Physical exercise in the control of pain or fatigue associated with viral infections: systematic review

Exercícios físicos no controle de dor ou fadiga associadas às infecções virais: revisão sistemática

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DOI 10.5935/2595-0118.20220048-en

ABSTRACT

BACKGROUND AND OBJECTIVES: Individuals after viral infections remain with persistent symptoms such as pain and fatigue. Physical exercises have been described as a promising alternative for the control of these symptoms, but there are no systematic reviews that verify the effectiveness of this therapy and that assess the quality of these studies. The aim of this study was to investigate the effect of physical exercise on pain or fatigue associated with viral infections.

METHODS: Systematic review registered with PROSPERO (CRD42021265174). Data collection was carried out between July 2021 and January 2022. Randomized clinical trials that addressed the practice of exercises, in individuals over 18 years of age, diagnosed with viral infection associated with the presence of pain or fatigue for more than 3 months were included. The search was carried out in the Pubmed, EMBASE, LILACS and Scielo databases, and the paired selection was carried out in the software (rayyan.ai); risk of bias analysis was assessed using the Cochrane risk-of-bias tool for randomized trials 2; certainty of evidence through GRADE; and for the construction of the meta-analysis, the Review Manager software.

RESULTS: Eleven clinical trials were selected in populations with acquired immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), chikungunya and poliomyelitis. For both pain and fatigue, the combination of aerobic exercise with resistance training, lasting 40 to 60 minutes, two to three times a week, was effective and safe. The methodological quality of the studies showed a high risk of bias in six studies due to the following domains: bias due to deviations from the intended interventions, bias due to lack of outcome data and bias in the selection of the reported outcome; rated as some concerns in one study due to the domain bias due to deviations from intended interventions; and the others were assessed as low risk of bias. The meta-analysis showed a result in favor of the intervention group on pain intensity in the studies for Chikungunya and in a study for HTLV, which points to a positive effect in favor of the active groups.

CONCLUSION: Exercises for the treatment of fatigue have very low evidence, while resistance exercises have moderate evidence for pain outcome. These are low-risk, low-cost resources with promising effects that should be better tested in people after viral infections.

Keywords: Pain, Physical exercise, Fatigue, Viral infections.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Indivíduos após infecções virais permanecem com sintomas persistentes, como a dor e a fadiga. Exercícios físicos têm sido descritos como alternativa promissora para o controle desses sintomas, porém não há revisões sistemáticas que verifiquem a eficácia dessa terapêutica e que avaliem a qualidade destes estudos. O objetivo deste estudo foi investigar o efeito de exercícios físicos na dor ou fadiga associados a infecções virais.

MÉTODOS: Revisão sistemática registrada na PROSPERO (CRD42021265174). A coleta de dados foi realizada entre julho de 2021 a janeiro de 2022. Foram incluídos ensaios clínicos randomizados que abordaram a prática de exercícios, em indivíduos com idade superior a 18 anos, com diagnóstico de infecção viral associada à presença de dor ou fadiga por mais de três meses. A busca foi realizada nas bases de dados Pubmed, EMBASE, LILACS e Scielo e, a seleção por pares foi realizada no *software* (rayyan.ai); a análise de risco de viés foi avaliada através da ferramenta *Cochrane risk-of-bias tool for randomized trials 2*; a certeza da evidência por meio da GRADE; e para a construção da meta-análise, o software *Review Manager*.

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Submitted on July 8, 2022.
Accepted for publication on September 23, 2022.
Conflict of interests: none – Sponsoring sources: The project has financial support from Higher Education Personnel Improvement Coordination (CAPES), with a master's scholarship at the BAHIANA - School of Medicine and Public Health.

HIGHLIGHTS

- Aerobic training combined with resistance training shows promising results for reducing pain and fatigue in this population after viral infection.
- Pilates is a method that significantly reduces pain intensity after HTLV-1 and Chikungunya infections.
- Exercise can benefit people with persistent pain and fatigue symptoms after viral infections.

