SUPERVISED WALKING IMPROVES AEROBIC CAPACITY, EXERCISE TOLERANCE AND FATIGUE IN WOMEN WITH PRIMARY SJÖGREN'S SYNDROME: A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Objective: The aim of this study was to evaluate the safety and effectiveness of a supervised walking program in women with primary Sjögren's syndrome (pSS).

Methods: Forty five sedentary women fulfilling the American European Consensus Criteria for pSS were randomized to a Training Group (TG, n= 23) or Control Group (CG, n= 22). Patients in the TG were submitted to supervised walking 3 times a week for 16 weeks. The patients of the CG were instructed to not perform any kind of regular physical exercise. Cardiorespiratory fitness, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), haematological tests and Medical Outcomes Study 36 (SF-36) were assessed at baseline and week 16. Patients were interviewed by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-Fatigue) and Beck Depression Inventory (BDI) prior to intervention, after 8 and 16 weeks. Patient global assessment of response to therapy (PGART) was completed at the final assessment. An intent-to-treat analysis was performed.

Results: The mean change after 16 weeks of maximum oxygen uptake (VO_{2max} (ml/kg/min)), distance and FACIT-fatigue were higher in the TG than in the CG (p= 0.016, p= 0.043 and p= 0.030, respectively). Improved cardiorespiratory fitness was associated with improvements in fatigue scores and physical components of quality of life measured using SF-36. Furthermore, improved fatigue scores were associated with reduced depression and improvements in the physical and mental components of the quality of life measures. Overall, 95.4% of patients in the TG rated themselves as clinically improved versus 62% of the patients in the CG (p= 0.049). There was no flare in disease activity and no serious adverse events with exercise.

Conclusions: This supervised walking program was demonstrated to be feasible and safe with improvements in the aerobic capacity, exercise tolerance, fatigue and patient perception of improvement in pSS patients.

KEYWORDS: Sjögren's syndrome, Fatigue, Exercise, Rehabilitation

INTRODUCTION

There is emerging evidence that exercise training can improve physical capacity, muscle function and several clinical symptoms, such as fatigue, pain and depression, in many autoimmune rheumatic diseases(1). Furthermore, exercise training may have an anti-inflammatory effect based on studies in older adults(2,3) and in low-grade systemic inflammation chronic diseases, such as type 2 diabetes mellitus and congestive heart failure(4,5). Aerobic exercise has been investigated in rheumatoid arthritis (RA)(6), systemic lupus erythematous (SLE)(7–11), ankylosing spondylitis (AS)(12) and systemic sclerosis (SS). Primary Sjögren's syndrome (pSS) is also a systemic autoimmune disease, but there is only one non-randomized controlled study on aerobic exercise with a small sample size, suggesting improvement in fatigue, aerobic capacity, depression and physical function(13). This disease is characterized by lymphocytic infiltration and progressive destruction of exocrine glands, leading to dry eyes and dry mouth(14). In addition, around 20-40% of patients present with severe systemic manifestations and most of them report pain and fatigue(15), decreasing their quality of life(16–19). There is also a high prevalence of depression(20) and sleep disorders(21).

When compared to healthy controls, pSS patients have reduced levels of physical activity(22,23) and cardiorespiratory fitness(22,24). In Ng *et al* study, fatigue was a predictor of vigorous and moderate intensities of physical activity, whereas symptoms of depression and daytime sleepiness accounted for 4.5% of the variance of total physical activity levels(23). In our preliminary cross-sectional study 20 pSS patients performed a maximum treadmill test and had their expired gas analysed by a computerized metabolic system. Lower levels of maximum oxygen uptake (VO_{2max}, ml/kg/min) were associated with worse symptoms measured by ESSPRI, mainly fatigue and dryness(25). Strömbeck *et al* also found an association between aerobic capacity (VO_{2max}, l/min), measured indirectly, and fatigue(24). Moreover, Wouters *et al* have shown that the combination of low physical activity and high activity avoidance was associated with more severe fatigue(26). In fact, patients often report that fatigue is their greatest problem and the most difficult to cope with(27), affecting up to 70% of the patients(28). However, its pathogenesis is unknown and, so far, there is no evidence of high quality of an effective treatment. These observations may imply that programmes designed to increase the levels of physical activity and cardiorespiratory fitness may ameliorate pSS symptoms, mostly fatigue.

