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Nociceptive and Inflammatory Evaluation of Water Jumping in Wistar Rats with a Rheumatoid Arthritis Model

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SUMMARY

Purpose. The aim of this study was to evaluate whether resistance exercise in an aquatic environment promotes the return of peripheral functionality and contributes to reducing leukocyte migration in the knee joint of rats with a model of rheumatoid arthritis (RA).

Methods. Forty male rats were divided into four groups: SHAM – Control; RA – Injury Group; SHAMEX – Exercise Group; and RAEX – Injury Group treated with resistance exercise. RA was induced by immunization at the base of the tail and intra-articular injection of complete Freund's adjuvant (CFA) into the tibiofemoral joint of the right knee. The exercise protocol was conducted three times a week in a water tank with an overload of 50% of the animal's weight for 22 days, gradually increasing the number of sets and repetitions every three sessions. The right hind limbs were evaluated for nociception, edema, peripheral function, and synovial infiltrate to analyze the repercussions following the injury in eight assessments.

Results. The induction of joint arthritis impaired joint function, but the RAEX group exhibited reduced pain, improved functional capacity, and a decreased presence of inflammatory cells in the synovial fluid.

Conclusions. Resistance exercise in an aquatic environment promoted functional improvement of the knee joint in Wistar rats with an RA model.

KEY WORDS

Autoimmune diseases;. rheumatoid arthritis; neurogenic inflammation; physical exercise; hydrotherapy.

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune inflammatory disease which is characterized by progressive destruction of joints and extra-articular structures, which gives it the property of systemic injury (1). RA commonly presents different levels of prognosis due to its variety of manifestations (2). The diagnosis is based on several clinical features that are present bilaterally and symmetrically, such as pain, morning joint stiffness, joint erosions, bone deviations (gale or hammer toes), and joint edema (3).

During disease clinical manifestations, the inflammatory phenomena occurring in the joint capsule are initiated by various physiological mechanisms, regulated by a network of chemokines and cytokines that result from the immune system activation. Consequently, in turn induce an infiltration of leukocytes infiltrate into the joint compartment. The

main infiltrating cells include monocytes, innate lymphoid cells, dendritic cells, T and B cells, and plasma cells (4). These factors are responsible for exacerbated inflammation and promoting the migration of synovial cells to the intra-articular region (5).

Disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, and glucocorticoids are used for the RA to control symptoms and slow down disease progression. However, pharmacological therapy alone is insufficient to control pain and restore biomechanical activity and function (6). Thus, drug therapy should be accompanied by lifestyle changes for individuals with RA, including physical rehabilitation, which should involve regular and supervised exercise, to address changes in joint structures, as well as the individual's ability to support weight and respond to physical stress (7, 8). Resistance exercise aims to improve strength, power, and endurance based on the recommended modality, volume, intensity, rest time, and frequency (9, 10). Aquatic rehabilitation is an alternative treatment method for individuals who have functional limitations due to rheumatic diseases (11). The thermal and physical properties of water, such as buoyancy, hydrostatic pressure, viscosity, and turbulence, allow for improved fluidity of joint movement. This facilitates the maintenance of synovial fluid homeostasis, reduces edema and increases the nociceptive threshold (12).

Viña *et al.* (13) state that the physical condition promoted by RA and osteoarthritis in the elderly would imply a contraindication of resistance exercises. There is also evidence that low-impact exercise would be the most suitable and safest option for individuals with chronic comorbidities such as RA (14). Therefore, it is essential to conduct studies to assess the impact of jump in aquatic environments on the treatment of RA, focusing on improving functionality, of reducing inflammation and pain, and promoting structural repair. This will ultimately contribute to a favorable clinical prognosis.

Thus, the results of this study are expected to contribute to the development of safe and efficient treatment protocols that optimize the duration of physical therapy rehabilitation. The study aimed to evaluate if the resisted jumping exercise in an aquatic environment promotes the restoration of peripheral functionality and contributes to reducing leukocyte migration in the rat knee joint subjected to a model of rheumatoid arthritis.

METHODS

This study was characterized as experimental and was carried out at Universidade Estadual do Oeste do Paraná (Unioeste). The procedures began after receiving approval by the Ethics Committee on Animal Use of Unioeste under protocol No. 19-19 – date of approval: July 25, 2019.