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RESULTADOS: Foram selecionados 11 ensaios clínicos nas populações com Vírus da Imunodeficiência Adquirida (HIV), Virus Linfotrópico da Célula T Humana (HTLV), Chikungunya e Poliomielite. Tanto para dor como para a fadiga, a conjunção de exercícios aeróbicos com treino resistido, com duração de 40 a 60 minutos, de duas a três vezes por semana, foram eficazes e seguros. A qualidade metodológica dos estudos demonstrou em seis estudos alto risco de viés, devido aos domínios: viés devido a desvios das intervenções pretendidas, viés devido à falta de dados de resultado e viés na seleção do resultado relatado; classificado como algumas preocupações em um estudo devido o domínio viés devido a desvios das intervenções pretendidas; e os demais foram avaliados como baixo risco de viés. Na meta-análise foi demonstrado resultado a favor do grupo intervenção sobre a intensidade da dor nos estudos para Chikungunya e em um estudo para HTLV, o que aponta para efeito positivo a favor dos grupos ativos.
CONCLUSÃO: Os exercícios físicos no tratamento da fadiga apresentam evidências muito baixas, enquanto para o desfecho dor os exercícios resistidos apresentam moderada evidência. São recursos de baixo risco e custo, com efeitos promissores, que devem ser melhor testados em pessoas após infecções virais.
Descritores: Dor, Exercício físico, Fadiga, Infecções Virais.

INTRODUCTION

At different times in human history, viral infections, whether by emerging or re-emerging viruses, have caused high rates of morbidity and mortality worldwide[1]. Newly emerged infectious agents initially brought an alert to local communities that spread across countries and continents, often becoming pandemics, as what happened with the Human Immunodeficiency Virus (HIV) and the Coronavirus[2,3-5]. Even with the efforts of different segments of contemporary society, there are still cases of these infections in several countries and, even in countries with a controlled situation, many individuals remain with sequelae to be faced after the active period of infection[6,7].

Most infected individuals, whether by HIV, Human T-Cell Lymphotropic Virus Type-1 (HTLV-1), Chikungunya Virus (CHIKV), Poliovirus or Coronavirus, remain with one or more symptoms, among the most common: fatigue and pain[8-14]. This persistence can generate the loss of functionality with an impact on the performance of activities of daily living and on quality of life[15-18].

The practice of physical exercise as a therapeutic procedure has been proposed to improve these symptoms. Exercises benefit the functioning of the autonomic nervous system, promote the regeneration of the musculoskeletal and cardiopulmonary systems, improve emotional and cognitive states in the most diverse populations[19-21], bringing well-being and biopsychosocial health. In individuals after viral infections, such as HIV, exercises have been important in controlling fatigue, increasing functional capacity and quality of life[22], as well as post-COVID-19, they are recommended by specialists in order for the individual to be rehabilitated from persistent symptoms of the disease[23], but there are no systematic reviews that verify the effectiveness of this therapy in the population after viral infection and that evaluate the quality of these studies. The aim of this study was to investigate the effect of physical exercise on pain or fatigue associated with viral infections.

METHODS

This is a systematic review with methodological writing based on the recommendations described by the Preferred Reporting Items for Systematic Reviews and Meta - Analyses - PRISMA (2020). Data collection was carried out between July 2021 and February 2022. The protocol of this systematic review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO), registered with the following number: CRD42021265174.

Randomized clinical trials that addressed the practice of physical exercise in participants over 18 years of age with a diagnosis of viral infection associated with the presence of pain or fatigue for more than three months were included. Interventions not considered as physical exercises such as joint mobilization, manipulation and passive movement were excluded. Any multimodal interventions were excluded if the effect of exercise was not analyzed separately.

The search was performed in Pubmed, EMBASE, LILACS and Scielo databases. For the construction of the strategy, the PICOS methodology was used, with the descriptors referring to the population, the intervention, and the outcome, with their respective synonyms, which were obtained through active search and consultation on the MESH and DECs platforms. Subsequently, the search strategy was configured using the Boolean operators OR and AND, in order to create a search algorithm. The strategy was briefly configured as follows: ((Viral Infection) OR (Viral Disease) AND (Exercise) AND (Pain) OR (Fatigue)).

Studies were collected, identified and organized by two researchers using the Rayyan software (rayyan.ai), which evaluated the inclusion or exclusion of articles with analysis blinding. In the first stage, title and abstract were read with the objective of verifying the congruence with the eligibility criteria or if there was duplication; in the second, articles were read in full. In cases of disagreement between the two researchers regarding the eligibility of a study, a third evaluator performed a new evaluation. To assess the reliability of study selection, the Kappa concordance index was used.

