ABCS HEALTH SCIENCES

ORIGINAL ARTICLE

OPEN ACCESS

Effects of low, moderate, and high-intensity aquatic exercise on joint edema in induced rat knee arthritis

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ABSTRACT

Introduction: Arthritis has prompted interest in using physical exercise as therapy. This study assesses the effects of low-, moderate-, and high-intensity exercise on induced arthritis in male Wistar rats. **Objective:** To evaluate the impact of low-, moderate-, and high-intensity physical exercise on induced arthritis. **Methods:** Twenty 60-day-old rats were divided into 5 groups: Control Group Arthritis (GCA), Control Group Placebo (GCP), Group Low Physical Activity (GL), Group Moderate Physical Activity (GM), and Group Intense Physical Activity (GI). The physical activity groups received intra-articular injections of Zymosan in the right knee, followed by aquatic activity, swimming with a dorsal load for 30 minutes, 4 times weekly, for five weeks. Exercise intensity varied: GL 1%, GM 5%, GI 15% of body weight. At the end of the 5th week euthanasia was performed, and soleus muscles were histologically. Group comparisons: one-way ANOVA with Tukey or Kruskal-Wallis with Dunn's post-test, contingent on data homogeneity Levene test. Weight changes: Student's T-test or ANOVA for repeated measurements, with Bonferroni's post-test for inter-week and first and last-week comparisons within each group. **Results:** There were no significant differences in inflammatory edema before or after exercise in joint diameter analysis. GI exhibited decreased inflammatory edema in the 3rd week post-activity. GM showed a substantial decrease in the 4th week compared to GL and GI. Post-intervention inflammation did not differ significantly among groups. **Conclusion:** Varying exercise intensities did not harm any group-induced arthritis in rats.

Keywords: arthritis; exercise; inflammation.

How to cite this article: Mioto et al. Effects of low, moderate, and high-intensity aquatic exercise on joint edema in induced rat knee arthritis. ABCS Health Sci. 2025;50:e025206 https://doi.org/10.7322/abcshs.2023057.2317

Received: Jun 14, 2023
Revised: Feb 06, 2024
Approved: Feb 22, 2024

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Declaration of conflicts: nothing to declare

INTRODUCTION

Arthritis is a broad term to describe a group of inflammatory joint disorders, each with unique characteristics and causes. It is not a single disease but rather a category that includes more than 100 different conditions. Osteoarthritis (OA), the predominant

subtype, entails progressive articular cartilage degeneration, notably affecting weight-bearing joints[1]. Conversely, rheumatoid arthritis (RA) is an autoimmune process that targets the synovial membrane, thereby initiating inflammatory cascades and joint pathology[2].

There are numerous functional limitations resulting from arthritis, intensifying the need for an early diagnosis and immediate onset of treatment to control the disease and prevent functional disability and irreversible joint damage[3].

Findings indicate that patients with arthritis can obtain beneficial results when performing physical exercises[4], such as pain reduction, and improvement of joint function, thus delaying functional disabilities[5]. It is believed that strength exercises in which the load on the joint is larger are better for cartilage growth affected by arthritis[1,2]. However, in the guidelines of the Osteoarthritis Research Society International, there are no significant differences between protocols of force, soil, or aquatic exercises for function or pain in patients[6-8].

The protocols of aquatic exercises observed in studies usually do not use loads, and when they do this, it is low being around 5 to 7% of the corporal weight like intensity[9-11]. Notably, certain aquatic exercise routines incorporate water-jump protocols, introducing a ground impact on the body[12].

However, it is crucial to emphasize that the specific study under consideration intentionally avoids this impact, presenting a unique opportunity. By sidestepping ground impact, this protocol opens avenues for elevating the load applied to muscles during aquatic exercises. This intentional omission of ground impact allows for increased muscle contraction without inducing excessive strain or eliciting responses from the ground, making it particularly advantageous for individuals with arthritis in their limbs[13,14].