Animals

The experiment used 40 male Wistar rats weighing 347.31 ± 25.1 grams, obtained from the Central Animal Facility of Unioeste. During the experiment, the animals were housed in plastic cages and subjected to a 12-hour light-dark cycle. The temperature was maintained at 21 ± 1 °C, and they were provided with water and feed ad libitum, the standard balanced feed was used (Biotec®, São Paulo, Brazil), since there are risks of low-intensity inflammatory processes when using high-fat diets (15). The animals were randomly distributed into four groups, with ten rats in each group:

1. SHAM (Control Group): no intervention, only simulating the lesion with saline.
2. RA (Injury Group): induction of RA model.
3. SHAMEX (Exercise Group): aquatic jumping exercise and simulating the lesion.
4. RAEX (Injury + Exercise Group): induction of RA and subjected to a water jumping protocol.

RA Induction Injury Protocol

For RA and RAEX, a method previously described (16) was used, which involves the use of Freund's Complete Adjuvant (CFA), *Mycobacterium butyricum* (0.5 mg/ml, Difco®), isotonic sodium chloride solution (0.9%, Aster®), and iodized alcohol (1%, Rialcool®). The animals were immunized by intradermal injection at the base of the tail after shaving the area and sterilizing the injection site with 1% iodized alcohol. Subsequently, a 1 mL syringe and a 13 × 4.5 mm needle were used and inserted approximately 1 centimeter into the subcutaneous region at the base of the tail. The RA and RAEX groups received pre-sensitization with 50 µl (microliters) of CFA (0.5 mg/ml, *Mycobacterium butyricum*). In the SHAM and SHAMEX groups, a saline solution (sodium chloride 0.9%) was injected in the same volume using a 26-gauge needle, which does not generate significant functional changes in the animals, but simulates the stress of injecting the RA groups (17).

Seven days after hair has been removed from the right knee region. Asepsis was carried out using iodized alcohol (1%). With the assistance of a 1 ml syringe and a 13 × 0.405 mm needle (26-gauge), the groups that underwent RA induction were administered a new injection of 50 µL (0.5 mg/mL) of CFA into tibiofemoral joint. The remaining groups received saline solution (0.9% sodium chloride). Both during sensitization and the intraarticular injection, no anesthesia was administered to avoid any potential interference in the subsequent functional evaluations.

Aquatic jumping

A tank filled with water at a temperature of 33 °C was used. Inside the tank, a cylindrical tube with a height of 55 cm and a diameter of 30 cm was placed, with the water reaching 45

cm. The SHAMEX and RAEX received an overload of 50% of their body weight, with the lead weight positioned in the abdomen area using a Velcro strap (**figure 1**). The animals were placed individually in the tube and submerged to the bottom of the tank. Each impulse to reach the surface was counted as one jump (18).

All animals, regardless of their group affiliation, were pre-trained, with the weight attached to their bodies for 3 days prior to the induction of RA or SHAM. The exercise protocol began 24 hours after the intra-articular injection and was carried out every other day until the 28th day of the experiment. In the first week were two sets of 10 repetitions. From the second week onwards, there was an increase in the number of sets, with three sets of ten jumps being performed. In the third week, the progression continued, with four sets of ten repetitions being done (**figure 2**). There was a one-minute interval between series (18, 19), at the end of each session, the animals were dried with a cotton towel.

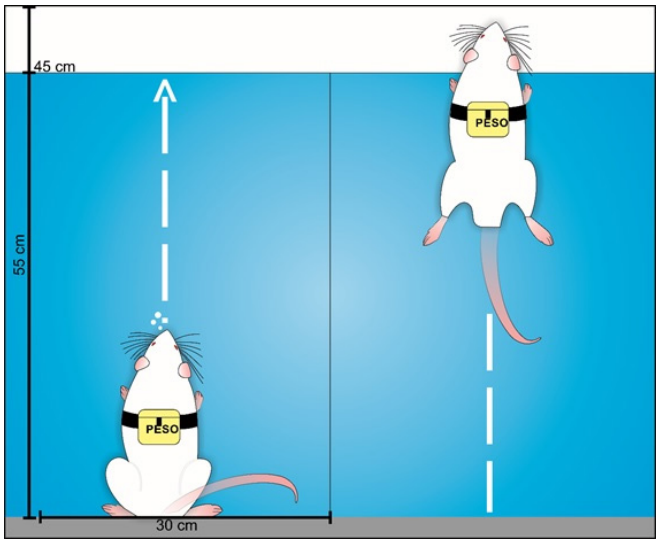

Figure 1. Illustration of the aquatic jumping exercise.

