

Is physical activity safe and beneficial for patients with juvenile idiopathic arthritis?

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Abstract

Juvenile idiopathic arthritis is one of the most common physically disabling conditions of childhood and its cause is unknown. Untreated, the disease has a natural oscillating evolution, with exacerbations and periods of low activity and, less frequently, episodes of spontaneous remission. Over time, the disease affects the body's functionality and greatly reduces its adaptation to the environment and quality of life.

The treatment used addresses both symptoms and structural and functional changes so that, along with anti-inflammatory and disease-modifying substances (synthetic or biological), regular physical exercise can be a form of prophylactic treatment of long-term complications.

In this regard, we set out to review a series of articles to highlight the impact of physical activity on children affected by juvenile idiopathic arthritis. Physical activity has been shown to have an impact not only on functional capacity, but also on a cellular level, with the final result of reducing inflammation and promoting a healthier intestinal environment by diversifying the intestinal microbiome.

In conclusion, physical activity is safe for children with juvenile idiopathic arthritis. Keeping a physical activity regimen brings benefits both at the systemic level, through cellular mediation, and at the musculoskeletal level.

Keywords: juvenile idiopathic arthritis, physical activity, functionality, quality of life, cellular impact, impact on intestinal microbiome.

Introduction

Data from the specialized literature emphasize that regular physical activity sustained by patients who are diagnosed with juvenile idiopathic arthritis (JIA) is an important element in the therapeutic management of the disease. However, at present in the medical world there are still delays in prescribing exercise to patients with JIA mainly for safety reasons. In this article we aim to review some data about the impact that exercise has on the evolution of the disease both clinically and biohumorally.

JIA is the most common chronic rheumatic disease in children and adolescents, and is characterized by the presence of arthritis of unknown etiology persisting for at least 6 weeks, which occurs before the age of 16 years (***, 2018).

Both endogenous and exogenous factors have been linked to the pathophysiological mechanism of the disease; at present, the disease is considered to be the result of the

interaction between genetic and infectious factors (Takken, 2010).

From a genetic point of view, JIA is considered a polygenic disease, the HLA region being the major locus of susceptibility which explains 13% of the genetic risk for JIA (Ravelli & Martini, 2007).

From a clinical point of view, JIA can manifest in several forms. There are 7 categories of JIA (Melson et al., 2005):

- a) Systemic arthritis
- b) Oligoarthritis
 - Persistent oligoarthritis
 - Extended oligoarthritis
- c) Polyarthritis (rheumatoid factor negative)
- d) Polyarthritis (rheumatoid factor positive)
- e) Psoriatic arthritis
- f) Enthesitis-related arthritis
- g) Undifferentiated arthritis

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The treatment of the disease is a multidisciplinary one. Along with medication with disease-modifying anti-rheumatic drugs (DMARDs) – conventional and biological, rehabilitation by physical therapy and psychotherapy have an important role.

JIA is a disease in which by careful management, patients diagnosed at childhood will not experience disabilities during adulthood. Early diagnosis, proper treatment, education and teamwork that includes family, patient and medical staff are factors that increase the success rate.

The objectives of rehabilitation in JIA include: controlling pain, preventing the development of mobility limitations, and improving ROM in the affected joints, improving and maintaining muscle tone, increasing and maintaining endurance for daily activities, minimizing the effects of inflammation, ensuring growth and development within normal parameters (Cakmak & Bolukbas, 2005).

The inability to perform normal movement can influence physical training, school performance, family life, recreational activities (social integration).

Unlike healthy children, children diagnosed with a chronic illness are most often absent from physical activities or sports programs (Apti et al., 2014). The altered general condition of children with a chronic inflammatory disease causes hypoactivity, which leads to a decrease in physical condition and enhances functional impotence, which generates a vicious circle (Metin et al., 2004).