The main outcome variables analyzed were intensity and impact of pain on the participant's life, assessed through scales or questionnaires; physical, psychological or social fatigue assessed with appropriate scales, questionnaires or tests. The articles found formed a flowchart, with the number of included and excluded in each step, as well as the reasons for exclusion. Those included were analyzed using a pre-defined collection form, which indicate the following information for each study: author/year, population/sample, intervention, comparator, primary outcome/measurement, results and conclusion.

Risk of bias analysis was performed using the Cochrane tool risk of bias tool for randomized trials 2 (Rob 2) for included randomized controlled trials. Structured in a set of domains, focusing on the design, conduct and reporting of the study; in each domain there are questions that address the risk of bias,

which generate a judgment algorithm based on responses such as "Low" or "High" risk of bias, or even "Some concerns".

The Review Manager 5.4 software (RevMan™, United Kingdom) was used to construct figures/graphs and analysis of the continuous outcome of pain intensity, which used the Visual Analog Scale (VAS) and the Brief Pain Inventory (BPI) as measures. The statistical method of the inverse of variance was used, with the model of random effects and the measure of the effect of the average difference. For that, mean and standard deviation values of the first evaluation after the intervention were used. In studies that presented this value in median and interquartile range[24,25], the research team asked authors for the mean and standard deviation values through the database or using the Hozo method[26]; which includes median, interquartile range, and sample size, validated for samples larger than 25[27]. In studies with three groups, these were divided so that each intervention group was compared to the control in isolation[24,27].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidence, which is very important as the usefulness of an estimate of the magnitude of the treatment effect depends directly on confidence in that estimate. Evidence is classified as high, moderate, low or very low quality, after verifying the factors that determine the reliability of the results. This assessment was performed by a consensus of two researchers.

RESULTS

In total, 296 studies were identified, of which 17 were duplicates. Therefore, 279 were selected for reading the title and abstract, but 262 were not congruent with the eligibility criteria. Therefore, 17 studies were selected for full reading, six of which were excluded for the following reasons: inadequate analyzed outcome[28-31], inadequate applied intervention[32] and lack of a comparative group[33]. Therefore, 11 studies were selected at the end, four of which had fatigue as an outcome[34-37] and seven, pain[24,25,27,38-41]. The total number of subjects who participated in the 11 included studies was 538, of which 222 were in the control group (Figure 1). The Kappa index was 0.76, which indicates a good level of agreement.

In four studies, the population consisted of individuals infected with the Human Immunodeficiency Virus (HIV), three with Human T-Cell Lymphotropic Virus (HTLV), two with Poliomyelitis Virus and two with Chikungunya Virus (Table 1). Among the 11 studies, seven addressed physical exercises compared to the control group, with pain assessed using the Visual Analogue Scale (VAS), Visual Numerical Scale (VNS) or Brief Pain Inventory (BPI). In these studies the interventions in general were aerobic exercise, resistance exercise or a combination of the two, or the Pilates method, which have as comparators: education in pain, usual care, clinical treatment or sedentary habits.

The authors[27] found that aerobic exercises performed for 20 minutes at an intensity of 40% of maximum heart rate in the first weeks and 60% in the others, combined with bilateral resistance exercises of the quadriceps, hamstrings, tibialis anterior and gastrocnemius muscles, with 40% of a repetition maximum (RM) in two sets of 10 repetitions with a 3-5 second rest interval, progressing to 60% of 1RM in three sets of 10 repetitions with 2-3 second rest, with a maximum heart rate of 40-65%, for 30 minutes, every other day, 3 times a week, for 12 weeks are effective and safe to reduce neuropathic pain in individuals after HIV infection. In a similar program of aerobic exercise and muscle strengthening combined with pain education[39], it was shown that both the combination of supervised exercises with educational programs, as well as the use of this last modality alone, is effective and viable in the treatment of pain in women with HIV.

