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Exercise therapy for juvenile idiopathic arthritis

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

EXERCISE THERAPY FOR JUVENILE IDIOPATHIC ARTHRITIS

by

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B.S., Denison University, 2016

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MADelyn KERN

ABSTRACT

Background

Juvenile idiopathic arthritis (JIA) is the most prevalent childhood rheumatic disease and significantly impacts a child's well-being by potentially leading to disability and long-lasting effects. It consists of all forms of arthritis developing before the age of 16, therefore managing this disease is not simple. JIA can lead to a host of different medical problems over time and requires early attention and adequate treatment to prevent these long-term consequences. However, many children still experience pain after traditional treatment, indicating a need for alternative treatment modalities. Exercise therapy is one form of treatment that can potentially enhance a child's quality of life.

Literature Review Findings

Multiple forms of exercise therapy have been shown to improve quality of life, functional ability and pain in patients with JIA. Exercise does not worsen disease activity, including the number of joints affected. While there are a limited number of studies in the JIA population, studies on patients with rheumatoid arthritis, a rheumatic disease diagnosed in adulthood, demonstrate the potential for exercise therapy to alter the pathophysiology of the disease and lead to better immune function. Exercise may have the ability to affect children with JIA in the same way as the two diseases share a similar pathophysiology.

Proposed Project

The goal of the proposed randomized control trial is to measure the impact of an exercise intervention on the quality of life of children with JIA, the effect exercise on participant immune function and variations in response between each subtype of JIA. Children will either complete high intensity interval walking training three times a week or no exercise intervention for 10 weeks. Various outcomes including quality of life, functional status, pain and fitness level will be measured before and after the intervention. Blood analysis to assess changes in immune function and further analysis between subtypes will also be conducted.

Conclusions

The use of exercise therapy as a management tool for JIA should be considered earlier on in the disease course. It has not been found to worsen the disease and has produced increases in quality of life, functional status and pain. The benefits of this therapy are widespread and are not limited to healthy individuals.

Significance

This will be the first time these analyses will be performed and, if improvement is seen, this could help guide a physician's disease management plan. Data from this study could provide information on how exercise modifies the disease and how to design more structured exercise programs appropriate to each subtype of JIA. Exercise may begin to be incorporated into the treatment plan for these children to increase disease remission rates, reduce the amount and severity of disease flares and provide both physical and psychological benefits.

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LIST OF ABBREVIATIONS

6MWT.....	6-Minute Walk Test
ACPA.....	Anti-Citrullinated Protein Antibody
ACTH.....	Adrenocorticotrophic Hormone
ASE.....	Adverse Side Effects
ANA.....	Antinuclear Antibody
BMD.....	Bone Mineral Density
BU.....	Boston University
BMC.....	Boston Medical Center
CBT.....	Cognitive Behavioral Therapy
CHAQ.....	Child Health Assessment Questionnaire
CHQ.....	Child Health Questionnaire
CI.....	Confidence Interval
CMP.....	Chronic Musculoskeletal Pain
CRP.....	C-Reactive Protein
CVD.....	Cardiovascular Disease
DAS28.....	Disease Activity Score 28
DMARD.....	Disease-Modifying Antirheumatic Drug
EMR.....	Electronic Medical Record
ERA.....	Enthesitis Related Arthritis
ESR.....	Erythrocyte Sediment Rate
GM-CSF.....	Granulocyte-Macrophage Colony-Stimulating Factor

HIIT.....	High Intensity Interval Training
HLA.....	Human Leukocyte Antigen
HR _{max}	Maximum Heart Rate
HRR.....	Heart Rate Reserve
HRQOL.....	Health Related Quality of Life
IFN- γ	Interferon Gamma
IGF.....	Insulin-like Growth Factor
IL.....	Interleukin
ILAR.....	International League of Associations for Rheumatology
INSPIR.....	Integrated Network for Subject Protection in Research
IRB.....	Institutional Review Board
ISO.....	International Standards Organization
JIA.....	Juvenile Idiopathic Arthritis
JRA.....	Juvenile Rheumatoid Arthritis
JAFAS.....	Juvenile Arthritis Functional Assessment Scale
MHAQ.....	Stanford Health Assessment Questionnaire
NSAID.....	Nonsteroidal Anti-inflammatory Drug
PA.....	Physical Activity
PedsQL.....	Pediatric Quality of Life Inventory
PsA.....	Psoriatic Arthritis
QOL.....	Quality of Life
RA.....	Rheumatoid Arthritis

RCT.....	Randomized Control Trial
RER.....	Respiratory Exchange Ratio
ROS.....	Reactive Oxygen Species
RF.....	Rheumatoid Factor
SD.....	Standard Deviation
sJIA.....	Systemic Juvenile Idiopathic Arthritis
TMJ.....	Temporomandibular Joint
TNF- α	Tumor Necrosis Factor Alpha
VAS.....	Visual Analogue Scale
VO _{2max}	Maximum Oxygen Uptake
VO _{2peak}	Aerobic Capacity

INTRODUCTION

Background

Juvenile idiopathic arthritis (JIA) is a childhood rheumatic condition that has the potential to significantly affect a child's physical and psychosocial health. JIA is the most prevalent chronic illness and cause of disability in children, often extending into adulthood.^{1,2} It is more common in children than both diabetes and epilepsy and produces a greater financial burden than asthma.¹ It is a general term that includes every form of arthritis presenting before age 16.¹ Each of the seven subtypes presents with slightly varying onset age, signs, symptoms and pathophysiology (Figure 1). JIA affects almost any joint and leads to symptoms such as joint stiffness/swelling, fatigue, pain, and impaired physical function. This disease can lead to movement and balance issues, muscle atrophy, sleep issues, and multiple metabolic and psychological disorders.^{3,4}

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

*Reported frequencies refer to percentage of all juvenile idiopathic arthritis.

Table 1: Frequency, age at onset, and sex distribution of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis

Figure 1: Frequency, age of onset, and sex distribution of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis adopted from Ravelli et al. (2007.)

Children with JIA often have diminished aerobic and anaerobic exercise capacity, such as in jumping, throwing, running and climbing stairs.⁵ These impairments lead to issues completing these simple daily activities at the same pace as healthy children.⁶ This can limit their time participating in physical activities, socializing with friends and overall quality of life.^{6,7} JIA children experience higher levels of stress, anxiety and depression, which can further increase pain and disability and can impact the entire family.⁸

The goal of JIA treatment is to halt disease progression and support normal growth and development. It includes early pharmacological intervention with NSAIDs, biologics, steroids and disease modifying agents.⁹ These treatments come with worrisome side effects, such as increased risk of infection, detrimental effects on growth and development, and even malignancy.⁹ Frequently, children are inadequately treated and continue to live with debilitating pain as their disease progresses. This indicates a need for alternative therapies and further management to improve quality of life in this patient population.⁹

The use of non-pharmacological treatments, such as exercise, has been found to aid in management of chronic rheumatic conditions and are appealing to parents due to the elimination of adverse side effects (ASE).¹⁰ Exercise is regularly recommended for healthy children due to the numerous physical and mental health benefits. While initially discouraged for individuals with arthritis or other rheumatic disease, regular physical activity has been shown to be just as valuable for patients with arthritis or other rheumatic disease as for the rest of the population.¹¹ Exercise is known to be helpful for

reducing pain, joint stiffness and tenderness in rheumatoid arthritis (RA), a common autoimmune disease in adults that share many features with JIA.¹² Exercise consistently shows positive effects, just like pharmacologic therapy for the disease.⁴ Studies have recently found similar results in children with JIA who include exercise as part of their disease management. *Klepper et al. (2007)* found that children who performed aerobic exercise for at least 30 minutes twice per week for 6 weeks experienced a decrease in disease symptoms including joint swelling, pain, and range of motion.¹³ In addition to medical management, non-pharmacological treatment should be considered to possibly eliminate the need for polypharmacy, decrease medication dosages and avoid the long term complications from ASE.¹⁴

Statement of the Problem

Tremendous focus has been placed on creating the most appropriate and effective pharmacological treatment for JIA with the goal of regaining full function and control of one's life and without disease limiting activities of daily living. Childhood arthritis can become a great burden to a child and his/her family and can lead to severe disability and progression even into adulthood.² Many children are highly deconditioned due to reduced physical activity and worry exercise will worsen disease. Their reduced fitness further contributes to long term outcomes and level of disability.¹⁴ Some of these complications are caused by medications themselves: steroids can lead to the development of osteopenia, growth arrest, or retardation; disease modifying antirheumatic drugs (DMARDs) can cause gastrointestinal symptoms and liver damage;

biologics suppress the immune system and can increase chances of infection.^{1,9} It is necessary to identify the disease and develop a treatment plan early to avoid complications that may stick with these children for life.