The level of physical activity and cardiopulmonary capacity of patients with JIA is significantly lower compared to healthy children. A meta-analysis (Metin et al., 2004) shows that the maximum oxygen consumption (VO_2 peak) was 21.8% lower in patients with JIA than in healthy subjects. The reduced cardiopulmonary capacity of children with JIA does not appear to be directly related to its status, whether the disease is active or in remission (Lelieveld et al., 2007). Melson et al. found small differences in physical capacity between subjects who had disease activity and were taking medication and those who were in remission and not taking medication (Melson et al., 2005).

Inactivity is also strengthened by the fear of physical exertion, the belief that physical exertion is harmful (Apti et al., 2014), or by the postponement of physical exertion during periods of increased disease activity (Kirchheimer et al., 1993).

Over time, numerous studies have looked at the relationship between physical exertion and pain in patients with JIA. A randomized, controlled, single-blind study in which the control group was placed on a waiting list by the end of the study showed significant differences in pain level (measured by VAS) in favor of the study group, who practiced physical exercise (Houghton et al., 2018; Tarakci et al., 2012). On the other hand, on a smaller scale, there are exceptions: in a pilot study, Singh-Grewal states that subjects with severe hip impairment gave up the exercise program due to worsening pain during exercise (Singh-Grewal et al., 2006). Other studies show that pain levels are correlated with disease activity rather than exercise (Atwood, 2007).

Regarding the relationship between physical exertion

and disease activity, Takken et al., through a meta-analysis conducted in 2008, evaluated the safety of exercise in patients with JIA and concluded that physical exertion does not appear to be directly responsible for exacerbations of arthritis (Takken et al., 2008). The results of a meta-analysis conducted by Kuntze in 2018 also advocate the safety of physical exercise by patients with JIA (Kuntze et al., 2018).

Thus, the main problems faced by patients with JIA are reduced exercise tolerance, reduced physical activity and disability due to joint damage (swelling, stiffness, reduced mobility, joint deformity), muscle (decreased strength, decreased motor performance), bone (fragility, damage to the growth cartilage with consecutive growth disorders), as well as emotional problems caused by the disease or the attitude of people with whom patients with AJI interact (parents, teachers, doctors).

A series of studies show that the prescription of physical exercise practiced either at home or in a specialized center, in aquatic environment or on land by patients with JIA has a positive impact both in the secondary prophylaxis of the disease and in the primary prophylaxis of the main comorbidities accompanying JIA (metabolic, endocrine, respiratory, cardiovascular, depressive syndromes) (Basile, 2017; Klepper, 2001; Long & Rouster-Stevens, 2010).

The types of physical activity proposed in the studies vary depending on the environment in which they are practiced (water, soil), depending on the intensity of the effort (from Pilates, Thai Chi to cardio exercises) and the goal (impact on joint mobility, strength, pain relief, increased quality of life, etc.). Lelieveld points out that a child's daily activities are generally anaerobic (jumping, throwing and catching objects, running short distances), which means a high energy requirement over a short period of time (Lelieveld et al., 2007).

The most suitable physical training program for patients with JIA is the one that targets the patient's posture, joint mobility problems, their physical capacity and muscular strength. It is recommended, depending on the patient's needs, to set the goals to be reached after exercise.

The most commonly monitored indices in clinical practice are: pain level, degree of joint mobility (ROM), number of affected joints, muscle strength, oxygen requirements and quality of life.

Decreased muscle strength in adolescents with JIA is another problematic issue. Exercises to increase muscle strength require extra attention and involvement from both the therapist and the patient and his/her family.

In a randomized controlled trial that included subjects with extended polyarticular or oligoarticular JIA, Eva Sandstedt observed a statistically significant increase in muscle strength after 12 weeks in subjects who performed exercises involving jumping or weightlifting compared to those who performed classic exercises. At the same time, the study shows that exercises involving weights or jumps can be performed safely, without significantly increasing pain, by patients with JIA (Sandstedt et al., 2013).

Following a prospective study evaluating 62 patients with JIA, Kirchheimer concluded that sports activities such as swimming or cycling do not adversely affect the upper or lower limb joints (Kirchheimer et al., 1993).