Therefore, the objective of this study was to evaluate the alterations that the different intensities of physical exercise can cause in the articular inflammation and the soleus muscle of rats submitted to the induction to arthritis.

METHODS

Experimental design

The animals were subdivided into five groups (control of arthritis, sedentary control, low-intensity exercise, moderate-intensity exercise, and high-intensity exercise) for the application of the respective training protocols. At the end of the respective protocols, the animals were euthanized to collect the material to be analyzed.

Animals

Twenty male Wistar rats, 60 days old, kept in collective plastic cages, were obtained from the Central Unity of Presidente Prudente. These animals were kept in groups of three to five animals per cage, with an average temperature of 20±1°C and a light/dark cycle of 12 hours, with free access to water and feed.

This work followed the principles of animal research and was approved by the animal ethics committee (Protocol number CEUA – 2358).

Arthritis Induction

For the induction of arthritis, initially, the rats were anesthetized with intraperitoneal ketamine and dosed according to animal weight (1 to 1.5 microliters of ketamine per gram of weight). After anesthesia, the animal was submitted to an intra-articular injection of 0.05 ml/100g Zymosam (1mg/50µL) in the right knee[15]. The animals in the control group Arthritis (GCA) received saline solution in the right knee instead of Zymosan, and the animals in the placebo control group (GCP) were submitted only to the stress of the needle.

Aquatic Training Protocol

To evaluate the effect of physical activity the animals were submitted to aquatic activity 48 hours after the arthritis induction. The animals were initially introduced to aquatic activity in a communal tank with a depth of 15 cm for 10 minutes, aiming to familiarize them with staying on the water's surface. After waiting 15 minutes, the animals were subjected to aquatic activity in a collective tank 40 cm deep for 30 minutes, where the overload was attached to the back, through vests. Exercise intensity for low (GL), moderate (GM), and intense (GI) physical activity groups was assessed by adding overload in the rats of each group[15]. In the GL group, 1% overload was added, in the GM group an overload of 5% of the mouse weight was added and for the GI group 15% of the mouse weight was added and in the arthritis control group no overload was added[16]. The training protocol was repeated 4 times a week for 5 weeks.

To quantify the inflammatory edema, a non-digital caliper was used to measure the lateral mean diameter of the articular (DA) each day, before and after physical activity. Data was presented as the difference between the means of the DA values measured daily before and after the aquatic exercise.

Euthanasia and muscle sample removal

The animals were submitted to euthanasia at the end of the fifth week using overdosage of the combination of ketamine hydrochloride and xylazine hydrochloride intraperitoneally, following the ethical principles in animal research. The soleus muscle was removed and dissected with caution to preserve its integrity.

For the histological analysis, the Unfixed Tissue Freezing Method was used[17]. In this method, a beaker containing 30 to 50 ml of N-hexane was used. Using a support the beaker was immersed in nitrogen, and, using a glass stick, the N-Hexane was stirred until it reached the pasty state, which occurs from -70 to -80 °C.

When it reached this state, the samples were immersed in 20 to 30 seconds. The samples were then transferred to the cryostat chamber (Microm, HM 505 E) (-20øC) and held for 20 to 30 minutes to establish thermal equilibrium. After this time, the samples were placed in identified plastic containers and stored at -75 °C in an ultra-low temperature freezer (CL580-80, COLDLAB) until the preparation of the histological slides.

The histological slides were prepared using a cryostat microtome at a temperature of -20 °C, in which cross-sections of the muscle fibers were cross-sectioned, with a thickness of 5 µm. Then the slides were stained and subsequently stained by the Hematoxylin and Eosin (HE) method[16]. The slides were analyzed using the light microscope (Nikon Eclipse, 50i), with photographic camera coupling (Infinity 1).

Histological analysis

The histological analysis was performed qualitatively on the blades stained by the HE method, using the software NIS-Elements D3. The qualitative analysis was based on the morphology of the muscle fibers, which were evaluated for fiber characteristics: size (normal, atrophic, hypertrophic), shape (polygonal, rounded, and angular), and connective tissue (endomysium and perimysium)[17].