Non-pharmacological treatments, including exercise therapy, are interventions that may reduce disease burden without added ASE. They can potentially reduce chronic medication dosages and extend the duration of remission and potency of disease flares.^{15,16} Currently, only a minority of patients use complementary and alternative medicine (CAM), but these treatment modalities are increasing in popularity as more research demonstrates the positive effects of these therapies.¹⁰ Many children with rheumatic conditions are inadequately treated and continue to experience pain even after receiving potent medical treatment.⁹ Exercise has specifically been shown to decrease stress on joints and provide many benefits to immune, cardiovascular, muscular and bone health.^{15,16} Additionally, exercise in JIA enhances quality of life and patient capacity without side effects. There is, however, limited data on the effect of exercise on immunity and inflammatory markers, the hallmark pathophysiology of an autoimmune disease.⁴ This study aims to understand how not only disease activity and physical fitness, but the impact of exercise on a patient's immune function.

Hypothesis

A high intensity interval walking training program in children with JIA will lead to greater changes in quality of life, functional ability and pain level when tested against a control group that only maintained pharmacological therapy.

Objectives and specific aims

The management of JIA is constantly being studied and is evolving. The goal is to control the disease to allow the child to live a normal life, and to prevent the long-term effects and disability. The mainstay of JIA treatment is medical management, however, complementary and alternative medicine, such as exercise therapy, should be integrated into the treatment plan to continue to improve overall health. The goal of this study is to identify how exercise can improve quality of life and alter the pathophysiology of the disease. Specifically, this study aims to:

1. Measure the effect of an exercise intervention on the physical and psychosocial health of children with JIA.
2. Measure the effect of an exercise intervention on immune function, a component of disease pathophysiology.
3. Compare results between different subtypes of JIA.

REVIEW OF LITERATURE

Overview:

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, affecting between 148 to 167 per 100,000 with a mean age of onset of 4.8 years. Its incidence and prevalence are variable throughout the world and may be underestimated.^{1,17} Previously known as juvenile rheumatoid arthritis (JRA), the International League of Associations for Rheumatology (ILAR) adopted the term JIA to describe seven forms of arthritis in children that begin before the age of 16 and persist for longer than 6 weeks.^{1,3,18} The term idiopathic indicates that these kinds of arthritis are of unknown cause. Similar to rheumatoid arthritis (RA), the cause of JIA is not completely understood. Studies show these diseases may be linked to genetic or environmental factors. For example, in those with a genetic tendency, the disease could be triggered by something in the environment, such as a virus.^{1,19,20}

JIA Subtypes

According to the ILAR, JIA is not one disease but rather a broad term that includes a group of seven subtypes: systemic JIA (sJIA), oligoarticular JIA, rheumatoid factor negative (RF-) polyarthritis, rheumatoid factor positive (RF+) polyarthritis, enthesitis-related arthritis (ERA), psoriatic arthritis (PsA) and undifferentiated JIA.¹⁸ While symptoms such as joint swelling, pain, stiffness, muscle weakness and atrophy, and movement restrictions are associated with all subtypes of JIA, each is unique.^{1,3}

Unlike many rheumatologic disorders, sJIA occurs equally in both boys and girls and is described as arthritis in addition to a fever of unknown origin lasting 2 weeks plus

one of the following: an evanescent erythematous rash, hepatomegaly, splenomegaly, lymphadenopathy, or serositis. Leukocytosis with neutrophilia can also be seen.²¹

Systemic JIA is considered an autoinflammatory process, where the innate immune system is activated, leading to inflammation.²⁰ Macrophage activation syndrome is a life-threatening complication that occurs in about 5-8% of sJIA patients and, therefore, it is crucial to recognize and treat this early. However, in patients with fever without preceding arthritis, it can be difficult to establish the diagnosis of sJIA early on.¹

Oligoarticular JIA is an early onset form of JIA peaking at ages 2-4. This form affects four or fewer joints during the first 6 months of disease. A review by *Ravelli and Martini (2007)* reports its frequency to be 27-56%, higher than all other forms.¹ The knee and ankle joints are most commonly affected. If greater than four joints become involved after the initial 6 months, the term extended oligoarthritis is used. A large number of oligoarticular patients have positive antinuclear antibodies (ANAs) and are at a higher risk for anterior uveitis, which can lead to long term visual impairment.¹

Rheumatoid factor- (RF) and RF+ polyarthritis affects five or more joints during the first 6 months of disease with or without the presence of the IgM RF. RF+ polyarthritis is similar to RF+ adult RA and is most commonly seen in adolescent girls. Resembling RA, it most often affects the small joints of the hands and rheumatoid nodules develop over the extensor surfaces in about a third of patients during the initial stages of the disease.^{1,21} In contrast, RF- polyarthritis is less well defined. It presents earlier in life than the RF+ form and often has a poor response to treatment.^{1,21}

Enthesitis-related JIA and PsA belong to the collection of spondyloarthropathies, a term that also includes children with juvenile ankylosing spondylitis and patients with undifferentiated spondyloarthritis.¹ Enthesitis-related JIA mainly affects male patients after the age of 6. Both enthesitis and arthritis are seen, most commonly at the calcaneal insertion of the Achilles tendon, plantar fascia, and tarsal area.¹ A juvenile PsA diagnosis is controversial and has been recently reclassified as “other JIA”. It requires occurrence of both a psoriatic rash and arthritis. If no rash is present, the diagnosis is made using a family history of psoriasis, dactylitis, or nail pitting in addition to arthritis. Undifferentiated arthritis includes those patients who fit into more than one category.^{1,21}

The current standard of treatment for JIA consists of use of early pharmacological intervention with NSAIDs, biologics, steroids and disease modifying anti-rheumatic drugs (DMARDs). Treatment approach varies between subtypes and is often not straightforward.^{1,9} NSAIDs have been the backbone of treatment for many years, however, recently the use of DMARDs earlier on has been shown to prevent long term sequelae of the disease.⁹ Intra-articular steroid use is also increasing earlier in the disease course. Systemic steroid usage is common and used for longer durations in sJIA or those with severe polyarticular JIA.²² A multidisciplinary team of rehabilitation professionals, physicians and nurses are required to halt disease progression and allow for regular growth and development.^{2,9}

Pathophysiology

The pathophysiology of JIA is not completely understood but has been discussed to be due to the imbalance between proinflammatory effector cells and anti-inflammatory

regulatory cells. This leads to chronic inflammation of primarily the synovium of the joints.²⁰ All subtypes involve triggering of the immune system, whether an autoinflammatory response of the innate immune system or an autoimmune response of the adaptive immune system.^{23,24} Each subgroup of JIA involves different components of the immune system and variation exists within each.

Systemic JIA is thought to be an autoinflammatory process from abnormal activation of phagocytes of the innate immune system, including monocytes, macrophages and neutrophils, due to unknown factors. These phagocytes release proinflammatory cytokines (IL-1, IL-6, IL-18), macrophage colony stimulating factor, tumor necrosis factor (TNF- α) and proinflammatory S-100-proteins, which contribute to multi-systemic inflammation.^{23,24} There is no definite link between sJIA and HLA genes or infection triggering the disease.

Oligoarticular and polyarticular arthritis are associated with autoimmune reactions and an abnormal adaptive immune system. Proinflammatory Th1 and Th17 cells produce the proinflammatory cytokines IFN- γ and IL-17. Immunosuppressive CD4+ regulatory T cells are inhibited and anti-inflammatory cytokine IL-10 is decreased resulting in the lack of immune tolerance to self-antigens. The imbalance between the pro- and anti-inflammatory cells causes synovitis of the joints.^{4,23,24} Immune reactions triggered by environmental factors in a genetically susceptible patient is associated with the development of these types of JIA. In oligoarticular JIA, positive HLA gene associations include HLA-A2, HLA-DRB1*11 and HLA-DRB1*08 exist. HLA-DR4 is associated with polyarticular JIA.²⁴

Clinical course

Similarities and differences in the clinical courses of each JIA subgroup exist. The chronic inflammation seen in JIA manifests as pain, fatigue, decreased fitness and activity level, sleep disturbance, diminished bone mineral composition, impaired quality of life (QOL) and growth disturbances. Low IGF-1 levels are seen in all types.^{1,4} *Packham et al. (2002)* investigated the long-term outcomes and functional levels of 246 patients with JIA that had progressed into adulthood and disease duration averaged 28.3 years.²² The authors found 43.3% had clinically active arthritis and 54.4% increased C-reactive protein (CRP). Severe disability was found in 42.9% of the patients.²²

Functional limitation and joint destruction increased into adulthood due to disease exacerbations and recurrent synovitis in affected or new joints. Persistent oligoarticular arthritis patients (fewer than 4 joints involved) have the most superior long-term prognosis of all JIA subtypes with higher levels of remission and decreased need for rheumatology follow-up. Therefore, this group, along with other milder forms of JIA were underrepresented in this study. Those that progressed to polyarticular disease represented 80% of the study population. Systemic and RF+ polyarthritis showed the worst prognoses with regards to functionality and disability. Uveitis was seen in 22% of the total study group and was significantly related to ANA positivity. A significantly higher proportion of those with oligoarticular and extended oligoarticular developed uveitis compared to those with systemic and RF+ polyarticular arthritis and 31% of patients with extended oligoarticular arthritis developed glaucoma.²²