Evaluations

Prior to sensitization, all the animals were adapted for 3 days to the equipment used in the evaluations. Eight evaluations were performed (**figure 2**), for each form of functional evaluation only one examiner, blinded to the group to which the animal belonged, was responsible for the analyses. On the thirty-first day of the experiment, the animals were submitted to an intraperitoneal injection of ketamine hydrochloride (95 mg/kg) and xylazine (12 mg/kg). They were then euthanized by guillotine decapitation in order to obtain the tissues.

Nociception assessment

We utilized a digital von Frey filament analgesimeter (Insight®). This device consists of an arm connected to a signal amplifier box, with a polypropylene probe end. With the aid of a raised containment apparatus with a mesh floor, the animal was placed in the stall and left undisturbed for 5 minutes to acclimate. The dimensions of the box used to hold the animals were 23 cm wide, 20 cm deep, and 18 cm high. The evaluator then positioned the filament perpendicular to the animal's right hind limb and applied increasing pressure on the plantar region until the animal withdrew its limb. Low values obtained indicate hypernociception or allodynia. Three values were obtained for each limb, and then the average of the total was calculated. The data was presented in grams (g) on the equipment's display (20).

Paw elevation time

The functional disability test used a a metal cylinder with a diameter of 30 cm, covered with a stainless-steel mesh (2 mm), connected to a motor that gives it three revolutions per minute. Metal shoes were adapted in both plantar regions, and the right shoe was connected to a wire directed to an amplifier box, which as then connected to a computer. Thus, the animal walked for 1 minute on the cylinder, while the paw elevation time (PET) was captured and record-

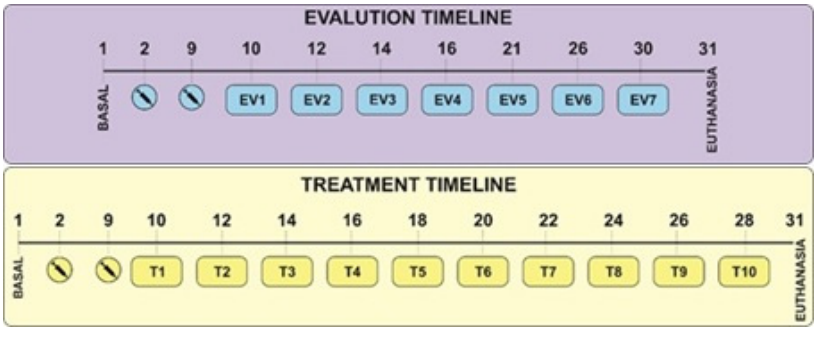

Figure 2. Treatment schedule.

Day 1 (Basal), day 2 (CFA sensitization in tail), day 9 (CFA intra-articular injection), T1-T12 (water jumping) and day 31 (Euthanasia). Schedule of evaluations. EV1-EV7 (Functional Evaluation Day) and day 31 (Euthanasia).

ed using the software Rise-Step Insight® (21). Times close to 10 seconds are considered normal for the animal's gait, and with advancing articular disability there is an increase in PET, so the data were presented in seconds (s), on the equipment's display.

Edema evaluation

The rat was immobilized, and subsequently, three measurements were obtained using a non-digital caliper, measuring the region of the knee joint interline, medially-laterally. The average of the values was taken (22). The data in centimeters was normalized using the measurements of animal 1 from the SHAM group.