Data analysis

The descriptive analysis was expressed as mean and standard deviation or median and interquartile range depending on the normality of the data tested by the Shapiro-Wilk test. The comparison between the groups was performed by the one-way ANOVA test with the Tukey post-test or Kruskal-Wallis test with Dunn's post-test, depending on the homogeneity of the data verified by the Levene test. For the comparison between the initial and decisive moments of the weight, the Student's t-test was used for dependent samples and the ANOVA test for repeated measurements with Bonferroni's post-test to compare joint edema between the weeks within each group. For all the tests, the SPSS 22.0 statistical program was used and the significance level adopted was 95% ($p<0.05$).

RESULTS

Table 1 shows the body weight data of the animals, where no significant difference was observed between the four groups. However, at the end of the experiment, the animals of the GCP, GCA, GL, and groups showed an increase in body weight (Table 1).

In the joint diameter analysis, it can be observed that there was no difference in inflammatory edema between groups and intergroups during the five weeks before physical exercise. After physical exercise, the GL, GM, and GI groups also did not show differences between the five weeks in both group and intragroup analyses (Table 2).

In the difference between the deltas of joint diameter gain related to the groups that performed physical activity, we noticed that in the third week after the activity, the GI group presented a significant decrease of the inflammatory edema (-0.4 ± 0.1 mm) compared to the GL groups (-0.09 ± 0.1 mm) and GM (-0.08 ± 0.1 mm). In the fourth week, there was also a significant difference between the groups, where GM (-0.5 ± 0.4) had a significant decrease in inflammatory edema compared to GL (0.1 ± 0.1 mm) and GI (- 0.07 ± 0.1 mm) (Figure 1).

Regarding inflammation, there was no significant difference between the groups after the intervention (Table 3). The presence of synovial fluid did not show any difference between the groups after the intervention (Figure 2).

Observing Figure 3 in the histological analysis of the soleus muscle, which had little presence of muscle inflammation in the high GI intensity group, this inflammation was lower in the GM, GL, and GCA groups and did not exist in the control group. When observed the presence of polymorphic, angular, or rounded cells appeared more frequently in the GI and GM groups. In the GCA group, these had higher frequency compared to the GL group, being almost absent in the GCP. The atrophic muscle fibers were found in the GCA group in greater quantity than in the other groups. Regarding the perimysium and muscle endomysis, this was unchanged in all the groups observed (Figure 3).

DISCUSSION

The main objectives of this study were to evaluate the alterations that the different intensities of physical exercise can cause in the joint inflammation of rats submitted to the induction of arthritis with Zymozan in the knee.

It was observed that the group of low-intensity GL, and the groups that did not exercise GCA and GCP, gained more weight compared to the medium-intensity group GM. Regarding joint

Table 1: Initial and Final Body Weights Among Experimental Groups

	GCP (n=4)	GCA (n=4)	GL (n=4)	GM (n=4)	GI (n=4)	p-value[a]
Initial (g)	254.5±26.9	248.5±20.1	266.8±28.0	252.5±19.4	267.3±19.6	0.700
Final (g)	293.1±28.3	291.8±33.3	291.0±20.3	276.5±16.7	301.0±31.9	0.708
p-value[b]	0.002*	0.014*	0.019*	0.216	0.058	

Data expressed as mean ± standard deviation. GCP: placebo control group; GCA: arthritis control group; GL: low physical activity group; GM: moderate physical activity group; GI: intense physical activity group. a: one way ANOVA with Tukey post test; b: student t test; * p<0.05.