Takken et al., in a Cochrane review conducted in 2008, show that there was no clinically important or statistically significant evidence that exercise therapy can improve functional capacity, quality of life, aerobic capacity, or pain. At the same time, no short-term negative effects of exercise therapy were found, and the data show that exercise does not exacerbate arthritis and that the short-term effects of exercise in patients with JIA seem promising, but the long-term effects remain unclear (Takken et al., 2008).

Why and how does physical therapy improve the course of the disease and improve the quality of life in patients with JIA? We find the answer at the cellular level.

JIA is currently classified as an autoimmune disease, being predominantly characterized by the activation of the innate immune system. However, for this to happen it is necessary to involve the adaptive immune system (Rochettea et al., 2015). The antigen is presented to T cells by macrophages, B cells, dendritic cells, fibroblasts, endothelial cells, and the activation of T lymphocytes takes place which stimulate the production of Th1 lymphocytes and B lymphocytes following the activation of Th17 cells. Pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α play a central role in the differentiation of naive T lymphocytes into effector T lymphocytes (Th1/Th17) (Mellins et al., 2011). Subsequently, innate immunity is activated - effector cells - macrophages, mast cells, NK cells, which leads to an even greater release of cytokines. Inflammation of non-lymphoid tissues can induce the differentiation of T lymphocytes into activated, specialized, memory-based subsets (eTreg) (Kim & Moudgil, 2017).

Data from the literature show that exercise can help reduce the effect of inflammation both by regulating the lymphocyte population by apoptosis correlated with increased plasma cortisol levels through exercise, and by quantitatively decreasing pro-inflammatory cytokines and increasing anti-inflammatory mediators (Gordon-Smith et al., 2015).

While the pro-inflammatory cytokines TNF- α and IL-1 β may show a slight decrease after physical training, IL-6 appears to decrease in prolonged training, but has a privileged anti-inflammatory pathway through both short-term exercise and prolonged training (Takken, 2003).

Anti-inflammatory mediators such as the IL-1 receptor antagonist (IL-1Ra), IL-10, the soluble receptor for TNF (TNF-R) increase after endurance exercise and resistance exercise. Exercise also has an effect on mi-RNA. There has been an increase in the circulating level of miR-146a, a molecule with anti-inflammatory effect, in trained people who perform episodic exercise (Rochettea et al., 2015).

It is known that during physical exertion the release of AMP is increased and the affinity of ecto-5'-nucleotidase for AMP increases. This causes an increase in the amount of adenosine released in the striated muscles, vessels, sympathetic nerve fibers, motor fibers.

A correlation was found in JIA between decreased adenosine production and disease severity. At the same time, the anti-inflammatory actions of methotrexate are mediated by the release of adenosine (from ATP molecules

by ectonucleotidases CD39 and CD73). Serum levels of adenosine deaminase (the inosin-converting enzyme) may serve as a marker of JIA activity (Mendonca et al., 2013; Ravelli & Martini, 2007).

Thermal shock protein 60 (HSP60) appears to be involved in disease remission in JIA. In experimental models, immunization with HSP10, HSP60, HSP70 or HSP90 can suppress arthritis in laboratory animals. This is possible because HSP60 plays a key role in modulating the interaction between the inflammatory process and cellular stress. The reduction of HSP60 correlates with the increase in the expression of inflammatory tissue cytokines produced by macrophages, such as IL-6 and TNF- α (Khadir et al., 2018). Sustained training programs can increase the level of HSP60: 3 months, three times a week: 10 minutes of warm-up, 10 minutes of cooling to a frequency of 50-60% maximum heart rate (MHR) and 40 minutes of intense exercise at a frequency of 65-80% MHR (Kim & Moudgil, 2017).

The intestinal microbiota is an important part of the human body and it is increasingly brought to the attention of scientific researchers. It seems that the intestinal microbiota plays an important role in inflammation. The microbiota intervenes, among other things, in the maturation of the immune system, helping to develop the lymphoid tissue associated with the intestine (Yulixaxis Ramayo-Caldas et al., 2016). By continuously stimulating the immune system, a physiological state of inflammation is maintained at a low level, which helps to better defend against other microorganisms (Cassidy & Petty, 2005).