Evaluation of leukocyte migration

Before euthanasia, the animals were anesthetized and 5 µL synovial fluid collection was collected using a 26-gauge needle from the sensitized right hind limb. The collected fluid was used to prepare a smear slide, which was later stained with May-Grunwald and Giemsa. The percentage of mononuclear and polymorphonuclear leukocytes was then determined using a light microscope with a 1000x objective. For the total leukocyte count, the joint cavity was washed using 100 µl of 0.9% saline solution and 4 µl of 5% EDTA 20 µl of the washed fluid was collected using a micropipettor and then diluted in Turck's fluid with a dilution factor ranged from 80 to 380 µl, depending on the cells' concentration in the synovial fluid. The cells were counted using a Neubauer chamber (cells/mm³) under a light microscope with a 40x objective. Four quadrants were adopted for the measurement of leukocyte quantity (23).

Statistical analysis

The SPSS 20.0 program was used to carry out the statistical analysis, with data presented as means and standard deviations. The inferential analysis was performed with Generalized Mixed Linear Models for the functional data, for comparison of the total leukocyte count Generalized Linear Models were used, in all cases, the post-test was the Fischer's least significance difference (LSD), for all the accepted significance level was 5%.

RESULTS

For assessment with a Von Frey analgesimeter there was a statistical difference for the right hind limb between groups ($WaldX^2(3;256) = 497.33$, $p < 0.001$), between assessments ($WaldX^2(7;256) = 38.305$, $p < 0.001$), and in the interaction ($WaldX^2(21;256) = 11.252$, $p < 0.001$). There was no difference at Baseline assessment. From EV1 to EV7 RA and RAEX showed lower values than SHAM and SHAMEX ($p < 0.05$). Being that in EV2, EV3, and EV7, RAEX showed higher values than RA ($p < 0.05$).

In the intragroup comparison, both SHAM and SHAMEX there was no statistical difference ($p > 0.05$). RA obtained reduction ($p < 0.05$) after the lesion in EV1, with a peak at EV2 ($p < 0.05$), but no return to baseline values until EV7 ($p > 0.05$). The RAEX group also showed reduction ($p < 0.05$), however, the results show an increasing average, with EV7 being statistically greater ($p < 0.05$) from EV1 (**table I**).

For the PET there was a difference between groups ($WaldX^2$ (3;256) = 176.273, $p < 0.001$), between evaluations ($WaldX^2(7;256) = 12.270$, $p < 0.001$), and interaction ($WaldX^2(21;256) = 6.204$, $p < 0.001$). At baseline, there were no differences between the groups. From EV1 to EV7, SHAM and SHAMEX showed no differences between them, but both showed shorter time than RA and RAEX ($p < 0.05$). And both in EV6 and EV7 the values obtained for RAEX were lower than those presented by RA ($p < 0.05$), indicating functional recovery, even if incomplete.

Table I. Data were presented as mean and standard deviation, for the different groups (SHAM, RA, SHAMEX, and RAEX) and evaluation times (BASAL, EV1-EV7), for the nociceptive threshold in grams (g).

	SHAM	AR	SHAMEX	RAEX
Basal	45.4 ± 5.1 Aa	45.5 ± 4.3 Aa	44.1 ± 5.4 Aa	43.1 ± 6.6 Aa
EV1	43.3 ± 2.1 Aa	17.2 ± 7.8 Bb	42.8 ± 3.3 Aa	14.2 ± 4.6 Bb
EV2	45.8 ± 4.2 Aa	9.5 ± 3.9 Bcd	45.0 ± 3.7 Aa	14.8 ± 5.7 Cb
EV3	42.5 ± 3.4 Aa	11.1 ± 4.8 Bce	43.5 ± 1.9 Aa	17.4 ± 8.8 Cbc
EV4	42.4 ± 4.5 Aa	13.7 ± 3.5 Bbde	44.4 ± 3.1 Aa	16.4 ± 8.2 Bb
EV5	40.9 ± 2.8 Aa	12.9 ± 4.8 Bbde	42.3 ± 4.2 Aa	14.6 ± 8.3 Bb
EV6	42.0 ± 2.2 Aa	14.0 ± 6.8 Bbde	40.3 ± 2.7 Aa	17.7 ± 5.5 Bbc
EV7	42.5 ± 2.7 Aa	15.5 ± 8.6 Bbe	44.1 ± 4.0 Aa	21.7 ± 8.0 Cc

Equal capital letters indicate statistical similarity in the comparison between groups; equal lower case letters indicate statistical similarity in the intra-group comparison.