Table 2: Joint diameter of inflammatory edema after induced arthritis before and after physical exercise

Week (initial)	GCP (n=4)	GCA (n=4)	GL (n=4)	GM (n=4)	GI (n=4)	p-value[a]
1st	9.0±0.5	9.1±0.3	9.1±0.2	9.5±0.2	9.2±0.3	0.253
2nd	9.0±0.2	9.2±0.2	9.3±0.3	9.2±0.2	9.4±0.4	0.436
3rd	9.1±0.4	9.3±0.2	9.1±0.2	9.2±0.3	9.5±0.3	0.384
4th	9.1±0.5	8.9±0.3	9.0±0.2	9.3±0.3	9.2±0.1	0.320
5th	9.0±0.4	9.1±0.2	8.9±0.3	9.2±0.3	9.3±0.2	0.353
p-value[b]	0.658	0.185	0.246	0.202	0.224	
Mean average (initial)	9.0±0.4	9.1±0.2	9.1±0.1	9.3±0.3	9.3±0.2	0.377
Week (final)	GCP (n=4)	GCA (n=4)	GL (n=4)	GM (n=4)	GI (n=4)	p-value[a]
1st	NA	NA	8.8(8.6-9.1)	9.1(8.6-9.1)	8.7(7.5-9.2)	0.456
2nd	NA	NA	8.8±0.4	9.2±0.4	8.9±0.2	0.414
3rd	NA	NA	9.0±0.1	9.1±0.2	9.1±0.2	0.792
4th	NA	NA	9.1±0.2	8.9±0.6	9.2±0.1	0.516
5th	NA	NA	8.7(8.5-9.0)	9.4(8.9-9.6)	9.2(9.0-9.5)	0.063
p-value[b]	NA	NA	0.320	0.390	0.200	
Mean Average (final)	NA	NA	8.9±0.1	9.1±0.3	9.0±0.3	0.654

Data expressed as mean±standard deviation and median and interquartile range (25-75%) of joint diameter (mm^2). GCP: placebo control group; GAC: arthritis control group; GL: low physical exercise group; GM: moderate physical exercise group; GI: heavy physical exercise group; NA: not applicable. a: One-way ANOVA with Tukey's post-test; b: ANOVA for repeated measures with Bonferroni's post-test; *p<0.05