Overall, the heights of those with JIA are shorter than the general population with a significant relationship between time using steroids and final height. In the sJIA group, 30.8% had leg length discrepancies over 2 cm and had undergone total hip replacements. Prosthetic joint replacements occurred at a young age and 51.2% of the study population had at least one joint replacement. Micrognathia, which leads to poor mouth opening and restricted temporomandibular joint (TMJ) movement, was more frequently seen in sJIA than other subtypes. Amyloidosis was seen in 8.9% of all patients with sJIA the most affected.²²

Other long-term outcome studies have shown that between 30 and 56% of patients with JIA have serious functional limitation, including joint deformity and destruction, growth abnormalities, osteoporosis (from corticosteroid use), pain, impaired psychosocial health and difficulties with activities of daily life.²² Furthermore, children with JIA lead a more sedentary lifestyle compared to healthy children. This leads to functional deterioration, deconditioning, and further inactivity.⁵ This cycle can have lasting effects on a child's cardiovascular health. Kids with JIA are at a higher risk of developing poor cardiovascular health and steps should be taken to address this potential outcome early on in the disease course.²⁵

Increased levels of inflammation and increased medication usage over time are found in individuals with uncontrolled, active JIA.²⁵ When correlated to healthy children, JIA patients with increased disease activity have significantly decreased physical activity levels leading to decreased aerobic and anaerobic capacity.^{5,6} Many

show developmental delays in growth and fine motor skills due to this decreased physical activity.^{7,13}

Exercise is beneficial to many aspects of one's overall health, including having an anti-inflammatory effect.⁴ Thus, exercise therapy is an influential part in treatment of a child with any form of JIA.^{1,2} Simple stretching, repetitive strengthening, and exercise as tolerated are generally recommended by rheumatologists. However, more structured and higher intensity exercises are currently being studied in JIA patients for their efficacy on decreasing disease progression and improving overall quality of life.

Exercise therapy and Rheumatoid Arthritis

Exercise therapy has increased in the adult RA population as well. RA and JIA share similar features but remain distinct diseases. RF+ polyarthritis shares the same characteristics as RF+ RA with differences in disease phenotype seen because of the difference in maturity of bone tissue at disease onset.¹ RA is the most common inflammatory arthritis in adults. It is also an autoimmune disease in which the cells of the adaptive immune system, with contribution from the innate immune system, produce antibodies that attack self-antigens in the joints leading to destruction of the synovium, joint effusions and pain. These immune cells, produce pro-inflammatory cytokines (IL-1, IL-6, TNF- α) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Peripheral blood monocytes also move to the synovial tissue and develop into macrophages that produce cytokines. These cytokines contribute to the formation of osteoclasts derived from CD14+ monocytes and further immune cell recruitment, which destroys the joints.^{26,27} RA is also correlated with systemic consequences including

fatigue and weight loss, rheumatoid nodules, cardiovascular illness (unexplained by the use of corticosteroids), anemia of chronic disease, secondary Sjogren's syndrome, uveitis, increased risk for lymphoma and osteoporosis.²⁸

As in JIA, the cause of RA is thought to be due to a mix of genetics and environmental triggers.²⁸ There is an relationship between the human leukocyte antigen (HLA)-DRB1 locus and those positive for RF and anti-citrullinated protein antibody (ACPA) antibodies. Infections producing heat-shock proteins have also been thought to trigger the production of RF.²⁸

Persistent synovitis and limited joint mobility over time leads to further physical inactivity, muscle atrophy and decreases in bone mineral density (BMD).¹² Joint effusions and swelling directly inhibit contraction of surrounding muscle groups and affect the biomechanical integrity of the joint. This leads to pain, altered loading responses and patterns of motion that are energy insufficient and further limit movement.¹² Decreased physical activity along with a high level of clinical disease activity and glucocorticoid use contributes to the progression of osteopenia and other negative health outcomes.²⁶ Although treatment traditionally indicated rest for affected joints, studies show that RA patients are able to tolerate a regular exercise program without exacerbating their clinical or immunological disease course.¹⁹ A paper by *Shephard et al. (1997)* looked at physical activity and RA and found high CD4+ counts and a pro-inflammatory shift in T-cell populations in patients with high levels of RF.¹⁹ The authors reported a decrease in the level of these CD4+ immune cells, enhancement of physical performance and no evidence of worsening disease activity following exercise.¹⁹

This indicates that exercise increases fitness, while having an effect on the pathogenesis and disease course of RA.

The inflammatory synovitis seen in JIA is consistent with that seen in adult RA and produces similar symptoms of swelling, pain and limited joint movement. Both diseases are due to an abnormal production of autoantibodies against self-antigens in the synovium, which leads to deformation of cartilage and bone. In some cases, further features including cardiovascular, pulmonary, psychological and skeletal disorders occur.^{23,24,29} Another shared characteristic of these two diseases is the involvement of cortisol, a catabolic hormone produced by the adrenal gland. Cortisol is a powerful anti-inflammatory agent and is released in response to adrenocorticotropic hormone (ACTH) from the pituitary gland. In RA patients, an impaired response to ACTH has been reported with a decrease in cortisol levels and subclinical adrenal glucocorticoid insufficiency. Abnormalities in the hypothalamus-pituitary axis (HPA) have also been suggested. This leads to insufficient cortisol secretion to stop continued inflammation in patients not receiving treatment. Exogenous corticosteroids are successfully used to treat patient with RA and JIA. Since physical activity increases cortisol secretion in healthy children, it can be hypothesized that it could also increase cortisol levels in JIA children.^{4,30} Future studies are needed to expand this hypothesis.

In the realm of JIA, there are few studies that investigate the effect of exercise therapy immune function. A review by *Rochette et al. 2015* investigated the effects of exercise on the pro/anti-inflammatory effects in JIA patients and suggests a regular exercise program in children is needed in order to produce these pro- and anti-

inflammatory systemic effects.⁴ It reports the need for more research on this topic to determine the intensity and duration of training needed to reach these effects. This is an area of research that could be explored to help further define the benefits of exercise therapy in JIA patients.

Benefits of Exercise Therapy:

Chronic musculoskeletal pain (CMP), a component of JIA, has traditionally been treated with rest and avoidance of activities that could trigger further inflammation.¹⁹ It was thought that increasing pressure on the joints through exercise would worsen pain, disease activity, or cause joint destruction.³¹ Many patients with CMP experience pain-related fear and avoidance of physical activity which leads to maintenance of pain and other disease related symptoms.¹⁵ In a study of patients with chronic low back pain, fear of injury correlated significantly with disability ($r=.44$).¹⁶ Patients with CMP fear that exercise will worsen their disease. By avoiding exercise, they become deconditioned over time. In theoretical pain research models, physical inactivity is a factor that maintains chronic pain. Reconditioning is used in pain rehabilitation to increase activity and reduce disability.^{15,16} The American College of Sports Medicine recommends exercising 3 to 5 days a week to increase cardiorespiratory fitness and body composition. Two exercise sessions a week is considered the lower limit of effectiveness, and one session is not effective in improving fitness in healthy adults.³² Repeated physical activity is as necessary for patients with CMP and rheumatic conditions, such as JIA, as it is for the general population.²⁹ Research emerging on the benefits of exercise therapy in

patients with chronic pain is proving physical activity in this patient population should not be avoided as it has been.

Studies in the adult RA population have shown success and no harmful side effects with physical activity. A systematic review on the effects of dynamic exercise therapy program in RA patients showed improvement in physical fitness, range of motion (ROM) and function through records of muscle strength and oxygen uptake. The authors recommend an exercise program of aerobic training combined with muscle strength training in RA.³¹ *Sandstad et al. (2015)* recommended 2-7 days/week of exercise in RA patients to improve maximal oxygen uptake (VO_{2max}), maximal heart rate (HR_{max}) and risk of cardiovascular disease (CVD).²⁹ This study showed physical activity to be effective in significantly reducing several CVD risk factors, including high blood pressure, total body fat, and BMI, and noted it can prolong disability in patients with arthritis.²⁹

Exercise has many benefits to one's physical, emotional and social health. These benefits are not limited to healthy individuals. Exercise has many anti-inflammatory effects and reduces the risk of CVD in RA patients as well.²⁹ CVD is the top cause of deaths in the RA population with chronic inflammation and cannot be explained by classic CVD predictors alone.²⁵ Children with JIA are also at risk for poor cardiovascular health due to decreased activity levels. They have been shown to have subclinical signs of atherosclerosis, including aortic stiffness, in individuals as young as 4 years old.³³ Therefore, prevention of CVD needs attention in both RA and JIA patients due to their increased risk at baseline.