In the comparison within groups, SHAM and SHAMEX again showed no differences at any time ($p > 0.05$). RA showed a gradual increase from EV1 to EV7 ($p < 0.05$). RAEX showed high values in EV1 until EV5, with a reduction in EV6 and EV7 ($p < 0.05$), again indicating that although there was no return to the basal values, there was a decrease in joint disability (**table II**).

Regarding the edema, there was a difference in the analysis of the right hind limb between groups ($WaldX^2(3;256) = 140.724$, $p < 0.001$), between evaluations ($WaldX^2(7;256) = 15.564$, $p < 0.001$), and in the interaction ($WaldX^2(21;256) = 3.234$, $p < 0.001$). At baseline, there were no differences between the groups. However, from EV1 to EV7, the RA and RAEX groups showed higher values than SHAM and SHAMEX ($p < 0.05$).

In the intra-group comparison, SHAM and SHAMEX again showed no difference ($p > 0.05$), while RA and RAEX showed increases in the values of EV1, indicating the formation of edema, with a reduction only from EV6 for RA and later (EV7) for RAEX, but in both there was no return to baseline values ($p < 0.05$) (**table III**).

For the total leukocyte count, there was a difference ($p < 0.001$) between the groups ($WaldX^2 (3) = 280.764$, $p < 0.001$). The mean number of inflammatory cells in the SHAM was statistically lower ($p < 0.05$). The SHAMEX had lower values than RA and RAEX ($p < 0.05$), and for the latter RAEX showed lower values than RA ($p = 0.010$).

For the differential leukocyte count, there was a statistical difference for mononuclear ($WaldX^2(1) = 4237.639$, $p < 0.001$); and polymorphonuclear ($WaldX^2(1) = 660.325$, $p < 0.001$) cells. The percentage of mononuclear cells was lower ($p < 0.001$) in the SHAMEX and RAEX groups when compared to the SHAM. No statistical difference between RA and the other groups. As for polymorphonuclear cells, there was a significant increase ($p < 0.001$) in the SHAMEX and RAEX compared to the SHAM. There was no statistical difference in the RA compared to the other groups (**table IV**).

Table II. Data presented as mean and standard deviation, for the different groups (SHAM, RA, SHAMEX, and RAEX) and assessment times (BASAL, EV1-EV7), for Paw Elevation Time – PET in seconds (s).

	SHAM	AR	SHAMEX	RAEX
Basal	15.1 ± 3.7 Aa	12.5 ± 2.3 Aa	13.7 ± 4.2 Aa	11.8 ± 4.1 Aa
EV1	11.8 ± 2.3 Aa	31.8 ± 9.5 Bb	12.3 ± 3.4 Aa	37.2 ± 9.2 Bb
EV2	12.8 ± 5.4 Aa	36.0 ± 8.2 Bbd	13.6 ± 6.2 Aa	34.7 ± 10.9 Bb
EV3	15.2 ± 6.7 Aa	34.6 ± 11.0 Bbe	15.1 ± 7.6 Aa	34.1 ± 9.4 Bb
EV4	13.4 ± 4.1 Aa	38.2 ± 10.2 Bbd	13.5 ± 3.3 Aa	37.9 ± 6.5 Bb
EV5	14.2 ± 1.6 Aa	38.0 ± 6.6 Bbd	14.0 ± 4.8 Aa	36.7 ± 9.4 Bb
EV6	14.7 ± 5.6 Aa	40.3 ± 6.2 Bcde	14.1 ± 5.1 Aa	27.5 ± 8.3 Cc
EV7	12.4 ± 3.7 Aa	41.2 ± 6.2 Bcd	12.5 ± 4.0 Aa	26.4 ± 10.4 Cc

Equal capital letters indicate statistical similarity in the comparison between groups; equal lower case letters indicate statistical similarity in the intra-group comparison.

Table III. Data were presented as mean and standard deviation, for the different groups (SHAM, RA, SHAMEX, and RAEX) and evaluation times (BASAL, EV1-EV7), for edema.