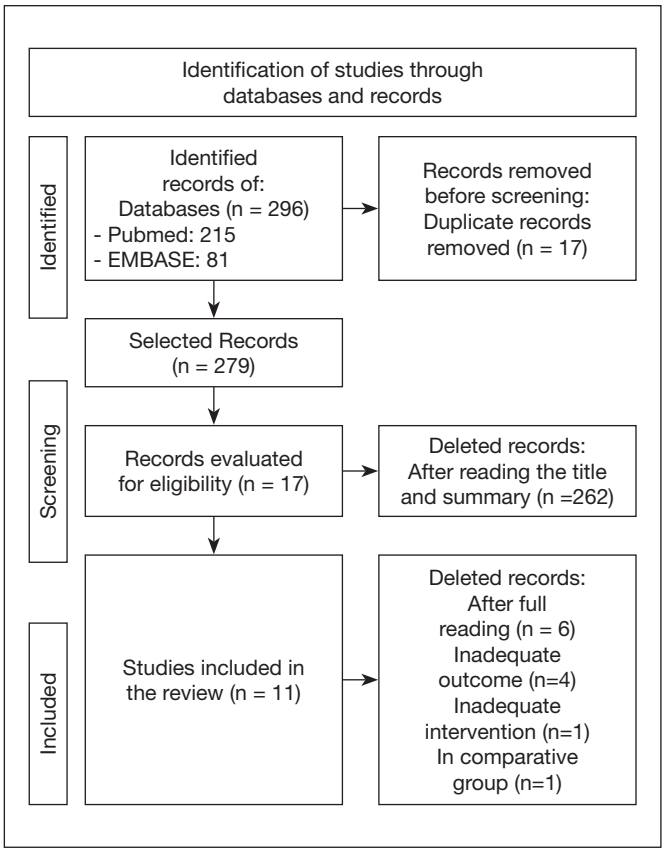

Figure 1. Study selection flowchart.

In a population of individuals after Chikungunya infection, it was observed that progressive resistance exercises performed with elastic bands involving the knee, ankle, shoulder, elbow and wrist joints; in two sets of eight repetitions, totaling eight per session, twice a week, for 50 minutes, for 12 weeks, significantly reduce pain intensity[41]. Still in this population, the Pilates method showed improvement of pain in the participants after 12 weeks of treatment, with two sessions per week of 50 minutes each, with light to moderate intensity, using a Swiss ball and elastic bands of medium intensity for strength exercises of the upper limbs, and strong intensity for stretching exercises for the muscles of the lower limbs[40].

This method in the population of individuals with HTLV-1, with exercises performed on the *Reformer* on one day of the week and on the *Cadillac* on the second weekly session, totaling

Table 1. Characteristics of the included studies

Authors	Population/ Sample	Intervention	Comparator	Primary Outcome/ Measurement	Main results	Conclusion
Smith et al.[34]	HIV/ n = 60 (8 women and 52 men)	Warm-up + aerobic (30") with 60-80% of max HR + relaxation. 3x/week, totaling 12 weeks	Usual activities	Fatigue: Time on the treadmill	Aerobic training had a significant effect on treadmill time (p: 0.01)	Supervised aerobic training safely decreases fatigue in HIV-1 infected individuals
Oncu, Durmaz and Karapolat[35]	Post-polio syndrome/ n= 28 (12 men and 16 women)	Flexibility + aerobic exercises (50-70% VO2 max., 13-15 on the Borg Scale). 3x/week, for 8 weeks and duration of 90 minutes per session	Exercises at home	Fatigue: FSS and FIS	Significant improvement in fatigue observed in the supervised exercise group compared to the home group, in the total FSS (p:0.002) and total FIS (p<0.001) scores	The physical exercise performed under supervision leads to more functional improvement in people later after polio than a similar program taught and conducted in home, unsupervised
Borges et al.[38]	HTLV-1/ n= 22 (16 women and 6 men)	Pilates method: 1 hour session, 2 times a week, totaling 30 sessions	Usual activities	Pain Intensity: VAS	There was a significant reduction in pain intensity after the protocol of Pilates exercises (p< 0.001)	Pilates proved to be a useful tool to reduce self-reported low back pain
Jaggers et al.[36]	HIV/ n= 49 (37 men and 12 women)	Aerobic (30" with 50-70% HR max.) + Resistance training (20"). 2 times a week/ for 6 weeks	Sedentary habits	Fatigue: POMS-30 – fatigue sub-scale	The exercise group compared to the control group showed a significant difference in the fatigue subscale (p<0.05)	Routine aerobic and resistance training at a moderate intensity may serve as a viable fatigue option
Koopman et al.[37]	Post polio syndrome/ n = 67 (30 men and 37 women)	Home aerobic training (60-70% of Fcmax, 28 to 38", 3 times a week) + Muscle strengthening and functional exercises, 1 hour, 1 time a week	Usual care and CBT	Fatigue: CIS20-F	There were no differences between the groups	Neither the exercise group nor CBT was superior to usual care in reducing fatigue or improving activities in severely fatigued post-polio syndrome patients
Parker Jelsma and Stein[39]	HIV/AIDS / n= 27 (all women)	Education program + aerobic exercise and muscle strengthening (20 minutes weekly for 16 weeks) + guided relaxation (2 hours total)	Education program	Pain Intensity: BPI	There were no significant differences between groups in the reduction of the PSS primary outcome at each time point between Week 0 and Week 16. There was no improvement in PIS during the 15 months of normal care between Baseline and Week 0, but the PSS reduced significantly for all participants between Week 0 and Week 4, Week 8, Week 12 and Week 16	Both supervised exercise and educational intervention or educational intervention alone appear to be a viable and effective method of treating pain in women living with HIV
Maharaj and Yakasai[27]	HIV/ n= 136 (79 women and 57 men)	AE= 20 minutes with 40 Fc max. in the first 6 weeks and 65% in the following PRE= 40% of 1 RM, 2 sets of 10 repetitions, 3-5 second interval; after 6 weeks 65% of 1 RM in 3 sets of 10 repetitions, 2-3 second interval. HR (40-65%) for 30 minutes, every other day, 3 times/week, for 12 week	HIV talks, video presentations and counseling	Pain Intensity: NRS	There were significant differences between the intervention and control groups (p<0.001)	Moderate-intensity aerobic and progressive resistance exercise is safe and effective for reducing neuropathic pain