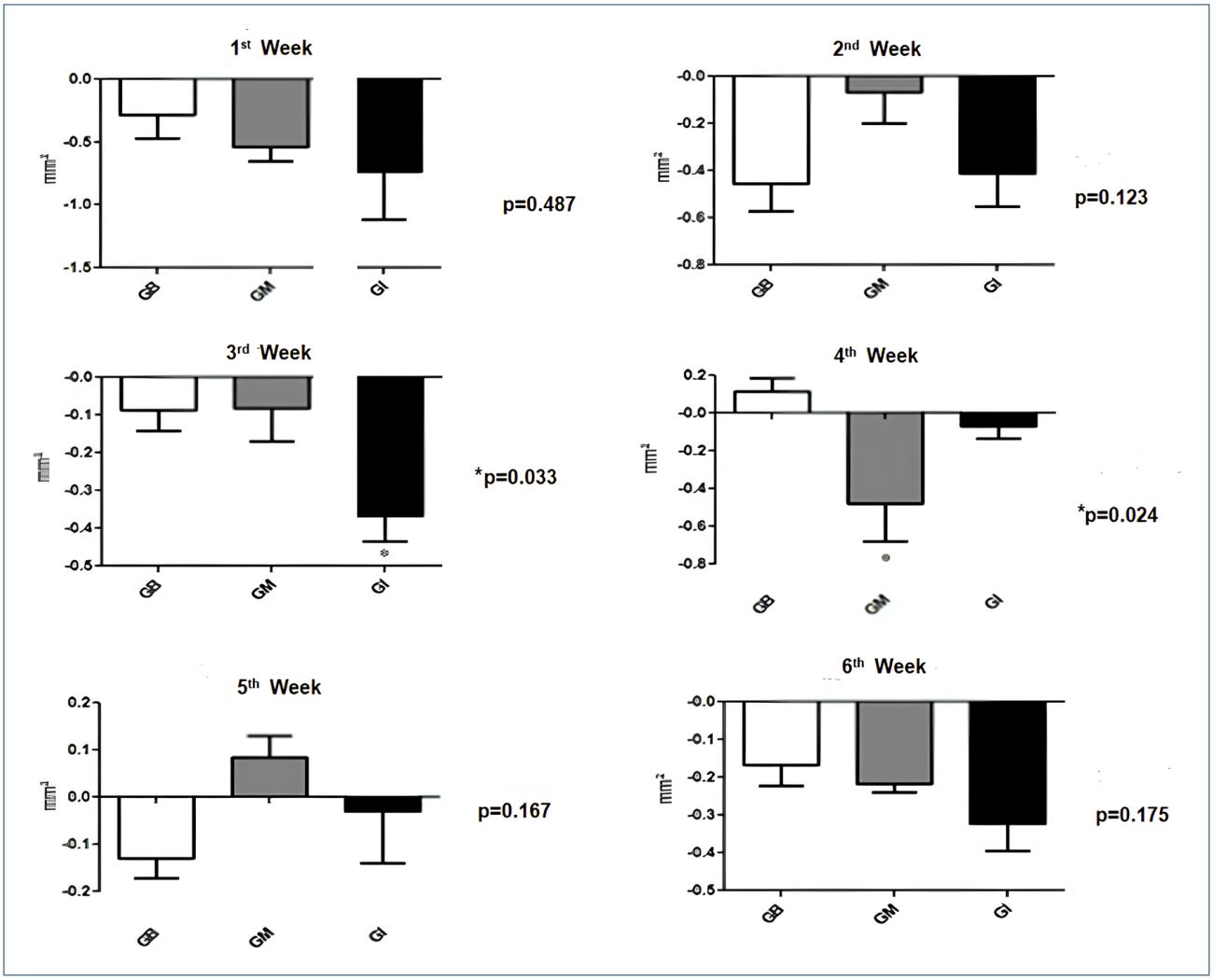

Figure 1: Delta's gain (final-initial) of the joint diameter of the inflammatory edema of the groups that performed physical exercise. There was a significant difference at week 3 where the high-intensity group GI (p=0.033) showed a reduction in inflammatory edema when compared to the groups GL and GM, and in the 4th week, the group GM (p=0.024) showed a decrease in inflammatory edema when compared to the groups GL and GI. ANOVA for repeated measures with Bonferroni's post-test; *p<0.05

Table 3: Inflammatory Cell Distribution by Group

	GCP (n=4)	GCA (n=4)	GL (n=4)	GM (n=4)	GI (n=4)	p-value[a]
Segmented (mm³)	20.5±3.3	15.0±10.5	14.8±11.2	20.8±8.4	23.0±12.2	0.801
Bastonets (mm³)	1.5 (0.3-2.0)	1.0 (0.3-17.5)	30 (0.8-6.8)	0.5 (0.0-6.3)	1.5 (0.3-5.0)	0.804
Lymphocytes (mm³)	76.3±3.4	76.5±5.1	79.3±7.9	72.5±14.1	70.8±11.9	0.792
Monocytes (mm³)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.0 (0.0-1.5)	2.0 (1.3-5.8)	1.0 (1.0-4.8)	0.087
Basophils (mm³)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-1.5)	0.0 (0.0-2.3)	0.530
Eosinophils (mm³)	1.0 (1.0-1.0)	1.0 (1.0-1.8)	1.0 (1.0-4.0)	0.5 (0.0-1.0)	1.0 (1.0-1.0)	0.130
Count (mm³)	0.0 (0.0-0.0)	2.0 (0.0-4.0)	1.0 (0.0-2.0)	0.0 (0.0-1.5)	0.0 (0.0-0.8)	0.410

