CONCEPTS AND TERMINOLOGIES OF EXERCISE SCIENCE

The following glossary comprises adaptations of the classical definitions of exercise physiology and sports training.¹⁶

Physical activity – Body movement produced by the contraction of the skeletal musculature, which implies energy consumption above baseline levels.

Physical exercise – Planned and structured sequence of movements aimed at enhancing or maintaining a specific physical capacity. Physical exercise is seen in the context of physical activity.

Sports – Cultural phenomenon characterized by competition. Contrary to common sense, sports practice is not always healthy, considering the high incidence of osteomyoarticular lesions in high-level athletes. Thus, the practice of certain sports modalities should be restricted in pediatric patients with chronic disease (to review, see Morris).¹⁷

Physical training – Sequence of exercises organized over a period of time to enhance physical performance.

Physical conditioning – Comprises the concepts of aerobic and neuromuscular conditionings and flexibility.

Aerobic conditioning – Also known as cardiorespiratory conditioning or aerobic endurance. It refers to the capacity of the circulatory and respiratory systems to provide oxygen during a prolonged physical exercise. The most used measure to represent aerobic conditioning is maximum oxygen consumption ($\text{VO}_2 \text{ max}$), which can be measured by indirect calorimetry or estimated by field tests.

Neuromuscular conditioning – Relates to the individual's maximum capacity of opposing an external resistance (maximum strength) or maintaining the production of submaximal strength for a prolonged period of time (strength endurance).

Flexibility – Refers to the ability to move a joint in an increased range of motion. Stretching exercises are used to enhance flexibility. Good flexibility development is related to promotion and maintenance of functionality.

Aerobic exercise – Exercise performed at submaximal intensity, allowing the maintenance of exertion for prolonged periods (> 10 min). It is characterized by contractions of the same muscular group rhythmically and repeatedly. Examples include swimming, cycling, walking, and medium- and long-duration running. When performed at adequate intensity and frequency, it enhances aerobic conditioning.

Intensity of the aerobic training – The intensity of the aerobic exercise can be prescribed based on a fraction related to the individual's maximal capacity, such as percentage of maximum oxygen consumption ($\text{VO}_2 \text{ max}$) or percentage of maximal heart rate (HR). The exercise is classically described as moderate when its intensity is adjusted to 40%-60% of $\text{VO}_2 \text{ max}$ (50%-70% of maximal HR), and intense when its intensity is > 60% of $\text{VO}_2 \text{ max}$ (> 70% of maximal HR).

Strength exercise or training – Exercise that uses external resistance (overload) to produce neuromuscular adaptations. The most common examples are weight lifting exercises, popularly known as bodybuilding. Strength exercises can be static (also known as isometric) or dynamic (also known as isotonic). Isometric muscle contractions refer to contractions in which external resistance equals internal strength (produced by muscles), so that no joint movement occurs. Concentric muscle contractions refer to those in which internal strength surpasses external resistance, while eccentric contractions are those in which external resistance surpasses internal strength.

Intensity of strength training – Intensity can be defined as high when external resistance is $\geq 75\%$ of the load that can be “lifted” one single time [$\geq 75\%$ of 1-RM (one repetition maximum)], and moderate when the external resistance is between 50% and 74% of the 1-RM.

Table 1

Pre-participation physical examination in physical exercise and sports programs for children and adolescents with pediatric rheumatic diseases

Anamnesis	What to assess?
Current symptoms and diseases	Joint pain, low back pain, fatigue, asthma, diabetes mellitus, arterial hypertension, and low bone mass
Drugs	Non-steroidal anti-inflammatory drugs, glucocorticoids, immunosuppressants, and biologics
Personal history	Osteomyoarticular injuries, previous diseases and surgeries
Family history	Cardiovascular disease, sudden death, osteoporosis
Physical examination	What to assess?
General	Weight, height, body mass index (BMI), body composition
Cardiopulmonary	Cardiac murmurs, arrhythmias, arterial hypertension, and bronchospasm
Musculoskeletal	Scoliosis, lumbar and cervical hyperlordosis, difference in lower limb length, knees (valgus, varus, and recurvatum), feet (normal, cavus, or flat), muscle shortening and hypotrophies, joint mobility (hypermobility or deformity), gait changes (hyperpronation or supination)

Adapted from Rice⁴⁶ and Garrick⁴⁷.