	SHAM	RA	SHAMEX	RAEX
Basal	0.98 ± 0.04 Aa	1.00 ± 0.04 Aa	0.95 ± 0.03 Aa	0.96 ± 0.05 Aa
EV1	1.00 ± 0.05 Aa	1.23 ± 0.07 Bbc	1.01 ± 0.05 Aa	1.26 ± 0.11 Bbc
EV2	1.00 ± 0.06 Aa	1.30 ± 0.10 Bb	1.00 ± 0.05 Aa	1.29 ± 0.11 Bb
EV3	1.01 ± 0.05 Aa	1.28 ± 0.12 Bbd	1.02 ± 0.05 Aa	1.30 ± 0.14 Bb
EV4	1.00 ± 0.06 Aa	1.23 ± 0.09 Bbc	1.02 ± 0.06 Aa	1.28 ± 0.15 Bbc
EV5	1.00 ± 0.05 Aa	1.23 ± 0.08 Bbc	1.02 ± 0.06 Aa	1.25 ± 0.16 Bbc
EV6	1.00 ± 0.04 Aa	1.20 ± 0.07 Bc	1.03 ± 0.06 Aa	1.23 ± 0.12 Bbc
EV7	1.00 ± 0.04 Aa	1.21 ± 0.07 Bcd	1.03 ± 0.03 Aa	1.21 ± 0.12 Bc

Equal capital letters indicate statistical similarity in the comparison between groups. Equal lower case letters indicate statistical similarity in the intra-group comparison.

Table IV. Data on total leukocyte count (cells/mm³) and the percentage of mononuclear and polymorphonuclear leukocytes.

	SHAM	RA	SHAMEX	RAEX
Leukocyte	6.87 ± 1.72 A	280.53 ± 75.15 B	25.35 ± 6.79 C	81.5 ± 19.25 D
Mononuclear	52.62 ± 6.38 A	45.67 ± 5.22 AB	36.56 ± 4.18 B	34.45 ± 3.73 B
Polymorphonuclear	48.00 ± 4.76 A	54.33 ± 4.49 AB	63.44 ± 4.49 B	65.55 ± 4.26 B

Equal capital letters indicate statistical similarity in the comparison between groups.

DISCUSSION

In this study, we investigated the effects of jumping in an aquatic environment on a model of RA. We specifically examined the impact on pain and inflammatory parameters in the knee induced by CFA. RA and RAEX injured groups exhibited arthritic symptoms, as described by Micheli *et al.* (24) which were analyzed through functional assessments. However, the RAEX showed signs of symptom regression.

For the observation of nociception using a Von-Frey analgesimeter, the groups injured with CFA demonstrated increased nociception. It should be noted that only male animals were used to avoid a possible effect of the estrous cycle on nociception (25). The main contributors to the presence of hyperalgesia in RA are the proinflammatory cytokines. These promote a critical and acute onset and continue a continuous, chronic, low intensity inflammatory process (26). Sensory neurons, sensitized by TNFα, IL-1β, IL-6, IL-17, and other inflammatory mediators, show increased excitability and thus contribute to significant joint pain (27).

However, the RAEX showed an elevation in the nociceptive threshold throughout the evaluation, demonstrating a beneficial effect of the exercise protocol. The physiological mechanisms of how exercise affects the immune system in RA are still unknown (28). Long-term exercise may promote the production of anti-inflammatory cytokines after training. During overload training, there is an increase in IL-6 expression due to the reduction in muscle glycogen resulting from the demands of contraction (29). It is hypothesized that this signal stimulates hepatic glucose production, which in turn triggers increased expression of IL-10 and IL-1ra (IL-1 receptor antagonist). This stimulation leads to a post-exercise anti-inflammatory potential, reducing peripheral inflammatory mediators (30, 31). The absence of inflammatory mediators biochemical analyses is a limitation of this study, and it is suggested that future studies should include them.

Pavan *et al.* (32) observed a reduction in pain among individuals with RA who participated in a hydrokinesiotherapy program of 10 sessions, twice a week, lasting 50 minutes each. The program included exercises targeting various physical capacities, including muscle strengthening. This aligns wits the data obtained, although the present study has only focused on the resistance modality. It has observed with beneficial effects in the reducing pain in animals with an RA model.

In the PET physical exercise also manifested a positive repercussion for the RAEX group in comparison with the RA, since the injured group obtained an increase in the mean, but throughout the treatment the injury-exercise group reduced the PET, indicating functional improvement of the joint. Among the behaviors related to pain, the alteration of motor activity and the lack of contact care for the painful limb are strongly associated with arthritic models (33). In addition, pain reduces an individual's ability to engage in physical activity, which in turn increases cardiovascular risk, decreases functionality, and intensifies arthritic pain activity (34).