Data expressed as mean±standard deviation and median and interquartile range (25-75%). GCP: placebo control group; GCA: arthritis control group; GL: low physical exercise group; GM: moderate physical exercise group; GI: intense physical exercise group; mm³: cubic millimeter to Kruskal Wallis, *p<0.05

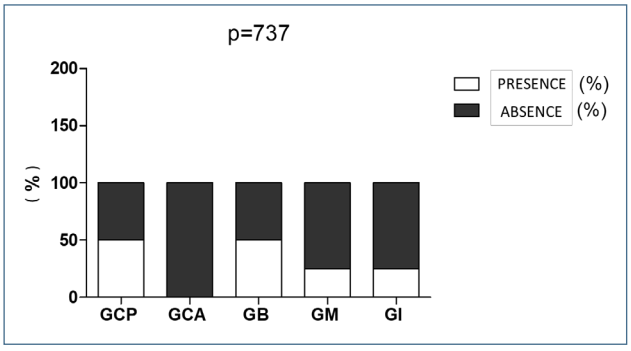

Figure 2: Presence of synovial fluid after the intervention. ANOVA for repeated measures with Bonferroni's post-test; *p<0.05

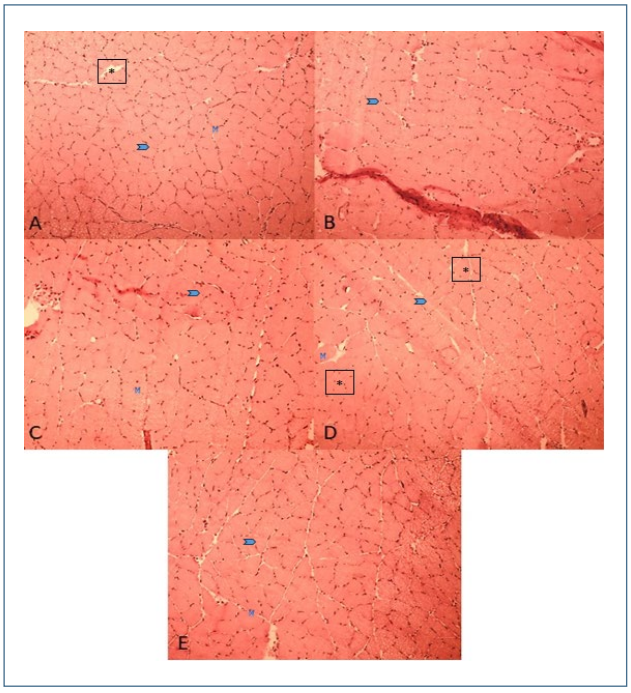

Figure 3: Hematoxylin and eosin histological images of the groups studied. A= high-intensity group (Gi), B= moderate intensity group (GM), C=low intensity group (GL), D=arthritis control group (GCA), and E=placebo control group (GCP). Magnification of 100x. Nuclei (arrows), Endomysium (asterisk), Myocyte (M)

diameter, the different intensities of physical exercise influenced the joint diameter gain from the third and fourth week after physical exercise.

In the third week, the GI group presented a significant decrease in inflammatory edema, when compared to the GL and GM groups. However, in the fourth week, the GM group had a significant decrease in inflammatory edema when compared to the GL and GI groups. As to the presence and absence of synovial fluid, there was no difference in any group, however, there was no synovial fluid present in the GCA group.

The treatment of arthritis aims at the prevention and control of joint injury and, therefore, the prevention of movement loss, analgesia, and the improvement of patients' quality of life. Thus, physical exercise is seen as adequate to bring benefits to patients suffering from arthritis, reduce pain, or delay functional disability through maintenance of joint function[16]. However, the intensity of physical exercise is of utmost importance to get satisfactory results.

Joint edema, commonly associated with arthritis, results from the accumulation of excess fluid in affected joints, leading to swelling and discomfort. For individuals grappling with arthritis-related joint edema, swimming emerges as a particularly advantageous low-impact exercise[17]. Swimming brings benefits, such as the low cost of equipment and no need for animal selection since all have an innate ability to swim. Disadvantages in this method, such as difficulty in determining intensity, temperature control, and stress promoted by contact with water are also relevant factors to consider during an experiment with swimming[16].