Pre-participation examination – It is a medical consultation that includes extensive clinical anamnesis and careful physical examination, including osteoarticular and postural assessment. The objective of this careful examination is to detect any physical change that can contraindicate or limit physical exercise practice. Table 1 shows an example of anamnesis that can be used by the pediatric rheumatologist during a pre-participation examination.

REST OR PHYSICAL ACTIVITY: WHAT IS BEST FOR YOUR PATIENT?

Despite the vast body of knowledge indicating that physical exercise can prevent and treat most chronic diseases, while a sedentary lifestyle is the major risk factor predisposing to chronic diseases, patients with rheumatic diseases are often recommended to rest, as a way to prevent disease activity or joint wear and tear.¹² The efficacy of this recommendation has been challenged. There is evidence that patients with rheumatoid arthritis participating in regular physical exercise programs have less frequent joint pain and stiffness and better performance in daily life activities as compared with their physically inactive peers.¹⁸

In past decades, children and adolescents have become increasingly sedentary. Concomitantly, a substantial increase in the incidence of pediatric chronic diseases, such as juvenile obesity, arterial hypertension, type II diabetes mellitus, and asthma, has been observed.¹⁹ It has been speculated that physical inactivity is closely related to dyslipidemia, insulin resistance, low bone mass, muscle weakness and atrophy, adiposity gain, increased blood pressure, low quality of life, and reduced self-esteem.¹⁹

Pediatric rheumatic patients have several clinical manifestations, such as fatigue, chronic pain, stiffness, synovitis and joint deformities, which predispose to a sedentary lifestyle.⁷ Thus, a dangerous vicious cycle is formed, with symptoms leading to physical inactivity, which in turn, worsens the patients' clinical findings. In that context, physical exercise becomes the only strategy capable of interrupting the cycle.⁷ Thus, physicians, nurses, and physical health professionals are strongly encouraged to recommend physical activity to patients with pediatric rheumatic diseases.

The same applies to parents who tend to overprotect their children with chronic diseases, isolating them from social contact, thus favoring, a sedentary lifestyle. Even in active diseases, studies in adults have shown that physical exercise, properly adapted to the patient, can be safe and effective.²⁰ There is no reason to believe it would be different in children. Undoubtedly, the benefits of physical activity compensate the deleterious effects of physical inactivity, and except for some conditions listed in Table 2, the patient with pediatric rheumatic disease should exercise.

EVIDENCE FOR PRESCRIBING EXERCISES TO PEDIATRIC RHEUMATIC PATIENTS

We describe the clinical manifestations and physical capacity deficits of patients with juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), juvenile systemic lupus erythematosus (JSLE), juvenile fibromyalgia (JFM), and other causes of chronic idiopathic musculoskeletal pain, which constitute the theoretical reference for using physical exercise as a therapeutic agent in pediatric rheumatic diseases. The results of the clinical studies involving exercise in the above mentioned diseases will also be assessed.

Table 2
Contraindications to physical exercise practice for children and adolescents with pediatric rheumatic disease

1 - Fever
2 - Anemia
3 - Acute renal failure
4 - Carditis, serositis, and ischemic response to the treadmill test*
5 - Non-controlled arrhythmias and arterial hypertension
6 - Severe malnourishment with body weight loss over 35%

*Exercise whose intensity is 10% below the ischemia threshold is allowed. In case of joint deformities, arthritis, or acute myositis, exercises should be tailored to spare the joint and muscle group affected.

Juvenile idiopathic arthritis

There is evidence that patients with polyarticular, but not pauciarticular, JIA have a reduction in their aerobic and anaerobic exercise capacities.²¹ In addition, children with JIA have shown low isometric strength as compared with their healthy peers.²² The strength reduction often observed in JIA is believed to be related to the muscle atrophy findings, which in turn, are associated with the localized arthritis, the chronic use of glucocorticoids, and the lack of use of the joint. Takken et al.²³ have also reported a positive association between anaerobic capacity and muscle function in patients with JIA, suggesting that physical deconditioning affects daily life activities in this disease.