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Table 1. Characteristics of the included studies – continuation

Authors	Population/ Sample	Intervention	Comparator	Primary Outcome/ Measurement	Main results	Conclusion
Macêdo et al.[24]	HTLV-1/ n= 49 (31 women and 18 men)	Stretching and muscle strengthening: 1 to 3 sets of 10 repetitions with a 1-minute interval between sets. 2 times a week/45-50 minutes	Exercise booklet-guided protocol and control group	Pain Intensity: BPI	There were no differences between the groups	The exercise protocol tested generated a small degree of pain relief, but did not affect aspects of pain reactions or quality of life
De Oliveira et al.[40]	Chikungunya/ n= 42 (39 women and 3 men)	Pilates: 12 weeks with 2 sessions/week, 50", light to moderate intensity	Clinical care	Pain Intensity: VAS	In the intragroup analysis, a significant improvement in pain intensity was observed after 24 Pilates sessions	Patients in the chronic phase of Chikungunya fever who participated in Pilates training have reduced pain, improved functional capacity and quality of life without the emergence of adverse effects
Patrício et al.[25]	HTLV-1/ n= 28 (9 men and 17 women)	GCT: Sensory-motor exercises applied through a virtual game coupled to Nintendo Wii® (20"/ 2 times a week, totaling 10)	CTG: protocol started after 10 weeks	Pain Intensity: BPI	There were no differences between the groups	Virtual game training did not improve pain intensity
Neumann et al.[41]	Chikungunya/ n= 31 (28 women and 3 men)	Progressive resistance exercises: 2 sets of 8 repetitions totaling eight exercises per session, 2 times/week, for 50"	Phone call about symptoms and drug use	Pain Intensity: VAS	Significant decrease in pain intensity after the intervention (p: 0.01)	Pain intensity is significantly reduced for patients in the chronic stage of Chikungunya who have performed progressive resistance exercises for 12 weeks

HR max = Maximum Heart Rate; VO2 max = maximum oxygen intake; FSS = Fatigue Severity Scale; FIS = Fatigue Impact Scale; VAS = Visual Analog Scale; POMS 30 = Profile of Mood States; CBT = Cognitive Behavioral Therapy; CIS20-F = Fatigue Severity Subscale = Checklist of Individual Strength; BPI = Brief Pain Inventory; AE = Aerobic; PRE = Resistance exercises; NRS = Numerical Rating Scale; GCT = Control Test Group.

30 sessions, is a useful tool to reduce self-reported low back pain[38]. Sensorimotor exercises applied through a virtual game coupled to a Nintendo Wii™ (Kyoto, Japan) video game did not improve pain intensity in this population[25] and may not be one of the best strategies for this purpose.

As for the fatigue outcome, it was evaluated in four studies by different instruments, such as: Fatigue Severity Scale (FSS); Fatigue Impact Scale (FIS); profile of Mood States (POMS-30) and Fatigue Severity Subscale; as well as time on the treadmill. In an HIV-infected population, aerobic training was performed for 30 minutes, at 60-80% of maximum heart rate, preceded by warm-up and followed by relaxation, three times a week for 12 weeks, safely reduced fatigue, measured by time on the treadmill[34]. In addition, aerobic training for 30 minutes was performed, with 50-70% maximum heart rate, twice a week for six weeks; followed by resistance training of upper limbs (chest, biceps brachii, deltoids and triceps) and lower limbs (quadriceps and hamstrings), a series of 12 repetitions for 20 minutes; totaling one hour of exercise, and it significantly reduced POMS-30 scores[36].