Until a long time ago, many researchers had some fear of using swimming in their laboratories, because they felt that there was a difficulty in determining the intensity of the effort produced. However, Gobatto et al.[16] suggested a protocol that establishes a criterion for determining the intensity of effort in rats during swimming, consisting of collection of blood lactate from the distal end of the animal's tail during the effort with progressive loads, where overloads of up to 5% of the weight of the animal are within the aerobic threshold.

A study by Prestes et al.[18] verified the effects of five consecutive swimming sessions on male Wistar rats. The authors performed a progressive increase in the load causing the intensity to increase from mild to moderate. To this end, additional loads of 5% of the animal's body weight were gradually added to their dorsal regions.

These researchers concluded that exercise-exercising animals had a significant reduction in serum TNF-α concentration[18]. This fact is relevant since this cytokine is considered a pro-inflammatory factor characteristic of arthritis being pointed as responsible for maintaining the active inflammatory process of this disease.

Another study by Prestes et al.[19] evaluated male Wistar rats at two months of age. These animals were divided into three groups: the sedentary control group (C), the EXL acute physical exercise group (which performed a single exercise session in light intensity to exhaustion), and the EXM acute physical exercise group (which performed a single session of exercise in moderate intensity until exhaustion). Considering that high-intensity exercises may cause an increase in some proinflammatory cytokines and that moderate-intensity training can lower them, the type of physical exercise, intensity, and duration should be well planned[20].

Another study investigated the effects of swimming and low-power laser therapy on arthritis in Sprague-Dawley rats. Tests were made to measure Interleukin-6 concentration, knee joint space, and hind paw thickness after. The results showed that both swimming and low-power laser therapy had positive effects on arthritis. These interventions led to a decrease in Interleukin-6 concentration and hind paw thickness, and swimming additionally increased the space of the knee joint. Overall, the study suggested that swimming and low-power laser therapy may be beneficial in managing arthritis symptoms in rats[21,22].

Finally, the purpose of this study was to analyze the different intensities of physical exercise in induced arthritis in rats and to demonstrate the intensity of changes (good or bad). Although the study did not find statistically significant results, it can be concluded that physical exercise did not negatively influence any groups.

Conclusion

In this way, despite the absence of statistically significant results, the study on the impact of different intensities of physical exercise on induced arthritis in rats revealed that exercise did not have a negative influence on any group.