This paper reports the first randomized controlled trial to evaluate the safety and effectiveness of a supervised aerobic exercise program in women with pSS.

METHODS

This is a randomized controlled trial with intention-to-treat analysis. Forty-five sedentary women fulfilling the American European Consensus Criteria for pSS(29) were recruited from the rheumatology outpatient clinic of an University hospital in the city of Vitória/Brazil, from 2012 to 2015, and randomized into Training Group (TG) and Control Group (CG). Patients were screened for entry into the study by just one investigator (rheumatologist) who was blind to forthcoming patients' allocation. This trial was open to patients between 18 and 65 years old. Patients with symptomatic cardiac failure, body mass index>40, using beta-blocker therapy, presenting severe systemic manifestations limiting or hindering walking performance, or those who had performed regular physical activity in the 6 weeks before trial were excluded.

To investigate the improvement in VO_{2max} (ml/kg/min) and its association with improvement of clinical outcomes, this study was powered to achieve an improvement in VO_{2max} of 3.8 ml/kg/min, given an estimated SD of 2.76 with a statistical significance at 1% and power of 95% leading to a recommended minimum of 19 patients per group. However, 45 patients were included and all of them were analysed.

[(9,13) Not clear to me what these limits refers to and I suspect they're not used in the power calculation anyway?]

The Centro de Ciências da Saúde Ethics Committee/UFES (number 084/11) approved the study according to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Procedures

Demographic and clinical assessments to evaluate disease activity were performed by a rheumatologist expert in Sjögren's syndrome. A trained interviewer, blinded to treatment allocation throughout the trial, conducted the other questionnaires. The treadmill tests were performed by a cardiologist and assisted by a laboratory technician and a physiologist.

At baseline, all patients had their demographic data collected, including age, body mass index (BMI), marital status, education level, working status and social class (Brazil Economic Classification Criteria-CCEB)(30). Clinical assessments, such as complains of xerostomia and xerophthalmia, comorbidities, medications in use, sialodenitis (focus score>1 on labial salivary gland biopsy) and unstimulated salivary flow rate (5 minutes) were taken at the moment of the evaluation and/or confirmed in patient's medical record. Haematological tests, including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), creatine kinase (CK), IgG, IgA, IgM, C3, C4 anti-Ro and anti-La were performed at the hospital's analytical laboratory and assessed at baseline and week 16. Physical fitness, disease activity and quality of life were also evaluated at baseline and week 16. Patients were interviewed to evaluate fatigue, depression and perception of pSS's symptoms prior to intervention, after 8 and 16 weeks.

Patients were allocated to groups by randomization drawing lots after the initial assessment: folded pieces of paper in which the group labels were written (either TG, or CG) were held in sealed envelopes. One of

the investigators, who remained unaware of screening and assessments of the patients, took the envelopes out of a container. Both groups received the usual pharmacological treatment. The patients of the CG were instructed to not perform any kind of regular physical exercise for 16 weeks. The patients of the TG were submitted to a supervised walking in an outdoor track field (400m), 3 times a week for 16 weeks, by two trained professionals who alternated weekly.

The ventilatory anaerobic threshold is considered the main measure of aerobic fitness(33), as other studies in SLE(31,32) and fibromyalgia (33–35) fail to achieve maximum effort when submitted to maximal exercise test protocol in the treadmill. Lemos *et al* has demonstrated, by using mathematical models, that for exercise prescription in the anaerobic threshold intensity for sedentary women with fibromyalgia, the percentage must be 75.5-80.9% HR_{max}. Once our preliminary results showed that pSS also do not achieve a maximum effort, the intensity of the exercise was based on the heart rate (HR) at 80% of the maximum heart rate (HR_{max}) reached in the treadmill test(34).

The HR of the patients was registered with a pulse watch (Polar® A1, Kempele, Finland) and ratings of the general perceived exertion (RPE) rated on the Borg RPE 0-10 scale [21] at the beginning, middle and end of the effective walking time. Each training session was preceded by a warm-up period, when patients were instructed to walk freely and slowly for 5 minutes, followed by 20 to 50 minutes of effective walking when they were instructed to maintain their paces to achieve the target HR, and ending with a cooling down period for 5 minutes (similar to warm up period). Increasing duration of exercise was made as follow: 20 minutes in the first 2 weeks, adding 5 minutes per week until eighth week, completing 50 minutes, which remains until the end of the program.