As in RA, studies have found that exercise in children and adolescents with JIA does not increase disease activity or worsen symptoms.^{13,34} Multiple side effects come with each of the pharmacological treatments used to manage JIA, while physical activity does not come with any of the serious systemic side effects.³⁴ Children with JIA have been found be able to perform land-based weight-bearing or aquatic exercise without disease exacerbations. Other benefits including increased ROM, strength, fitness, improved bone health and decreased stress on joints has also been observed after exercise in JIA patients.^{35,36} In general, exercise programs, particularly those including jumping/plyometrics, have been shown to support a healthy lifestyle and prevent injuries in children.³⁷

Existing Research

JIA and RA have traditionally been treated with modifications of activities of daily living, rest of affected body parts and pharmacologically. Current modalities are relatively effective at treating these rheumatologic diseases, however, some patients are still refractory to treatment and maintain active disease states without gaining complete control of the disease.^{1,19,38} The goal of treatment is to preserve physical and psychological strength, alter long term progression, disability and achieve clinical remission.^{1,28} RA patients have lower fitness levels, movement and balance abnormalities and can tolerate and benefit from exercise programs.³¹ Similar studies in children and adolescents with JIA have shown similar benefits.^{2,3} JIA and RA are the most common forms of inflammatory arthritis in children and adults, respectively,

warranting further research of non-pharmacological treatment, such as exercise therapy, to further investigate its benefits.^{3,26}

Exercise therapy is also being utilized more often in JIA as it shares similar characteristics with RA. In a review of JIA by *Ravelli and Martini (2007)*, physiotherapy is noted to be an important component of the treatment to any patient with JIA.¹ They also mention that parents tend to protect their children and restrict their activities similar to adult RA patients avoiding exercise in fear of injury.^{1,15} Avoidance of activity not only affects a child's physical fitness and functionality but it can also affect their social skills and development of personality. Restriction from certain activities, such as sports and physical activities at school, decreases time socializing with others and can have long term effects on emotional and social health.²² Psychological support is yet another important part of the multidisciplinary approach to management of JIA.¹

Effect of Exercise Therapy on Juvenile Idiopathic Arthritis

One of the earliest high quality randomized control trials (RCT) was conducted by *Singh-Grewal et al. (2007)* and allocated 80 JIA children, 40 in each arm, to complete a program of either high-intensity aerobic cardio-karate consisting of 3 sessions per week for 12 weeks (experimental) or low-intensity Qigong non-aerobic exercises (control).³⁹ The aim of the study was to study peak oxygen uptake, peak power and self-reported physical function in JIA patients. After treatment, no difference was found between groups in $VO_{2submax}$ while treadmill walking at 3 km/hour ($p=0.43$). A clinically relevant, but not statistically significant, decrease in the number of active joints and improvement in ROM was seen in the cardio-karate group. Also, both groups showed improvement in

CHAQ scores indicating improved physical function. However, there was no difference between groups potentially indicating no additional benefit from high-intensity aerobic training. Exercise was tolerated well in both groups, though adherence was higher in the control. Although not significant, these results suggest aerobic exercise may only be superior in terms of decreasing the number of active joints and increasing ROM. Both exercises are safe and produce clinical benefits, such as improved physical function and quality of life. The non-aerobic group also had higher adherence to the program suggesting a decrease in intensity may be easier to comply with while still potentially providing benefits to the child's health.^{2,3,39} A limitation of this study is the absence of a non-exercise cohort. Without this type of control, one does not know how JIA patients would perform without a structured exercise program. The Hawthorne effect may have led to participants showing improvements in the study merely due to the fact they are enrolled in a program and being observed.

Another RCT by *Mendonça et al. (2013)* studied the impact of Pilates exercises on the quality of life in children with JIA.⁴⁰ A total of 50 participants with JIA, aged 8-18 years old, were randomly sorted into either a Pilates group (II) or conventional exercise group (I) and completed two 50 minute sessions a week for 6 months. All sessions were supervised and standardized in both groups, strengthening the internal validity of this study.⁴⁰ The Pediatric Quality of Life Inventory (PedsQL 4.0) score was used to measure improvement in the primary outcome measure, health-related quality of life (HRQOL), at the beginning (t0) and end (t6) of the 6 month intervention. A significant difference was observed between the two groups at in both physical (MD ±

SD, 37.4 ± 5.1 ; $p < 0.001$) and psychosocial (MD \pm SD, 36.5 ± 4.3 ; $p < 0.001$) PedsQL 4.0 scores after intervention. In the Pilates group alone, total PedsQL 4.0 score increased by 38.8 points (SD = 3.9; $p < .001$) from t0 to t6. The conventional group did not show statistically significant improvements.⁴⁰ Significantly greater improvements in pain intensity (MD, 3.1mm; 95% CI, 1.85-4.24; $p < 0.001$), functional ability (MD, 0.83; 95% CI, 0.35- 0.91; $p < 0.0001$) and joint ROM (MD \pm SD, 0.10 ± 0.20 ; 95% CI, 0.001- 0.20; $p = 0.002$) were also found in the Pilates group. The study had no dropouts, adverse effects or worsening of disease activity. These findings highlight the safety and positive impact of an exercise program, such as Pilates, on improving the physical and psychosocial quality of life, pain, functional ability, and ROM of a child with JIA. It further strengthens the argument that exercise should become part of disease management in children with JIA.² A limitation the authors noted is that Pilates exercises are more motivating which could be a potential confounding factor. It may have contributed to the sense of well-being in those participants in this group and impacted the PedsQL 4.0 Scores.⁴⁰ Also, this exercise intervention may not be generalizable when implemented unsupervised, at-home due to loss of external motivation.

Takken et al. (2003) performed a RCT to study the effects of aquatic exercise on functional ability in JIA.⁴¹ A total of 54 children, 27 in each group, were randomly allocated to participate in a structured aquatic exercise program (experimental) or a control group that continued to be managed pharmacologically but did not exercise. Those in the experimental group completed a 1-hour aquatic session once a week over 6 months. Functional ability was measured using the CHAQ and the Juvenile Arthritis

Functional Assessment Scale (JAFAS). HRQOL was measured using the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and the Child Health Questionnaire (CHQ), a survey of physical and psychosocial health of children 5 years of age and older developed for the general population and children with chronic conditions.⁴² Joint status was measured by the number of tender and swollen joints and physical fitness was assessed using a maximal exercise test (MXT) and submaximal 6-min walking test (6MWT).⁴¹ Although not significant, the experimental group improved 27% in CHAQ score while the control group only improved 5% over 6 months. There was a significant relationship between baseline CHAQ score and improvement after intervention ($p < 0.05$) in which patients with increased levels of disability benefited the most in the aquatic program.⁴¹ No significant differences were seen in HRQOL, however, there was a trend for the control group to deteriorate while the experimental group remained stable. The number of swollen and tender joints decreased, with a 55% decrease in the experimental group and 21% increase in the control group, a clinically significant change, but was not statistically significant ($p = 0.07$). Physical fitness did not significantly change.

While limited, these results show a clinically but not statistically significant, benefit of an aquatic exercise program on the number of tender and swollen joints in JIA patients, especially those living with more severe disability and limited functional status. There were no negative effects on disease status or increase in pain indicating this type of intervention is safe.

The frequency of sessions (once per week) is a limitation to this study. The authors state it was impossible to increase the number of training sessions due to limited

pool access and busy family schedules. They suggest including a home-based exercise component in future studies. According to the guidelines of the American College of Sports Medicine, a minimum of two sessions per week on non-consecutive days is regarded as the lower limit to be effective in improving cardiorespiratory fitness and body composition in adults.²⁸ An increase to the number of exercise sessions in this study may have resulted in significant results.

A study by *Tarakci et al. (2012)*, investigated if a strengthening exercise regimen, primarily unsupervised by health professionals and completed at home, would impact quality of life and pain control in children with JIA.⁴³ Participants were randomly allocated to either an exercise group or control group that did not exercise. The exercise group completed 4 sessions a week of increasing intensity (1 supervised and 3 unsupervised at home) over 12 weeks. At the end of 3 months, outcomes including 6-minute walk test (6MWT), functional ability using the CHAQ score, pain using the visual analogue scale (VAS) along with CHAQ, and QOL using the Pediatric Quality of Life Inventory (PedsQL) were assessed. The 6MWT has been found to be a valid test for measuring functional status of children with JIA and requires patients to walk the farthest span in 6 minutes.^{7,43} After intervention, all outcome measures showed significant improvements in the exercise group ($p < 0.001$) and only the VAS decreased significantly in the control group ($p < 0.01$).⁴³ The 6MWT increased significantly by 30.79 meters in the exercise group while the control group only increased 0.63 meters. Except for VAS ($p = 0.29$), the difference in means between groups for all outcome measures were

significant ($p < 0.001$) and in favor of the exercise group. This study had high adherence, suggesting the design of this exercise program is feasible for children.

These results indicate an aerobic, land-based exercise program may benefit the functionality and quality of life of patients with JIA by decreasing joint stiffness and fatigue, even when completed mostly at home without the supervision of a health professional.⁴³ It suggests that an at home design may be more practical and increase adherence to exercise and allow for an increase in the number of sessions per week. For example, when compared to the study conducted by *Takken et al. (2003)*, only 1 aquatic-based exercise session per week was possible.⁴¹ CHAQ and QOL were not significantly increased and the aquatic intervention was only found to clinically minimize the tenderness and amount of swollen joints.⁴¹ However, *Tarakci* found these outcomes were significantly increased following exercise, suggesting an increase in quantity of exercise may lead to stronger results.