In patients with JIA, intestinal permeability is increased compared to children who do not have a chronic inflammatory disease, being disrupted by the role of mechanical barrier and leading to changes in the composition of the intestinal microbiome. The composition of the intestinal microbiome in children with JIA is different from that of healthy children, as they have high concentrations of Bacteroides species and high concentrations of Firmicutes species. Actinobacteria and Fusobacteria are present only in patients with JIA, while the genus *Lentisphaerae* is missing (Ramayo-Caldas et al., 2016).

Studies show that the intestinal microbiome can be modulated by physical activity. The effect of exercise on the modulation of the intestinal microbiome varies depending on the intensity of the physical effort practiced, the level of training and the level of fitness.

Moderate exercise results in a diversification of the Firmicutes phylum species (including *Faecalibacterium prausnitzii*, species of the genus *Oscillospira*, *Lachnospira*, and *Coprococcus*), which contributes to a healthier intestinal environment (Sule & Fontaine, 2019).

Regarding the implementation of exercise therapy, a strategy is needed for the clinician. Given that there is no consensus in the medical world about how to perform exercise, some basic rules that can be derived from studies conducted so far can be followed.

The recent literature supports the importance of combining: stretching exercises, muscle toning, proprioceptive reeducation and balance reeducation and underwater activities. Numerous studies propose an

intensive program of physical activity and exercise therapy, performed 3 times a week for 12 weeks.

The difference between physical activity and therapeutic physical exercises is given by the purpose and ways used to practice the form of movement.

Therapeutic exercise consists of a set of activities designed and prescribed for specific therapeutic purposes such as restoring normal musculoskeletal function and reducing pain (Lelieveld et al., 2007).

Physical activity is any bodily movement produced by skeletal muscles and performed with energy consumption. It includes non-therapeutic activities (domestic, professional, sports) and the main goal is to increase the level of fitness (Cassidy & Petty, 2005).

Physical activity can turn into therapeutic exercise when the activities become planned and structured for people with medical conditions (occupational therapy).

For home exercise programs, 3 basic rules related to cost, customization and quality can be taken into account. First of all, the most convenient treatment is the simplest, least painful and cheapest; secondly, stretching and muscle toning exercises should be customized according to the daily activities which the patient has difficulty performing; thirdly, all treatment measures must be done under the careful guidance of a medical professional (Cakmak & Bolukbas, 2005).

The contraindications to exercise are fever, severe anemia, acute renal failure, heart failure, serositis, uncontrolled arrhythmias, uncontrolled hypertension, severe malnutrition (with a body weight loss of over 35%), joint pain and excessive swelling.

Ideally, children and adolescents would need more than one hour of moderate-intensity physical activity each day and more than one hour of high-intensity physical activity for at least 3 days each week.

Conclusions

1. The literature supports the importance of practicing physical exercise by patients with JIA. Moreover, data shows that physical exertion can be practiced safely, that it does not contribute to the exacerbation of the disease activity or to the increase of the perceived pain level.

2. Physical effort is worth considering in the therapeutic management of children and adolescents with JIA. Regular exercise can help improve the range of motion, increase muscle strength, decrease pain intensity and increase quality of life. Moreover, it can improve the intestinal microbial flora and has a positive impact on modulating the inflammatory process.

3. The concrete objectives of practicing physical exercise are managing pain and inflammation, maintaining range of motion, maintaining muscle strength and coordination, limiting strain on inflamed joints, increasing fitness, controlling disease activity, maintaining the physical and mental integrity of the child / adolescent, and increasing quality of life.

4. Ideally, children and adolescents would need more than one hour of moderate-intensity physical activity each day and more than one hour of high-intensity physical activity for at least 3 days each week.

Conflict of interests

There are no conflicts of interests.

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