Physical fitness outcomes

All patients performed a maximal exercise test on the treadmill (Super ATL, Inbramed, Porto Alegre, Brazil), directed by the software Ergo PC (Micromed, Brasília, Brazil) and supervised by a cardiologist, who performed a screening process for cardiac risk. The protocol begins with a warm-up period of 3 minutes at 3 km/h and increases 1 km/h each minute until 7 km/h, from this moment 2,5% inclination is added until 15% in the 13º minute(33,36). The electrocardiogram (Micromed, Brasília, Brazil) and blood pressure were closely monitored throughout the exercise test which was interrupted when appearance of abnormal signs or at patient's request in case of any discomfort.

The maximum oxygen uptake (VO_{2max}, ml/kg/min) was calculated by the walking metabolic equation of the American College of Sports Medicine (ACSM): VO_2 = 0.1(speed) + 1.8 (speed) (fractional grade) + 3.5(37,38).

The highest value obtained in the last load was taken as peak heart rate (HR_{peak}). The distance reached during the test was also recorded.

Clinical outcomes

The disease activity was measured by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (15,39), fatigue by the Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-

Fatigue) (40), perception of pSS's symptoms by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (27,41), depression by the Beck Depression Inventory (BDI)(42) and quality of life by the Medical Outcomes Study 36 (SF-36) (43).

Patient global assessment of response to therapy (PGART)

At the final assessment the patients responded on the PGART using a 5-point scale (1=much better, 2 =better, 3=slightly better, 4=no change, and 5=worse).

Statistical analysis

The main hypothesis was that aerobic exercise improves VO_{2max} (ml/kg/min) and clinical outcomes, such as fatigue, pain, depression and quality of life without exacerbating disease activity. An intent-to-treat analysis was performed and a level of significance of $p<0.05$ was accepted for the trial. To compare the effects of the two groups, the independent and dependent variables and the RPE over the time were analysed using a repeated-measures analysis of variance (ANOVA). Independent sample t-tests or Mann–Whitney U tests were used in the between groups comparison when interaction time (baseline, 8 and 16 weeks) x group (TG and CG) was statistically significant and in the between groups comparison of the mean change after 16 weeks. Chi-square test and binomial test with Bonferroni correction were used to determine differences in rates of improvement between the groups. Pearson's and Spearman's correlation coefficients were used to investigate the association between the improvement of VO_{2max} (ml/kg/min) and clinical outcomes. The comparison between the HR at the final time of the third session in each week of the training and the target HR was analysed by paired t-test and Pearson's correlation coefficient. The last-observation-carried-forward method was performed for missing data. A statistician blinded to the groups performed the analysis using version 19.0 of the SPSS software system.

RESULTS

A flow diagram showing the movement of participants through the study is shown in Fig. 1. Forty five eligible patients were randomized to groups (TG: 23; CG: 22). Four patients in TG and 2 in CG discontinued the intervention. One patient in the TG refused to undergo evaluations at week 8 and week 16 after reporting chest pain in the 1st week, and 1 patient in the CG refused to undergo evaluation at week 16 due to personal problems. Three patients in the TG could not perform the exercise test at week 16 following adverse events unrelated to the exercise program: the first reported an acute low back pain in the 6th week, the second suffered a foot fracture due to a fall from the stairs in the 7th week, and the third a trochanteric bursitis in the 10th week. One patient of the CG could not perform the exercise test at week 16 due to hip arthralgia.

There were no statistically significant differences between study groups at baseline (Table 1 and Table 2) with one exception: the number of patients using non-steroidal anti-inflammatory drugs was higher in the TG than in the CG (52.2% vs. 22.7%, p=0.042) (supplementary table S1). None of them were smokers. Patients discontinuing the intervention scored slightly lower on the mental component summary (MCS) of the SF-36 (p=0.041) compared to those completing the study (Table 1).