In another RCT conducted by *Sandstedt et al. (2013)*, muscle strength and physical fitness were studied to understand how medically managed JIA patients can further improve their health with exercise.⁴² Significant changes in muscle strength were seen and warrant discussion. In this study, 54 children and adolescents aged 9-21 were randomized into an exercise or control group. Children in the exercise group performed a mixture of strength training exercises using free weights and jump rope at home 3 times a week, while the control group did no exercise. Muscle strength, fitness and wellbeing were noted before and after a 12-week training program and at a 6-month follow-up. The exercise group showed significant changes in muscle strength from baseline to 12-weeks

for shoulder abduction, elbow flexion, hip extension, hip abduction, knee extension and ankle dorsiflexion ($p < .03$). These improvements illustrate that JIA children can tolerate and potentially benefit from a weight bearing exercise program to improve muscle strength without increasing pain.⁴²

Quality of life and well-being were measured using the (CHAQ), and the Child Health Questionnaire (CHQ).⁴² No differences were found between the exercise and control group in this study. However, there has been debate that these questionnaires lack sensitivity to changes in rehabilitation. The ability to detect changes in well-being in this study may have been limited by the fact that subjects had only moderate impairment and their disease was not active at the time of study. The authors also point out the complexity of JIA pathogenesis and the fact that medical management often does not alleviate all symptoms. Many of the disease's effects on self-esteem and well-being do not respond to traditional medical therapy. They argue this further supports the idea that non-pharmacological interventions such as exercise should be included with medical treatment for better outcomes on overall health.⁴²

A study by *Obeid et al. (2015)* took a different approach than the studies above and looked at the response of peripheral blood levels of endothelial progenitor cells (EPCs) to exercise in both healthy and JIA children.²⁵ These cells contribute to vascular repair via paracrine secretion of angiogenic factors or differentiation into mature endothelial cells. They are inversely correlated with markers of endothelial dysfunction and predict occurrence of cardiovascular events. They are also known to be decreased in the active RA population.²⁵ RA patients being treated had EPC levels resembling those

of healthy controls. Untreated RA patients with high levels of TNF- α , a marker of inflammation, were shown to have lower EPCs compared to the treated and healthy patients. In prior studies, the authors state a single episode of exercise was shown to increase peripheral blood endothelial progenitor cells (EPCs) from 66-309% and 83-170% in healthy adults and children, respectively.²⁵ This study found resting levels of EPCs to be similar in JIA children and healthy controls. After moderate intensity, continuous exercise (MICE), the concentrations of EPCs in healthy controls was significantly higher than that of JIA children ($p < 0.001$). The healthy controls had ~100% increase in EPCs while the levels in JIA children did not change. No change was seen after high intensity, intermittent exercise (HIIE) in either group. The lack of EPC increase in JIA children could be a result of disease related inflammation, medication use or recruitment of EPCs from the blood to the synovium.²⁵

These findings suggest JIA patients are at further risk for CV events due to a decreased EPC response and, thus an understanding of how exercise relates to changes in EPC levels in children is warranted. Furthermore, those in the MICE group completed a total of 60 minutes of exercise, while those in the HIIE group only completed a total of 6 minutes of exercise. HIIE was designed to mimic the typical physical activity patterns of children.²⁵ Since there was no response to HIIE in either group, one could infer that the typical activity of a child is not sufficient for change and longer periods of exercise may be needed.

Overall, these RCTs show no increase in level of pain or clinical deterioration in JIA patients. Positive effects on functional status, quality of life and physical fitness

were seen. However, there is not much data physical activity and its impact on disease activity, the immune system and pathophysiology of the disease. There have been stronger exercise intervention studies with promising results in RA patients, a disease with similar pathophysiology to JIA. The results suggest similar research should be conducted in patients with JIA.

Effect of Exercise Therapy on Rheumatoid Arthritis

In a prospective study by *Hakkinen et al. (2001)*, a group of 70 recent onset RA patients were randomly distributed to at-home strength training or control (range of motion exercise without resistance) groups.¹² Over two years, participants completed exercises twice a week, were prompted to participate in exercise-related activities 2-3 times a week and keep training logs that were inspected every 6 months. Muscle strength, bone mineral density, physical function, joint damage, disease activity and walking speed were measured. The results showed that in the strength training group, the maximum strength of all muscle groups examined increased significantly when compared to the control ($p = 0.002-0.025$). Significant between group differences, in favor of the strength training group were observed for clinical disease activity, as measured by ESR, pain, morning stiffness, DAS28 and Larsen score ($p < 0.05$) and HAQ scores at 18 and 24 months ($p < 0.01$ and $p < 0.05$ respectively). The mean \pm SD walking speed increased by $16 \pm 17\%$ ($p < 0.001$) in the strength training group and by $9 \pm 12\%$ ($p = 0.025$) in the control group. No significant changes were seen in BMD in either group.¹²

The authors of this study also assessed the groups at 5 years to determine if the initial 2 year at-home exercise intervention produced lasting effects. Of the initial 62

patients, 59 were reassessed and the initial muscle strength gained in the first 2 years was maintained after self-monitored exercise over the subsequent 3 years. BMD remained constant and radiographic damage to peripheral joints remained low at 5 years.⁴⁴ The results of this study indicate that with minimally supervised strength training, strength and physical function can improve and be sustained in patients with RA without worsening the disease. In those with RA, an increase in muscle strength is important as it can decrease risk of falling and increase daily activity levels.¹² Decreased activity and high levels of disease activity also impact the development of osteopenia. While BMD was not shown to have decreased over the span of 5 years, a limitation of this study is that it included only those with a recent (<2 years) diagnosis of RA with mostly normal BMD at baseline.⁴⁴ A study looking at bone mineral density in patients with much older RA diagnoses may be more informative regarding the development of osteopenia.

A paper by *Sandstad et al. (2015)* studied the effects of 10 weeks HIIT on a group of seven women with RA and eleven women with adult-JIA (age 20-50 years with disease diagnosis in childhood).²⁹ The study was designed as a cross-over study with patients acting as their own controls. After the first period of training or control, a two month “washout period” occurred. *Thomsen et al. (2018)* defines HIIT as organized cardiorespiratory training with multiple rounds of short duration intervals at 80-95% of HR_{max} followed by intervals of lower intensity as active recovery.⁴⁵ HIIT has been shown to improve cardiovascular health so this study tried to determine whether a HIIT intervention could be physically managed by patients with RA and would lead to improvements in risk factors for CVD. Participants performed 4 x 4 min intervals on

spin bikes at 85-95% of HR_{max} twice a week for 10 weeks. Maximum oxygen uptake, heart rate recovery (1-minHRR), blood pressure, body composition, blood biomarkers (lipid panel, white blood cell count, C-reactive protein), disease activity calculated by DAS28, and functional disability, assessed by the Stanford health assessment questionnaire (MHAQ), were measured before and after intervention. After intervention, VO_{2max} increased by 12.2% (p<0.001), 1-minHRR increased 2.9% (p=0.02), BMI, total body fat, and waist circumference decreased by 1.2% (p=0.04), 1.0% (p=0.04), and 1.6% (p=0.004), respectively, while no change was observed in the control group.²⁹ Blood analysis revealed serum levels of ferritin (a biomarker for inflammation) decreased 24.0% (p=0.006). A clinical, but not statistically significant, decrease in CRP from 1.98 to 1.23 (p=0.08) was seen, reflecting less joint inflammation. No differences were seen in disease activity and pain in either group.²⁹

Overall, this study demonstrated no negative effects on RA and adult-JIA patients who underwent a high intensity exercise program and showed significant improvements in CVD risk factors. *Sandstad et al. (2015)* showed a 12% increase (4.4 ml/kg/min) in VO_{2max} indicating RA and JIA patients respond to exercise and decrease their risk of all-cause mortality and CV events similar to healthy individuals.^{29,46} Furthermore, slow and abnormal 1-minHRR is associated with inflammatory markers and contributes to CVD. This study found significant improvements in 1-minHRR after intervention and improved CVD risk factors.²⁹

The main limitations of this study were the small sample size and cross-over design. Trends found in the study may have been found to be significant with a larger

study population. Participants randomized to the HIIT group first may have experienced long-term benefits during the subsequent control period.²⁹ This was the first study to look at HIIT in rheumatologic patients and the authors conclude HIIT to be a favorable alternative treatment for patients with RA and adult-JIA.²⁹ This study was able to establish that regular physical activity is beneficial for those with arthritis, similar to the general population. HIIT can improve pain, function, mood and QOL and delay the onset of disability without worsening disease severity.^{11,29}