Studies involving physical exercise programs have produced satisfactory results in patients with JIA. In a recent review, Klepper¹⁵ has shown that the most important benefits reported were an increase in flexibility strength and an improvement in pain, joint stiffness, and quality of life. The physical training protocols varied in intensity (60%-70% of maximal HR), duration (30-60 minutes), frequency (one to three sessions per week), composition (strength training, aerobic training, flexibility, sports modalities or a combination of them), and follow-up (6-20 weeks). It is interesting to note that physical exercises in the water promote benefits similar to those performed on the ground.²⁴ Thus, high and low intensity programs seem to be equally effective and safe.²⁵ There is no report of adverse events due to physical training in patients with JIA; thus, physical exercise should be encouraged.

Juvenile-onset dermatomyositis

Patients with JDM frequently do not tolerate physical effort.^{26,27} There are several factors that may explain this finding, such as increase in muscle concentrations of inflammatory cytokines, systemic inflammation, inflammation of the capillaries that

irrigate the musculoskeletal system, hypoactivity, and chronic use of glucocorticoids, which are known to impair protein synthesis and increase body fat.²⁷ Furthermore, studies with magnetic resonance spectroscopy have shown bioenergetic abnormalities, such as a 35%-40% reduction in phosphoryl-creatine intramuscular concentrations, in children with JDM.²⁸

As for adults with dermatomyositis, aerobic and strength training can increase muscle strength and function, aerobic conditioning, and lean mass in patients with both controlled and active disease.¹² Despite the therapeutic potential of exercise in JDM, controlled studies still lack.

Our group has recently shown that one child with chronic JDM responded to a supervised program combining strength and aerobic training similarly to her healthy homozygous twin sister.²⁹ In this study, the patient showed clinically significant improvements in dynamic and isometric strengths, in addition to an improvement in aerobic conditioning. Although the physical training could not completely solve the physical capacity deficiency, to our knowledge, this was the first evidence that regular exercise could be effective for and well tolerated by a child with JDM. It is certainly a promising intervention that requires further investigation.

Juvenile-onset systemic lupus erythematosus

Patients with JSLE usually do not tolerate physical effort, and have muscle weakness and exacerbated fatigue as compared with their healthy peers.^{7,30} In addition, obesity, dyslipidemia, insulin resistance and low bone mass are prevailing characteristics of the disease.^{7,31} Considering the wide range of action of physical exercise, one can speculate that it can improve strength, tolerance to effort, aerobic conditioning, body composition, and quality of life in patients with JSLE. Surprisingly, however, controlled studies confirming that possibility still lack.

Our group has investigated the effects of aerobic training in children and adolescents with JSLE. One of the patients stood out, because he was also diagnosed with antiphospholipid syndrome (APS, with deep venous thrombosis of the lower limb and vena cava thrombosis) secondary to JSLE and was on anticoagulation therapy with warfarin. This patient underwent an intensely supervised aerobic training for three months. A substantial benefit in aerobic conditioning was observed, with an increase in VO_{2max} , greater tolerance to effort, and better running economy. In addition, the patient's quality of life, functionality, and self-esteem also improved. Although bleeding resulting from trauma was a constant preoccupation during the training, it is worth noting that no adverse effect was observed. A prospective study of a significant population with JSLE is being conducted.

Juvenile-onset fibromyalgia and other causes of chronic idiopathic musculoskeletal pain

Patients with JFM may have diffuse chronic pain, sleep disorders, chronic anxiety, tension, headache, fatigue, and poor quality of life.^{32,33} Similarly, one might speculate that a regular physical training program can improve muscle function, pain, sleep quality, and quality of life of patients with JFM.