The compliance rate for the exercise program sessions averaged 72.4% (21 - 92%). In case of pain or fatigue, training intensity was maintained but the duration of the session reduced. Three patients in the TG group reported fatigue, 5 widespread pain, 2 low back pain, 4 knee arthralgia, 2 hip/ankle arthralgia, 1 shoulder arthralgia and 2 hand/wrist arthralgia during the exercise program. However, all of them were transitory and did not affect the continuity in the exercise program and patients did not attribute these symptoms to exercise. The complaints of the patients in CG were not registered weekly, but 1 reported worsening in fatigue, 2 widespread pain pain, 1 knee arthralgia, 1 hip arthralgia and 2 hand/wrist arthralgia at week 16.

Three patients of the TG modified the pharmacological treatment during the trial: the first exchanged the hydroxychloroquine for methotrexate (pruritus in skin), the second started the use of methotrexate and corticosteroids (vasculitis in legs), and the third started the use of azathioprine (worsening of xerostomia and xerophthalmia). Methotrexate was introduced for one patient of the CG (persistent arthritis in hands).

Physical fitness

At baseline only 52% of the patients in the TG and 50% in the CG reached the maximal effort in the treadmill test. The VO_{2max} (ml/kg/min) increased in both groups (p=0.025) and HR_{peak} remained the same. However the distance covered on the test increased only in TG (p=0.020). The mean change in VO_{2max} and distance after 16 weeks was higher in the TG than in the CG (p=0.016 and p=0.043, respectively) (Table 3 and Fig. 2).

There was correlation between the improvement of VO_{2max} and improvement of the FACIT-fatigue (r=0.418, p=0.047), SF-36 domains physical functioning (r=0.557, p=0.006) and general health (r=0.525, tp=0.010) and SF-36 physical component summary (PCS) (r=0.478, p=0.021) only in TG.

The mean difference of the training HR and the target HR was higher than 5 beats per minute (bpm) only in the 6th, 13th and 16th week of the exercise program. There was a high correlation between the mean training HR and mean target HR (r=0.943, p=0.006, Pearson). The mean of the general RPE was 3.18 ± 0.33 (2.6 - 3.9) with no difference over the exercise program (p=0.818).

Eleven patients (47.8%) in the TG and 5 (22.7%) in the CG had an improvement over 15% in VO_{2max} at week 16. While this difference was not statistically significant (p=0.079), those patients in the TG with 15% VO_{2max} gain showed significant improvements in FACIT-fatigue (p=0.047), ESSPRI fatigue (p= 0.044) and BDI (p=0.037) compared to those with less than 15% gain in VO_{2max}. In TG, the number of patients presenting with widespread pain at baseline was higher in the subgroup of patients with no gain in VO_{2max} compared to those with improved VO_{2max} gain (10 vs 4, p= 0.021) (Table 4).

Clinical data

Fatigue measured by FACIT-fatigue improved only in TG (p=0.017). There was no difference in the ESSPRI domains and total score in both groups. Depression measured by BDI improved in TG and CG over time (p=0.001), from baseline to week 8 (19±10 to 15±9 and 20±12 to 18±12, p=0.005, respectively) and from baseline to week 16 (19±10 to 15±10 and 20±12 to 16±12, p=0.001, respectively). Both groups showed improved MCS of the SF-36 (p=0.009). There were no differences in the PCS of the SF-36, despite the tendency of improvement in the TG (Table 3). There was a difference between groups in mean changes after 16 weeks only in FACIT-fatigue (p=0.030) (Table 3).

The improvement of fatigue (FACIT-fatigue) in the TG was correlated with the improvement of the VO_{2max} (ml/kg/min) (r=0.418, p=0.047), ESSPRI-fatigue (r=-0.677, p<0.001), ESSPRI pain (r=-0,429, p=0,041), ESSPRI-total (r=-0.630, p=0.001), BDI (r=-0.474, p=0.022), SF-36 domains physical functioning (r=0.682, p=0.001), role-physical (r=0.552, p=0.006), general health (r=0.423, p=0.044), social functioning (r=0.425, p=0.043) and mental health (r=0.586, p=0.003), SF-36 PCS (r=0,522, p=0,011) and SF-36 MCS (r=0.456, p=0.0290). While in the CG there was association between the improvement of fatigue (FACIT-fatigue) only with ESSPRI-fatigue (r=-0.694, p<0.001), ESSPRI-total (r=0.496, p=0,019) and BDI (r=-0.477, p=0.025).