A recent RCT by *Thomsen et al. (2018)* also looked at the effects of a HIIT exercise program but in a cohort of patients with psoriatic arthritis, another type of inflammatory arthritis and one of the subtypes of JIA.⁴⁵ Its goal was to evaluate the impact of HIIT on disease activity and patient disease perception. At the end of the trial period, the HIIT group reported less fatigue, as measured by the patient global assessment (PGA), than the control group (mean difference of -12.83; 95% CI -25.88 to 0.23, $p = 0.05$) and HIIT showed no clear increase of disease activity with psoriatic arthritis. After 3 months, patients completed exercise on their own time. These results were not maintained at 9-month follow-up with low continued adherence to exercise. This indicates a challenge for health care providers to continue to set exercise goals and keep their patients active.⁴⁵ Although no long term effects of HIIT were shown, this study, as well as *Sandstad et al. (2015)*, provides strong evidence against the idea that vigorous physical exercise leads to increased disease activity.^{29,45}

It is clear from the studies discussed above that, similar to JIA, physical activity is beneficial to those with RA and should be encouraged. These studies found no increase

in disease activity and physical function by monitoring outcomes such as QOL, number of affected joints and pain. However, they did not investigate whether exercise affects the pathology of the disease. *Luo et al. (2018)* studied the correlation of CD64 expression on monocytes in patients with RA with markers of autoimmune response, inflammation, disease activity and serum cytokines.²⁶ In comparison to healthy individuals, the occurrence of these monocytes was significantly elevated in RA patients. Classical (CD14⁺⁺CD16⁻, regulators of inflammation) and intermediate (CD14⁺⁺CD16⁺, proinflammatory role) monocytes were elevated and positively correlated with ESR, CRP, RF, ACPA and DAS28, all indicative of inflammation in RA. Intermediate monocytes were also found to be associated with serum concentrations of IL-6, a proinflammatory cytokine.²⁶ These findings suggest the classical and intermediate monocyte elevation impact the progression of RA and positively correlate with disease activity.

Bartlett et al. (2018) utilized this information and applied it to RA patients in an exercise program.⁴⁷ The authors studied the effects of a high-intensity interval training program in older adults with stable RA and found exercise correlated with a lower level of disease activity and improved immune function in RA patients.⁴⁷ The goal of the study was to determine whether 10 weeks of walking-based HIIT would improve disease activity and aerobic fitness and whether HIIT was associated with improved immune function. They specifically look at antimicrobial/bacterial functions of neutrophils, cells that dominate the synovial fluid, and monocytes, cells that infiltrate the synovium. Both of these cells are highly differentiated, apoptosis-resistant innate immune cells, which, in

addition to the proinflammatory cells in the joint, characterize the pathology of RA.⁴⁷ RA is a disease that leads to an impaired immune system and is often treated with immunosuppressive drugs that further increase the risk of opportunistic infections. The authors sought to find ways to avoid further suppression of the immune system. They argued that since exercise improves immune function in healthy adults, it had the potential to improve immune function in RA.⁴⁷ The authors found a significant increase in cardiorespiratory fitness, as measured by VO_{2peak} , by a mean \pm SD of $9 \pm 4\%$ ($p < 0.001$), reduction in resting HR ($p = 0.009$) and reduction of mean arterial BP ($p = 0.044$). They found a 38% reduction in disease activity, as measured by DAS28, due to a decrease in the number of swollen and tender joints and improved global health ($p = 0.001$). A significant reduction in ESR by a mean of 58% was also found ($p = 0.02$).⁴⁷

The intervention also improved innate immune function, indicating a potential reduced risk of infection and inflammation. Neutrophil movement of isolated RA peripheral blood neutrophils toward chemokine ligand CXCL-8 increased ($p = 0.003$), as well as phagocytosis of *Escherichia coli* ($p = 0.03$) and ROS production ($p < 0.001$). There were also significant decreases in the prevalence of both nonclassical CD14⁺ CD16⁺ and intermediate CD14⁺⁺CD16⁺ monocytes (both $p < 0.05$).^{26,47} These results suggest exercise has the potential to enhance antibacterial function and reduce risk of infection/inflammation. A limitation of this study is the lack of an age-matched healthy control group. A comparison between an experimental and control group would produce stronger evidence that the exercise intervention is the reason for change in outcomes.

METHODS

Study Design

This multi-site RCT study will articulate the effectiveness of 10 weeks of HIIT walking for strengthening physical and psychosocial health in children with JIA, while also investigating the differences noted between subtypes of JIA. Furthermore, it will assess whether this intervention is associated with improved immune function.

Study Population and Sampling

The participants recruited for this trial will be 5- to 18-year-old children diagnosed with any type of JIA in accordance with the ILAR criteria and on stable dosage of medication/treatment consisting of nonsteroidal anti-inflammatory drugs, disease modifying anti-rheumatic drugs, immunosuppressive medication, and/or steroids. During the 6-month period prior to enrollment in the study, participants will not have followed any standardized exercise program. Patients will be excluded from the study if they have: significant cardiac, pulmonary, rheumatologic, or metabolic comorbidity; active disease that requires therapy modification during study; any medical condition determined by their physician to be a contraindication for physical exercise; or take opioid pain medication. Also, those who are unable to walk unaided on a treadmill or miss 3 consecutive training sessions during intervention period will be excluded from the study. These criteria were adapted from *Mendonca et al (2013)* and *Tarakci et al. (2012)*.^{40,43}

The sample size and power were calculated using the UCSF Clinical and Translational Science Institute sample size calculator with data from a study of JIA patients by *Tarakci et al (2012)*.^{43,48} An effect size of 20.6, the mean difference between the exercise and control group, and the exercise group's higher SD of 14.23 points were chosen for a more conservative estimate.⁴³ An estimated sample size of 18 patients, 9 in each group is needed to detect this difference between the exercise and control groups with 80% power, an α of 5%, and a 1:1 intervention to control proportion.^{43,48} This study will have a larger sample size of estimated 150 patients, 75 in each group, with the goal of recruiting higher numbers of patients from each of the different subtypes of JIA for analysis between subtypes. The sites included will be Boston Medical Center in Boston, MA, Boston Children's Hospital in Boston, MA, Cincinnati Children's Hospital Medical Center in Cincinnati, OH, Ann & Robert H. Lurie Children's Hospital of Chicago in Chicago, IL, and Hospital for Sick Children in Toronto, Ontario, Canada. Multiple sites were chosen due to the larger sample size.

Intervention Groups

The participants will be randomly assigned to either the HIIT walking group (Group I) or control group (Group II) with no supervised exercise intervention. One case will be randomized for each control. Both groups are to continue their regularly prescribed medications and standard of care. Participants will be randomized by two Boston Medical Center (BMC) research assistants blinded to all data regarding patients' participation in this study. A staff member will generate 150 random numbers in a

Microsoft Excel spreadsheet while the another staff member will randomly allocate each number to a patient from a list containing names of participants ordered based on date of recruitment. The list will then be securely delivered to the research team. Patients assigned numbers 1-75 will comprise group I and numbers 76-150 will comprise group II.

Physicians and those responsible for administering fitness testing, data collection and statistical analysis will also be blinded to the study. All participants and their parent/guardians will be instructed to not discuss study to other possible participants.⁴⁰

Exercise training (Group I)

Over the course of 10 weeks, group I members will participate in high-intensity interval walking. As stated above, a child's day to day activities are of anaerobic nature, so HIIT was chosen to mimic this.⁶ Training will consist of 3 x 30-minute sessions per week of treadmill walking for a total of 30 planned sessions per patient. Each training session will be performed with supervision of an exercise physiologist trained to administer the same level of encouragement across all locations. Interventions will be standardized to avoid variation at each location and increase internal validity. During each training session, heart rate (HR) will be measured using Polar H10 heart rate sensors given to each patient enrolled in the study. These are Bluetooth compatible with iOS mobile devices with iOS 11 or later and Android mobile devices with Bluetooth 4.0 capability and Android 5 or later. Exercise physiologists will ensure HR remains in target zones as described earlier.

For the exercise intervention, VO₂ reserve was chosen to represent cardiovascular fitness and will be calculated using percentage of maximal HR (%HR_{max}) as previously described.¹⁰ Patients will be given between 3-6, 20 minute sessions to become accustomed to exercise. Exercise sessions will be 30 minutes and consist of a 5-minute warm-up, ten 60-second high intensity intervals, each followed by 60-second active recovery, and a 5-minute cool-down. High intensity intervals are designed to elicit a HR_{max} of 85 ± 5%, corresponding to 80-90% of VO₂ reserve, followed with active recovery periods of 50-60% VO₂ reserve. Treadmills will not exceed walking pace, and if patient is unable to achieve HR goal by walking at 1%, treadmill gradient will be increased to elevate HR. This design was adapted from *Bartlett et al. (2018)*.⁴⁷

Control (Group II)

The control group will be administered all tests described below before and after a 10-week period. During this time period, they will be instructed to continue with their normal disease management routine as per their rheumatologist.