REFERENCES

1. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. Lancet. 1998;352(9134):1137-40. https://doi.org/10.1016/S0140-6736(97)12004-9
2. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996;14(1):397-440. https://doi.org/10.1146/annurev.immunol.14.1.397
3. Bértolo MB, Brenol CV, Schainberg CG, Neubarth F, Lima FAC, Laurindo IM, et al. Atualização do consenso brasileiro para o diagnóstico e tratamento da artrite reumatoide. Rev Bras Reumatol. 2007;47(3):151-9.
4. Vlieland TPMV. Rehabilitation of people with rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2003;17(5):847-61. https://doi.org/10.1016/S1521-6942(03)00043-3
5. Shih M, Hootman JM, Kruger J, Helmick CG. Physical activity in men and women with arthritis. National Health Interview Survey, 2002. Am J Prev Med. 2006;30(5):385-93. https://doi.org/10.1016/j.amepre.2005.12.005
6. Abell JI, Hootmann JM, Zack MM, Moriarty D, Helmick CG. Physical activity and health-related quality of life among people with arthritis. J Epidemiol Community Health. 2005;59(5):380-5. https://doi.org/10.1136/jech.2004.028068
7. Benhamou MAM. Reconditioning in patients with rheumatoid arthritis. Ann Readapt Med Phys. 2007;50(6):382-5. https://doi.org/10.1016/j.annrmp.2007.03.023
8. Iversen MD. Physical therapy for older adults with arthritis: what is recommended? Int J Clin Rheumatol. 2010;5(1):37-51. https://doi.org/10.2217/IJR.09.67
9. Hernández-Hernández MV, Díaz-González F. Role of physical activity in the management and assessment of rheumatoid arthritis patients. Rheumatol Clin. 2017;13(4):214-20. https://doi.org/10.1016/j.reuma.2016.04.003
10. Leandro C, Nascimento ED, Manhães-de-Castro R, Duarte JA, de-Castro CMMB. Exercício físico e sistema imunológico: mecanismos e integrações. Rev Port Cienc Desp. 2002;2(5):80-90.
11. Antunes HK, Santos RF, Cassilhas R, Santos RVT, Bueno OFA, Mello MT. Exercício físico e função cognitiva: uma revisão. Rev Bras Med Esporte. 2006;12(2):108-14.
12. Milares LP, Assis L, Siqueira A, Claudino V, Domingos H, Almeida T, et al. Effectiveness of an aquatic exercise program and low-level laser therapy on articular cartilage in an experimental model of osteoarthritis in rats. Connect Tissue Res. 2016;57(5):398-407. https://doi.org/10.1080/03008207.2016.1193174
13. Rossato JS. Papel do sistema nervoso simpático sobre o metabolismo e na resposta imunológica de monócitos circulantes de ratos durante o exercício agudo de intensidade moderada (natação). [master´s thesis]. [Porto Alegre]: Universidade Federal do Rio Grande do Sul; 2009.
14. Marques-Neto JF, Gonçalves ET, Langen LFOB, Cunha MFL, Radominski S, Oliveira SM. Multicentric study of the prevalence of adult rheumatoid arthritis in Brazilian population samples. Rev Bras Reumatol. 1993;33(5):169-73.
15. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI Guidelines for the Non-Surgical Management of Knee Osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-88. https://doi.org/10.1016/j.joca.2014.01.003

16. Gobatto CA, Mello MA, Sibuya CY, Azevedo JR, Santos LA, Kokubun E. Maximal lactate steady state in rats submitted to swimming exercise. Comp Biochem Physiol A Mol Integr Physiol. 2001;130(1):21-7. https://doi.org/10.1016/s1095-6433(01)00362-2

17. Saremi A, Khajavi D, Parastesh M, Tahmasebi S, Ramezani N. Swimming Exercise Improves Rheumatoid Arthritis in Rat (An Animal Study). Iranian J Orthopaedic Surg. 2021;19(2):68-75.

18. Gomes RP. Atividade física no tratamento de artrite induzida por adjuvante de Freund: efeitos na nocicepção, edema e migração celular. [master´s thesis]. [Florianópolis]: Universidade do Estado de Santa Catarina; 2008.

19. Prestes J, Frollini AB, Dias R, Guereschi MG, Ferreira CKDO, Donatto FF, et al. Influência do exercício físico em diferentes intensidades sobre o número de leucócitos, linfócitos e citocinas circulantes. Rev Bras Med. 2008;65(3):56-60.

20. Prestes J, Ferreira CKO, Frollini AB, Dias R, Donatto FF, Guereschi MG, et al. Influência do exercício físico agudo realizado até a exaustão sobre o número de leucócitos e citocinas circulantes. Fit Perform J. 2007;6(1):32-7. https://doi.org/10.3900/fpj.6.1.32.p

21. Cooney JK, Law RJ, Matschke V, Lemmey AB, Moore JP, Ahmad Y, et al. Benefits of exercise in rheumatoid arthritis. J Aging Res. 2011;6(8):16-40. https://doi.org/10.4061/2011/681640

22. Park MH, Rho MH, Lee HO, Koo BO, Hwang SM. The effects of swimming and low power laser on the concentration of interleukin-6 for rheumatoid arthritic rats. Phys Ther Korea. 2008;15(1):69-76.