Immunological data and ESSDAI

There was no difference in ESSDAI, erythrocyte sedimentation rate (ESR), IgG, IgA, IgM and C3 over time. The C reactive protein (CRP) (p=0.005), creatine kinase (CK) (p=0.018) and C4 (p<0.001) levels increased in both groups. There was no difference between groups in all these data (supplementary Table S2).

At baseline, 65.2% of the patients in the TG were classified as having low disease activity by ESSDAI classification [25], 26.1% moderate and 8.7% high; and in the CG the percentages were 63.6%, 31.8% and 4.5%, respectively. There was no difference within-groups after 16 weeks (p=0.538) and between groups (p=0.809).

PGART

The categories of the PGART were statistically different at the final assessment between groups (p=0.049). From the TG, 95.4% of the patients rated themselves as clinically improved versus 62% of the patients in the CG.

DISCUSSION

This is the first randomized controlled trial with intention-to-treat analysis to demonstrate that a 16-week supervised walking program improves the cardiorespiratory fitness, exercise tolerance, fatigue and patient perception of improvement without exacerbating disease activity in women with pSS.

The TG improved the cardiorespiratory fitness (VO_{2max}) more than the CG, demonstrating that the program was effective in enhancing cardiorespiratory fitness. This is consistent with a study of supervised aerobic exercise in patients with SLE(8). In a study of Nordic walking exercise performed three times a week for 12 weeks in pSS(13), VO_{2max} (l/min) improved significantly, but not the VO_{2max} (ml/kg/min). However these patients were supervised just once a week. The improvement of the cardiorespiratory fitness was not observed in the other 4 exercise studies in SLE(7,9–11), an autoimmune disease with several clinical similarities to pSS(44), probably because the exercises were not supervised during the whole program. It may be that such supervision is important to the cardiorespiratory fitness improvement. Unexpectedly, the there was a small but statistically significant improvement (151.1±18.6 vs. 152.3±17.8, p=0.023) in [what] in the CG though this may be attributable to treadmill exercise learning.

The intensity of our exercise program at 80% of the HR_{peak} reached in the treadmill test and the gradually increasing duration of exercise showed to be appropriated to the pSS patients since there was no difference between the training HR and the target HR in most of the weeks and the perceived exertion (BORG scale) remained moderate over the entire program. This might have contributed to provide a good adherence to the exercise program (72%). The intensity of the exercise prescribed in previous SLE and pSS studies(7,9–11,13) increased progressively over the training from 60% or 70% to the maximum of 80% of the HR_{max} and most of them improved fatigue and exercise tolerance(9–11,13). While largely safe (9–11) these studies did not improve cardiorespiratory fitness as mentioned before. In addition to supervision, the only study in SLE that improved cardiorespiratory fitness used the HR training corresponding to the ventilatory anaerobic threshold during the whole program(8). The same method of prescription was used for patients with fibromyalgia also with an improvement in cardiorespiratory fitness(45,46). Lemos et al have demonstrated that the percentage of the exercise prescription in the anaerobic threshold intensity for sedentary women with fibromyalgia syndrome must be from 75% to 80% of the HR_{max} reached in the treadmill test(34). These percentages are higher than the ACSM recommendation (55-64% HR_{max}) to sedentary [] (47), which may be owing to the fact that patients with fibromyalgia do not take maximum effort and HR_{max} is underestimated. While there is no comparable study in pSS, our results showed that pSS patients also do not take maximum effort. This suggests that the same method of exercise intensity prescription might extrapolate to other diseases sharing reduced cardiorespiratory fitness and concomitant symptoms, such as fatigue, musculoskeletal pain and autonomic dysfunction.

The change in exercise distance of the TG is likely to be due to improved exercise tolerance and cardiorespiratory fitness and is important because improved exercise capacity may reflect improvements in physical disability. Although this was not supported by any significant changes in self-perceived measures of physical function, probably due to the small sample size to detect differences in SF-36

between groups, a significant moderate association was found between the improvement of cardiorespiratory fitness and the improvement of fatigue and all physical domains of the SF-36. In fact, fatigue measured by FACIT-fatigue in TG improved more than in CG, and the mean difference of the ESSPRI fatigue domain was of -1 in the TG. This is considered clinically significant(48), but not statistically significant, consistent with other reports that it is insensitive to change(49). These findings suggest an important role of the physical fitness in the pathogenesis of the fatigue in pSS.