Study Variables and Measurement Tools

Baseline characteristics, including demographics, JIA subtype, disease state, and medications will be collected from each patient's' electronic medical record (EMR) at each hospital location. A fasting blood sample will be collected in both groups at baseline to measure complete blood count differentials using a commercial clinical analysis company (LabCorp).

All outcomes will be assessed, as below, before and after 10-week intervention for members of both groups. Testing will be finished prior to starting training and 24 hours or more after group 1 finishes its last exercise session. Group II will be measured at the beginning and end of a 10-week period.

The primary outcome, health related quality of life (HRQOL) will be measured by the PedsQL 4.0 in interview format. Designed and modified by *Varni et al. (2003)*, the PedsQL 4.0 assesses pediatric physical, emotional, social and school functioning.⁴⁹ It is specifically tailored to pediatric rheumatology and a reliable and valid tool for assessing pediatric QOL. Scores range from 0-4 with higher scores representing better quality of life. Functional ability will be measured by the CHAQ, a frequently used functional health status measure in children with JIA, in interview format which takes approximately 10 minutes to obtain. CHAQ is scores range from 0-3, and higher scores reflect greater disability.¹⁴ Pain intensity will be measured using the 10-cm VAS-joint pain scores ranging from 0-10, with 0 representing no pain and 10 representing the worse pain. This scale has been shown to be reliable and valid when evaluating JIA patients.⁵⁰

Cardiorespiratory fitness, measured by VO_{2peak} will be assessed by continuous walking test on a treadmill starting at 2mph/0% grade with speed or incline increasing each minute until individual reaches fatigue. No specific increase in speed or incline will be used as fitness levels may vary. An exercise physiologist will supervise these tests and increase speed or incline based on the child's heart rate, respiratory exchange ratio and overall appearance. A 12-lead electrocardiogram, ventilation, and gas exchange will be continuously monitored and documented as 20-second averages using a Parvo

Metabolic Cart (Parvo Medics, Sandy, UT, USA). Highest 20-second values will be used to determine VO_{2peak} . A child will have met VO_{2peak} criteria when $RER > 1.1$ and age-predicted maximal HR are met.^{39,47}

Blood tests including, ESR and CRP will be performed on blood samples by hospital lab. ESR and CRP are standard markers of inflammation but are subject to variation from many causes. To further assess immune function and inflammatory potential, peripheral blood mononuclear cells will be isolated by Ficoll-Plaque density gradient centrifugation. CD14 and CD16 monocyte surface receptor expression will be determined after cells are stained, incubated and analyzed by flow cytometry.⁴⁷

Recruitment

Patients and their parent/guardian will be offered to participate in this study by pediatric rheumatologists at each participating hospital. These rheumatologists will be informed of the study via email from their department chair. Patients with any subtype of JIA are eligible for enrollment. After agreeing to participate in this study, the patient and his/her parent/guardian will be informed of all aspects of study by a research assistant, including goals and design, and formal informed written consent will be obtained. Patients will then be examined by their rheumatologist and primary care physician to assure they meet inclusion and exclusion criteria of the study. Recruitment will close when appropriate sample size is achieved. Recruitment within each subtype of JIA may not be equal due to varying frequencies (Figure 1).^{30,43}

Data Collection

Participants in both groups will be assessed by a pediatric rheumatologist before and after the 10-week intervention period to obtain clinical characteristics, health and disease activity and medication use. Research assistants will access EMR and enter data into REDcap, an online research data management tool that is both secure and meets HIPAA compliance standards.

A trained research assistant will administer and then score the PedsQL 4.0, CHAQ and 10-cm VAS-joint pain tests in interview format to patients at time of rheumatology clinic visits. Electrophysiologists will supervise the fitness testing and enter VO_{2peak} into EMR. Results of ESR and CRP blood tests will be reported by hospital labs and CD14 and CD16 monocyte surface receptor expression will be reported from outside facilities. Blood samples will be prepared promptly for plasma and immune cell isolation, and compatible samples will be stored at -80°C until analysis. All scores and testing results will be uploaded to EMR and added to REDcap by research assistants.

Data Analysis

Baseline characteristics will be collected and recorded as mean \pm SD, n (%) and values in groups I and II will be compared to determine whether there are any statistically significant differences in patient characteristics between the two groups prior to intervention (Table 1). The outcome measurements discussed above will assess the patient's response to exercise intervention. Pre-HIIT and post-HIIT QOL, functional status, pain, cardiorespiratory fitness, and inflammatory marker values will be reported as

mean \pm SD and a student T-test will be used to detect variation between groups I and II before and after intervention.^{40,47}

All plasma analyses were adapted from *Bartlett et al. (2018)* and will be completed before and after HIIT intervention.⁴⁷ CRP and ESR will be log-transformed and reported as mean \pm SD and a student T-test will be performed before and after intervention.⁴⁷

Further analysis will be performed to determine if there is variation between subtypes of JIA. The pathophysiology of sJIA is thought to be due to an autoinflammatory process while oligoarthritis and polyarthritis are thought to be due to an autoimmune process. Within groups I and II, participants will be sorted based on JIA subtype. PedsQL, CHAQ and 10-cm VAS-joint pain will be reported as mean \pm SD. Analysis as described above will be performed on each subgroup looking for subtype specific change in effect sizes after exercise intervention. A limitation of this analysis is a low recruitment number in some subtypes of JIA. Figure 1 shows the frequency of each and illustrates variation between subtypes. We estimate that this study will have sufficient power for a total sample size of 18 patients, 9 in each group. By increasing the sample size to 150 higher recruitment may allow for analyses within subtypes to reach statistical significance. All statistical testing will be conducted by a trained statistician and statistical significance will be accepted as $p \leq 0.05$.

Table 1: Baseline Characteristics

Variable	Group I (n = 75) Summary Statistic	Group II (n = 75) Summary Statistic	Comparison Between Groups: Statistical Test
Age (year)	Mean ± SD	Mean ± SD	T-test
Female	N (%)	N (%)	Chi-square test
Schooling			
Elementary	N (%)	N (%)	Chi-square test
Secondary	N (%)	N (%)	Chi-square test
JIA Subtype			
Systemic	N (%)	N (%)	Chi-square test
Oligoarticular	N (%)	N (%)	Chi-square test
Polyarticular RH+	N (%)	N (%)	Chi-square test
Polyarticular RH-	N (%)	N (%)	Chi-square test
Enthesitis-related	N (%)	N (%)	Chi-square test
Psoriatic	N (%)	N (%)	Chi-square test
Undifferentiated	N (%)	N (%)	Chi-square test
Diagnosis age (Y)	Mean ± SD	Mean ± SD	T-test
Active disease	N (%)	N (%)	Binomial test for a difference of proportions
Medications			
NSAID	N (%)	N (%)	Binomial test for a difference of proportions
DMARD	N (%)	N (%)	Binomial test for a difference of proportions
Biologic	N (%)	N (%)	Binomial test for a difference of proportions
Systemic Steroids	N (%)	N (%)	Binomial test for a difference of proportions
White Blood Cells			
Total Count	Mean ± SD	Mean ± SD	T-test
Neutrophils	Mean ± SD	Mean ± SD	T-test
Lymphocytes	Mean ± SD	Mean ± SD	T-test
Monocytes	Mean ± SD	Mean ± SD	T-test
Eosinophils	Mean ± SD	Mean ± SD	T-test

Timeline and Resources:

An ongoing study in children with juvenile fibromyalgia, another chronic pain syndrome in children, is also studying an exercise intervention. It is evaluating whether a combined cognitive behavioral therapy (CBT) and neuromuscular exercise training program is more effective in reducing disability compared to CBT or a graded aerobic exercise alone (3 groups). It is a multi-site RCT with an estimated enrollment of 420 participants. It has an actual start date of January 2, 2018 and estimated study completion date of January 2023.⁵¹

The current study is also a multi-site RCT with only two groups and a smaller sample size. Since the prevalence of JIA is greater than that of juvenile fibromyalgia, it is reasonable to estimate the current study will require three years for recruitment and trial completion.^{1,52} Following submission and approval by the IRB, recruitment will be ongoing over the first two years. Participants will be able schedule initial rheumatologist visits and undergo initial testing as soon as they have been evaluated for inclusion criteria by their primary care physician. Participants will not be required to complete 10-week intervention concurrently, however, the intervention will be standardized for each patient as described above.

Pediatric rheumatologists at each hospital location must be informed and agree to participate in study. Trained research assistants must be available for delivering PedsQL, CHAQ and 10-cm VAS-joint pain scales at rheumatology clinic appointments before and after 10-week intervention. Lab technicians must be available at participating hospital labs on day of clinic appointment. Exercise physiology lab access must be granted and

scheduled for each participant in group 1 to complete three supervised HIIT walking sessions. Exercise physiology labs must have access to treadmill, heart rate monitor, and parvo medical cart. Each participant in group 1 will be given a Polar H10 heart rate sensors. Group II participants will use lab heart rate monitors configured to their individual settings. An estimated three exercise physiologists will be needed at each hospital location to supervise an estimated five sessions, three days a week. This number was calculated assuming the 75 group II participants will be split equally between locations and completed their sessions on the same days and over the same 10-week time span. This number may vary by location based on recruitment time and size. Study investigators at each location will collect data from labs and afterwards complete analysis.