To our knowledge, only one study has been conducted with these patients. Stephens et al.³⁴ have investigated the efficacy and feasibility of a physical training program in children and adolescents with JFM for 12 weeks. Patients were randomized to a high- or low-intensity aerobic training program. Both groups showed an improvement in muscle function, disease symptoms, quality of life, and pain, although patients undergoing the more intense training experienced gains in a higher number of clinical parameters. These findings confirm the benefits expected from physical training in JFM and stress the need for new studies in this area.

Hypothetically, physical training might also be therapeutic in other causes of chronic, non-inflammatory, idiopathic musculoskeletal pain. One example is the pain related to the prolonged use of computers and video games, known in adults as repetitive strain injury (RSI) or work-related osteomuscular disorder (WROD). With the appearance of informatization, children and adolescents have spent more and more time in front of technological devices; consequently, they become physically inactive individuals more prone to chronic pain, tendinitis, and myofascial syndrome.³³ The regular practice of physical activity, muscle strengthening and joint flexibility enhancement could at least relieve these symptoms.

Another possible cause of musculoskeletal pain is joint hypermobility (JH). The association of JH with pain and/or musculoskeletal system lesions constitutes the benign joint hypermobility syndrome (BJHS), which is not related to congenital entities, such as Marfan and Ehlers-Danlos syndromes. Our group carried out a study in a school in the city of São Paulo, and found a BJHS prevalence of 10% among adolescents.³² Several studies,³⁵⁻³⁸ although not all,³⁹ have suggested that patients with BJHS may have lower levels of physical activity and of tolerance to effort, muscle weakness, neuromuscular disorders, and delayed motor development as compared with their healthy peers. Recent evidence^{40,41} has indicated that the combination of dynamic and isometric strength exercises promotes gains in proprioception, strength, balance, muscle function, reduces

pain, and improves the quality of life of patients with BJHS. These data suggest that the practice of physical activity can be of great help for these patients. Nevertheless, controlled studies with larger populations are necessary to confirm these initial findings.

PERSPECTIVES AND FINAL CONSIDERATIONS

Over the past decades, the survival rate and the prognosis of patients with pediatric rheumatic diseases have markedly improved. However, the concern about short-, medium-, and long-term adverse events, due to pharmacological treatment or disease itself and that affect negatively the patients' physical capacity and quality of life, has increased.^{31,42,43} Considering the enormous therapeutic potential of physical exercise for the treatment of those diseases, the limited number of studies about it is worth noting. Thus, several hypotheses require further investigation.

Firstly, randomized clinical trials are clearly required to assess the therapeutic effects of exercise in all pediatric rheumatic diseases, including solid outcomes, such as quality of life and long follow-ups (over one year). In addition, it is worth noting that the presence of a control group is paramount. The unstable natural course of many pediatric rheumatic diseases, in addition to changes in body composition and physical capacity characteristic of the process of sexual maturation at puberty, might lead to mistakes in data interpretation.

It is highly unlikely that one single type of exercise promotes the highest benefits to all pediatric rheumatic patients. Based on the adult rheumatic literature, high-intensity strength training is known to result in greater gains in strength and lean mass in patients with inflammatory idiopathic myopathies,¹² while low-intensity aerobic training produces better clinical results in patients with fibromyalgia.⁴⁴ Empirically, isometric rather than dynamic training has been recommended aiming at preventing joint injury. However, that recommendation is not scientifically supported. In fact, the latter could even be better than the former regarding functional performance in daily life activities. Thus, the ideal training types for pediatric rheumatic diseases should be sought, considering the clinical manifestations and functional limitations inherent in each one.

Finally, as emphasized in a recent review,⁴⁵ regular physical training can attenuate systemic inflammation in chronic diseases. The possible anti-inflammatory effects of exercise could be extremely useful in pediatric rheumatic diseases, possibly reducing the number and/or doses of immunosuppressant drugs.

Despite the limitations found in the literature, there is already sufficient body of knowledge to consider physical exercise as a therapeutic agent in chronic rheumatic diseases. Clinically, understanding the exercise science is fundamental for the pediatric rheumatologist, who can count on a valuable therapeutic tool. Regarding scientific research, a new and promising investigation field is about to be explored.

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