Surprisingly, both groups showed improved depression score and MCS of the SF-36. Patients of the CG had 5 more meetings with health-care professionals due to the study than the usual of 2 meetings/year. This additional attention could have been a factor in increasing mood, motivation, and effort. In contrast with Strömbeck, Theander and Jacobsson study(13), there was no difference in depression between TG and CG groups. However, our correlation analysis shows that improvements in fatigue are associated with improvements in depression scores. Furthermore, the complementary analysis in TG showed that an increase above 15% in VO_{2max} improves both fatigue and depression. Exercise is known to increase tryptophan transport into the brain and serotonin production, which is one of the crucial mechanisms of an antidepressant action(50).

It's possible that the three patients of the TG who modified the pharmacological treatment during the trial had some improvement in their clinical data and physical fitness, but one patient of the CG also started the use of a new drug, extending the effect for both groups. The patient of the TG who started the use of methotrexate and corticosteroids due to the worsening of vasculitis in legs was evaluated by the rheumatologist, who recommended the continuity of the exercise program to conclude that it was not a worsening of the disease activity.

In general, as with SLE patients(7,9–11), there was no flare in disease activity and no serious adverse events with exercise, showing that patients with pSS can undergo physical training without damage. Although both groups had an incomprehensible increased of CRP, CK and C4 levels after 16 weeks, ESSDAI had a slight non-significant reduction, which means that patients remained stable regarding on disease activity. Two patients of the CG related worsening at the final assessment and only one in the TG, but she is the one who discontinued the intervention due to the low-back pain. This patient had only 56% compliance, severe depression by BDI, reported worsening of widespread pain, and serious personal problems. On her magnetic resonance imaging scan there was no evidence of injury, implying a strong emotional influence on her pain symptoms. As we did not systematically registered emergence of new or transitory symptoms in CG, such as pain and fatigue, it seems that patients of the TG had more complaints, but most of them did not attribute these symptoms to the exercise program, with the exception of one patient suffering from trochanteric bursitis with prior history in the past.

Given reduced physical capacity and function(24,51) and lower levels of physical activity in patients with pSS when compared to healthy people(22,23), aerobic exercise becomes an important intervention to improve cardiorespiratory fitness, decrease fatigue and probably the risks of developing secondary chronic disease.

The limitations of the study are the indirect measurement of the VO_{2max}, non-validation of the ACMS metabolic equation to this population, lack of weekly monitoring of the new symptoms in the CG and lack of a follow-up to date investigating the long-term effects of the exercise program.

In conclusion, this supervised walking program was demonstrated to be feasible and safe with improvement of the cardiorespiratory fitness, exercise tolerance, fatigue and perception of clinical improvement in women with pSS patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

NOTE

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REFERENCES

1. Perandini LA, de Sá-Pinto AL, Roschel H, Benatti FB, Lima FR, Bonfá E, et al. Exercise as a therapeutic tool to counteract inflammation and clinical symptoms in autoimmune rheumatic diseases. Autoimmun Rev; 2012;12(2):218–24.

2. Sardeli AV, Tomeleri CM, Cyrino ES, Fernhall B, Cavaglieri CR, Chacon-Mikahil MPT. Effect of resistance training on inflammatory markers of older adults: A meta-analysis. Exp Gerontol. 2018;111:188–96.

3. Colbert LH, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, et al. Physical activity, exercise, and inflammatory markers in older adults: Findings from the health, aging and body composition study. J Am Geriatr Soc. 2004;52(7):1098–104.

4. Mathur N, Pedersen BK. Exercise as a mean to control low-grade systemic inflammation. Mediators Inflamm. 2008;2008:109502.

5. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005;98(4):1154–62.

6. Rongen- van Dartel, SAAA, Repping- Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB et al. The effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis. Arthritis Care Res (Hoboken). 2015;67(8):1054–62.

7. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology.;42(9):1050–4.