Siqueira *et al.* (35) evaluated the effect of a program of aquatic exercise for the lower limbs, conducted three times a week for 16 weeks, on 82 women with RA. The study found a significant improvement in pain levels, disease activity, and functional capacity. In the present study, it was observed that, even with a shortened treatment period of 4 weeks, aquatic exercise had a positive impact on analgesia and functionality in the hind limb of injured and treated animals.

Another inflammatory indicator observed in the present study was the presence of joint edema. This result is attributed to a potential increase in prostaglandins due to the presence of enzymes COX-1, COX-2, and prostaglandin synthase in the synovial fluid of the joint. This in turn, promotes a significant extravasation of exudates, which is characteristic of autoimmune inflammatory responses (36). In addition, the central nervous system exerts a complex inflammatory regulation associated with angiogenesis and other vascular effects (37).

Research shows that individuals with RA tend to choose a sedentary lifestyle and do not engage in an appropriate amount of physical activity (34). However, there is strong evidence that exercise can modulate C-reactive protein (CRP) levels, especially in individuals who have high base-

line CRP levels, such as patients with RA (38). The results described here also reinforce this premise, since resisted exercise in an aquatic environment improved the hypernociceptive and functional status of the animals. However, it should be borne in mind that only one anaerobic exercise protocol was used, which is another limitation of this study. Among the advantages of exercising in water, the presence of hydrostatic pressure stands out. It promotes the displacement of intracorporeal fluids and optimizes cellular transport and peripheral vascular return (39). Thus, the compressive effect may contribute to reducing edema in the lower limbs; however, this impact was not observed in the present study. It is hypothesized that the water temperature has favored a vasodilation process, impairing the reabsorption of joint fluid (40). It can also be considered that with the chronicity of the disease, the composition of synovial fluid in arthritic joints is altered. This alteration includes a reduction in the quantity and molecular weight of local hyaluronic acid, which leads to pain and stiffness, making it difficult to reabsorb the local exudate (41).

Finally, regarding the leukocyte quantification, it was observed that there was an increase of inflammatory infiltrate in the injured groups when analyzing the total number of cells. This result corroborates the literature that suggests that the inflammatory model proposed for RA induction leads to an influx of immune system cells, guided by chemokines, into the synovial fluid (42). The RAEX had a lower quantity of inflammatory cells compared to RA.

In rheumatoid arthritis, monocytes are primarily composed of macrophages that migrate to the synovial membrane. These macrophages are correlated with the severity of the disease as they are responsible for producing a large amount of cytokines (43). Polymorphonuclear cells are also found in abundance, highlighting the presence of neutrophils in the synovial fluid and pannus, where proteoglycan degradation occurs (44). Despite being an experimental model, which is a limitation of the study, the use of CFA mimics some of the characteristics of this disease in animals, and rodent models are widely used (mainly rats and mice) due to their low cost, homogeneity and easy handling (45). Exercise can promote leukocyte demargination, which is associated with increased blood flow, blood pressure, and cardiac output. This leads to the mobilization of inflammatory cells in response to exercise (46).

We were able to observe the arthritis induced by CFA and confirm the advantages of resistance exercise conducted in water in reducing pain, enhancing functionality, and assisting in the modulation of inflammatory parameters. Future research should focus on inflammatory markers of tissue cytokines and evaluations that quantify the effects of aquatic exercise compared to land-based exercise for individuals with RA, since, although experimental, there are indications that this form of therapy may also be useful in humans.

CONCLUSIONS

Resistance jumping exercises in an aquatic environment are effective in reducing hypernociception, improving peripheral functionality, and reducing leukocyte counts in the knee of rats subjected to a model of rheumatoid arthritis.

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DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

ALFT, MN, TCS, LAP: data collection. ALFT, TSSL, LFCR, GRFB: results analysis and interpretation. TSSL, LFCR, GRFB: supervision. ALFT: writing – original draft. TSSL, LFCR, GRFB, MN, TCS, LAP: writing – review & editing.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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