Institutional Review Board:

The study protocol involves interaction and intervention with human subjects and involves accessing private information. Therefore, it will be submitted for IRB review to the Boston University Medical Campus IRB under INSPIR II criteria due to the noninvasive study design. This study qualifies for expedited review because the design is of minimal risk and it requires collection of data through a noninvasive procedure and does not involve general anesthesia or sedation.

CONCLUSION

Discussion

The goal of this study is to determine the effect of a HIIT walking exercise program on children with JIA by analyzing QOL, functional ability, disease activity, cardiorespiratory fitness and various inflammatory markers. The cause and pathophysiology of this disease is not fully understood and these children often require multiple medications with serious side effects. Some do not reach clinical disease remission and are inadequately treated, indicating a need for alternative therapies. Exercise is regularly recommended to healthy children and leads to numerous physical and mental health benefits. It has been shown to be as beneficial in patients with other rheumatic disease as it is in healthy individuals. For this reason, it should be recommended to children with JIA and be incorporated into the standard of care.

Most studies of exercise therapy in JIA use small samples, most recruiting only around 50 participants. A strength of this study is its larger sample size of 150 patients. With a larger sample size, randomization will more likely be successful. This study also aims to analyze the effects of exercise within the subtypes of JIA, something that has not previously been done. Due to differences in the pathogenesis implies different treatment strategies may be needed, making this type of analysis valuable. This study will help determine which subtypes benefit from exercise therapy and, thus, in which it should be considered for treatment. Furthermore, the current study analyzes serum samples from each patient before and after intervention to look for changes in specific monocyte

phenotypes associated with inflammation. This is the first time these types of analyses will be done on patients with JIA.

This study design requires those in group 1, the exercise group, to come to a hospital 3 times per week for supervised HIIT walking. Each child's HR will be monitored throughout the entire 30-minute session and maintained in goal ranges. While this will allow us to analyze the maximum effects of this intervention, it is not generalizable. The design of this study, HIIT, was chosen to mimic the anaerobic nature of a child's day to day activity. However, outside of a controlled research setting, most children will not wear HR monitors and achieve the same exercise intensity, leading to smaller effects. Furthermore, the intervention may have limited generalizability due to a potential sampling bias as not all children with JIA will have parents who can afford to bring their child into the hospital three times a week for this therapy. If we do not see significant outcomes from the current study, it is unlikely children will benefit with less controlled, at home exercise regimes.

There are several limitations to this study, particularly related to assessment of QOL, functional ability and pain, all of which are measured by patient interview. A reporting bias is present. When patients give consent to be a part of this clinical trial, it is not possible to blind them to treatment due to design of the intervention. Quantitative results based on serum analysis are less likely to be influenced by this bias. Although participants will not be blinded, those collecting data and performing analyses will be blinded. This eliminates any interviewer bias, as well as bias during statistical analysis to skew results to better match the hypothesis.

Maintenance of results after the study completion may be a challenge, due to the intensive nature of the study design and close monitoring of each participant. The results may be difficult to maintain at home. This occurred in the study *Thomsen et al. (2018)* and is possible with the current study. The intensive study design may also lead to dropouts if a patient misses more than three sessions.

Another possible obstacle is the recruitment of enough participants in each subtype of JIA to allow for appropriately powered analysis. Some subtypes may not be analyzed due to low recruitment. This study only includes patients who have the ability to walk on a treadmill, therefore excluding potential participants with more severe disease.

Summary

Exercise can lead to a variety of benefits in children with JIA based on research reviewed here. Exercise has consistently been recommended to healthy children and adults and should not be limited in children with chronic disease. The notion that exercise will worsen disease state and activity is changing due to the results of the newly published research in this field. The studies reviewed included a variety of exercise interventions, including therapeutic exercises (aerobic, muscle strengthening, flexibility), water and land-based sports, weight-bearing activities and mind-body exercises, such as Pilates. All measured varying health outcomes including pain, physical function, quality of life, disease activity and ROM. Many showed significant positive results and none showed worsening disease after exercise, a common fear in those with arthritis.

The study proposed here will go one step further and look for a decrease in the number of inflammatory CD14⁺⁺CD16⁺ intermediate monocytes, which have been shown to be involved in the pathophysiology in RA. In a study of patients with RA, these were shown to significantly decrease following HIIT walking training. Due to similarities in the pathophysiology of the two diseases, a similar finding is possible in children with JIA. Regardless of the benefit of exercise on immune function, this study can highlight the importance of using an exercise intervention as part of JIA management. If no decrease is found in the number of inflammatory monocytes following intervention, it is highly likely we will see an increase in other outcomes based on previous research and the low sample size needed to detect difference in this study.

This study also aims to analyze the difference in outcomes within the subtypes of JIA. The proposed pathophysiology of subtypes varies and may lead to different responses. Oligoarticular and polyarticular JIA are considered autoimmune diseases, while systemic JIA is considered an autoinflammatory disease and involves systemic features along with joint disease. With this information, clinicians will have a better understanding of when to recommend exercise therapy and who is most likely to benefit based on the child's disease type.

Clinical and/or Public Health Significance

Juvenile idiopathic arthritis is the most common chronic rheumatic disease in children and a significant cause of short- and long-term disability. It encompasses all forms of arthritis that begin before the age of 16 and persist for more than 6 weeks. Studies have

shown between 40-60% of patients achieve clinical remission, but many carry the disease with them into adulthood. The disease burden can be tremendous on a child's physical, mental and social health and the effects extend to a child's family. Prediction of long term outcome is imperfect, however indicators of poor outcome include greater severity or extension of arthritis at onset, symmetrical disease, early wrist or hip involvement, presence of RF, persistent active disease and early radiographic changes.¹ It is crucial to diagnose and treat the disease promptly to prevent its progression.

The management of JIA includes a combination of medications with multiple side effects. Physical, occupational and psychological treatments are often used. The goal of therapy is to control the disease by allowing the child to resume normal activities of daily living and prevent any long-term disability that may arise. The use of structured exercise therapy early on in the disease will potentially decrease the need for added medications, many of which have side effects with long lasting effects. It may also prolong remission and decrease severity of disease flares which can lead to permanent joint damage and joint surgeries or replacement later on in life.

This study has the potential to show exercise should not be avoided, but encouraged in JIA. The results may indicate that exercise not only improves quality of life but also can alter the pathophysiology of the disease. Parents who may shy away from activity with the thought that it will worsen their child's disease may begin to encourage it. The results may also be used to help tailor a management plan specific to each subtype of disease. There is a clear need for further treatment beyond typical pharmacological management and exercise is one of many ways to meet this demand.

With further data on how exercise therapy modifies the disease, more structured exercise programs may become a mainstay of treatment. They could become incorporated into a multidisciplinary care plan for children with JIA earlier in the disease course to increase remission rates, reduce the number and severity of disease flares in addition to the physical and psychosocial benefits exercise provides.

LIST OF JOURNAL ABBREVIATIONS

Ambul Pediatr	Ambulatory Pediatrics: The Official Journal of the Ambulatory Pediatric Association
Ann Ig Med Prev E Comunita	Annali di igiene : medicina preventiva e di comunità
Arch Phys Med Rehabil	Archives of Physical Medicine and Rehabilitation
Arthritis Care Res	Arthritis Care and Research
Arthritis Res Ther	Arthritis Research and Therapy
Arthritis Rheum	Arthritis and Rheumatology
Autoimmun Rev	Autoimmunity Reviews
BMJ	British Medical Journal
Clin Exp Rheumatol	Clinical and Experimental Rheumatology
Cochrane Database Syst Rev	The Cochrane Database of Systematic Reviews
Curr Opin Rheumatol	Current Opinion in Rheumatology
Eur J Appl Physiol	European Journal of Applied Physiology
Exerc Immunol Rev	Exercise Immunology Review
Exp Ther Med	Experimental and Therapeutic Medicine
Health Educ Behav	Health Education and Behavior: The Official Publication of the Society for Public Health Education

J Rehabil Med	Journal of Rehabilitation Medicine
J Rheumatol	Journal of Rheumatology
JAMA	The Journal of the American Medical Association
Lancet	The Lancet
Lancet Child Adolesc Health	The Lancet. Child and Adolescent Health
Med Sci Sports Exerc	Medicine and Science in Sports and Exercise
N Engl J Med	New England Journal of Medicine
Orthop Clin North Am	Orthopedic Clinics of North America
Pain	Pain
Pediatr Rheumatol Online J	Pediatric Rheumatology Online Journal
Rheumatol Oxf Engl	Rheumatology (Oxford)
Scand J Rheumatol	Scandinavian Journal of Rheumatology
Sports Med Auckl	Sports Medicine (Auckland)

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CURRICULUM VITAE