8. Carvalho MRP De, Sato EI, Tebexreni AS, Heidecher RTC, Schenkman S, Neto TLB. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus. Arthritis Rheum. 2005;53(6):838–44.

9. Robb-Nicholson LC, Daltroy L, Eaton H, Gall V, Wright E, Hartley LH, et al. Effects of aerobic conditioning in lupus fatigue: a pilot study. Br J Rheumatol. 1989;28(6):500–5.

10. Daltroy LH, Robb-Nicholson C, Iversen MD, Wright E a, Liang MH. Effectiveness of minimally supervised home aerobic training in patients with systemic rheumatic disease. Br J Rheumatol. 1995;34(11):1064–9.

11. Ramsey-Goldman R, Schilling EM, Dunlop D, Langman C, Greenland P, Thomas RJ, et al. A pilot study on the effects of exercise in patients with systemic lupus erythematosus. Arthritis Care Res. 2000;13(5):262–9.

12. Verhoeven F, Guillot X, Prati C, Mougin F, Tordi N, Demougeot C, et al. Aerobic exercise for axial spondyloarthritis - its effects on disease activity and function as compared to standard physiotherapy: A systematic review and meta- analysis. Int J Rheum Dis. 2018;1:1–8.

13. Strömbeck BE, Theander E, Jacobsson LTH. Effects of exercise on aerobic capacity and fatigue in women with primary Sjogren's syndrome. Rheumatology. 2007;46(5):868–71.

14. Bowman SJ, Rao V. Sjögren's syndrome. Medicine. 2014;42(3):162–6.

15. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis. 2010;69(6):1103–9.

16. Segal B, Bowman SJ, Fox PC, Vivino FB, Murukutla N, Brodscholl J, et al. Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. Health Qual Life Outcomes. 2009;7:46.

17. Cho HJ, Yoo JJ, Yun CY, Kang EH, Lee H-J, Hyon JY, et al. The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's sicca patients. Rheumatology. 2013;52(12):2208–17.

18. Lendrem D, Mitchell S, McMeekin P, Bowman S, Price E, Pease CT, et al. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis. 2014;73(7):1362–8.

19. Meijer JM, Meiners PM, Huddleston Slater JJR, Spijkervet FKL, Kallenberg CGM, Vissink A, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology. 2009;48(9):1077–82.

20. Cui Y, Li L, Yin R, Zhao Q, Chen S, Zhang Q. Depression in primary Sjögren ' s syndrome : a systematic review and meta-analysis. Psychol Health Med; 2017;8506:0.

21. Hackett KL, Gotts ZM, Ellis J, Deary V, Rapley T, Ng W, et al. An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature. Rheumatology. 2017;56(4):570–80.

22. Dassouki T, Benatti FB, Pinto AJ, Roschel H, Lima FR, Augusto K, et al. Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjögren's syndrome. Lupus. 2017;26(7):690–7.

23. Ng W-F, Miller A, Bowman JS, Price JE, Kitas GD, Pease C, et al. Physical activity but not sedentary activity is reduced in primary Sjögren's syndrome. Rheumatol Int. 2017;37(4):623–31.

24. Strömbeck B, Ekdahl C, Manthorpe R, Jacobsson LTH. Physical capacity in women with primary Sjögren's syndrome: a controlled study. Arthritis Rheum. 2003;49(5):681–8.

25. Miyamoto S, Altoé R, Carletti L, Perez A, Sauer D, Dias L, et al. Oxygen Uptake, Fatigue and Quality of Life in Primary Sjögren's Syndrome (Abstract). Scand J Rheumatol. 2015;81:366–7.

26. Wouters EJM, van Leeuwen N, Bossema ER, Kruize A a, Bootsma H, Bijlsma JWJ, et al. Physical activity and physical activity cognitions are potential factors maintaining fatigue in patients with primary Sjogren's syndrome. Ann Rheum Dis. 2012 71(5):668–73.

27. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Ann Rheum Dis. 2011;70(6):968–72.

28. Ng W-F, Bowman SJ. Primary Sjogren's syndrome: too dry and too tired. Rheumatology. 2010;49(5):844–53.

29. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002 61(6):554–8.

30. ABEP - Associação Brasileira de Empresas de Pesquisa. Critério de Classificação Econômica Brasil. 2008. Available from: www.abep.org

31. Keyser RE, Rus V, Mikdashi JA, Handwerger BS. Exploratory study on oxygen consumption on-kinetics during treadmill walking in women with systemic lupus erythematosus. Arch Phys Med Rehabil. 2010;91(9):1402–9.

32. Keyser RE, Rus V, Cade WT, Kalappa N, Flores RH, Handwerger BS. Evidence for Aerobic Insufficiency in Women With Systemic Lupus Erythematosus. 2003;49(1):16–22.

33. Valim V, Oliveira LM, Suda AL, Silva LE, Faro M, Neto TLB, et al. Peak oxygen uptake and ventilatory anaerobic threshold in fibromyalgia. J Rheumatol. 2002 Feb;29(2):353–7. A

34. Lemos MCD, Valim V, Zandonade E, Natour J. Intensity level for exercise training in fibromyalgia by using mathematical models. BMC Musculoskelet Disord. 2010;11:54.

35. Gaudreault N, Boulay P. Cardiorespiratory fitness among adults with fibromyalgia. Breathe. European Respiratory Society; 2018;14(2):e25–33.

36. Fairshter RD, Walters J, Salness K, Fox M, Minh VD, Wilson AF. A comparison of incremental exercise tests during cycle and treadmill ergometry. Med Sci Sports Exerc. 1983 J;15(6):549–54.

37. Glass S GB. ACSM's Metabolic Calculations Handbook. Baltimore: Lippincott Williams & Wilkins; 2007.

38. Hall C, Figueroa A, Fernhall B, Kanaley JA. Energy expenditure of walking and running: comparison with prediction equations. Med Sci Sports Exerc. 2004 D;36(12):2128–34.

39. Serrano É V., Valim V, Miyamoto ST, Giovelli RA, Paganotti MA, Cadê NV. Transcultural adaptation of the "EULAR sjögren's syndrome disease activity index (ESSDAI)" into Brazilian Portuguese. Rev Bras Reumatol. 2013;53(6).

40. Webster, K., Odom, L., Peterman, A., Lent, L., & Cella D. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: Validation of version 4 of the core questionnaire. Qual Life Res. 1999;8(7):604.

41. Paganotti MA, Valim V, Serrano EV, Miyamoto ST, Giovelli RA, Ferreira Silva Santos MCL. Validation and psychometric properties of the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) into Brazilian Portuguese. Rev Bras Reumatol. 2015;55(5).

42. Gorenstein C, Andrade L. Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. Brazilian J Med Biol Res. 1996;29(4):453–7.

43. Ciconelli, Rozana Mesquita; Ferraz, Marcos Bosi; Santos, Wilton; Meinão, Ivone; Quaresma MR. Brazilian-Portuguese version of the SF-36 questionnaire: A reliable and valid quality of life outcome measure. Revista Brasileira de Reumatologia. 1999;39:143–50.

44. Jacobsson LTH, Stro B. The role of exercise in the rehabilitation of patients with systemic lupus erythematosus and patients with primary Sögren's syndrome. Curr Opin Rheumatol. 2007;19(2):197–203.

45. Valim V, Oliveira L, Suda A, Silva L, de Assis M, Barros Neto T, et al. Aerobic fitness effects in fibromyalgia. J Rheumatol 2003;30(5):1060–9.

46. Assis MR, Silva LE, Alves AMB, Pessanha AP, Valim V, Feldman D, et al. A randomized controlled trial of deep water running: clinical effectiveness of aquatic exercise to treat fibromyalgia. Arthritis Rheum. 2006;55(1):57–65.

47. American College of Sports Medicine. Principles of exercise prescription. ACMS's guidelines for exercise testing and prescription. 6th ed. Wilkins LW&, editor. 2000. 91-108 p.

48. Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, et al. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2014;74.

49. Seror R, Bootsma H, Saraux A, Bowman SJ, Theander E, Brun JG, et al. Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis. 2014;75(2):382–9.

50. Dey S, Singh RH, Dey PK. Exercise training: Significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol Behav. 1992;52(6):1095–9.

51. Hackett KL, Newton JL, Frith J, Elliott C, Lendrem D, Foggo H, et al. Impaired functional status in primary Sjögren's syndrome. Arthritis Care Res. 2012;64(11):1760–4.