In people with post-polio syndrome, flexibility exercises (stretching the lumbar spine, cervical spine, upper and lower limbs) combined with aerobic training have also been shown to be beneficial in improving fatigue, both supervised and at home[35]. Also in this population, home aerobic training was tested using a cycle ergometer, combined with muscle strengthening and individually adapted functional exercises, compared to Cognitive Behavioral Therapy (CBT) and usual care; however, there was no significant difference between groups in reducing fatigue or improving activities in severely fatigued post-polio syndrome patients[37].

Studies that met the inclusion criteria were evaluated according to five Rob 2 domains: bias in the randomization process, deviations from intended interventions due to missing outcome data, outcome measurement, and selection of reported outcomes. Studies presented a high risk of bias in totality, in which the bias of the intended interventions was the one with the highest percentage, followed by missing outcome data and the selection of reported results (Figure 2). At the end, four articles showed a low risk of bias in all domains[25,27,40,41], one study clas-

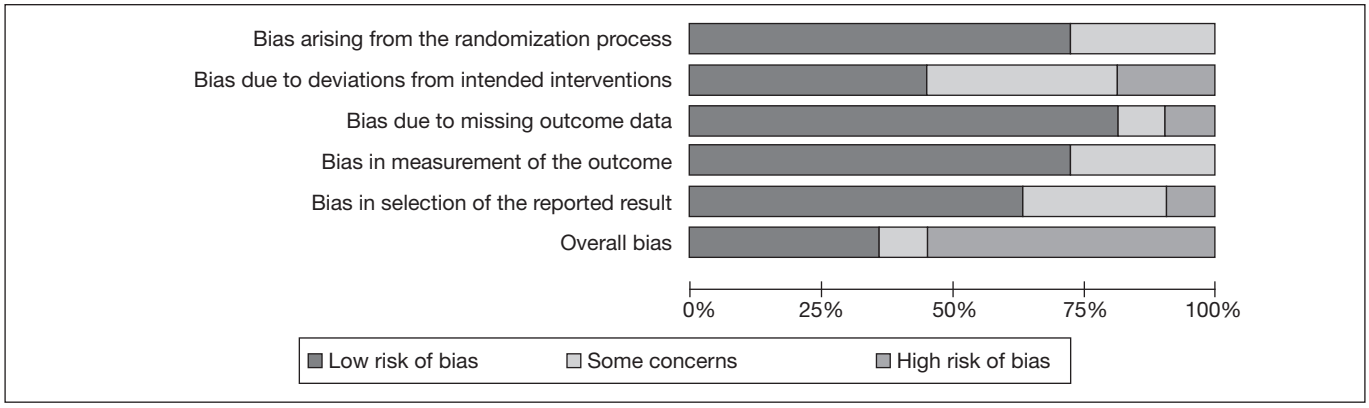

Figure 2. Methodological quality chart: analysis of the authors' judgment on each study presented as a percentage.

	Bias due to missing outcome data	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias in selection of the reported result	Bias in measurement of the outcome	Overall bias
Borges et al.[38]	+	?	+	+	+	?
Jaggers et al.[36]	?	−	−	?	?	−
Koopmanet al.[37]	+	?	+	+	−	−
Macêdo et al.[24]	?	+	+	?	+	−
Maharaj and Yakasai[27]	+	+	+	+	+	+
Neumann et al.[41]	+	+	+	+	+	+
de Oliveira et al.[40]	+	+	+	+	+	+
Oncu, Durmaz and Karapolat[35]	+	?	+	+	?	−
Parker, Jelsma and Stein[39]	+	?	+	+	?	−
Patrício et al.[25]	+	+	+	+	+	+
Smith et al.[34]	?	−	?	?	+	−

Figure 3. Summary of methodological quality: assessment of authors' judgments on each domain for included studies.

sified it as "some concerns"[38] and the others reported high risk of bias (Figure 3).

Eight studies with adequate randomization methods were identified, which made clear how the process took place. However, three articles[24,34,36], showed some concerns in this domain, either due to lack of information or inadequate methods for randomization. Five articles that contemplated the intended interventions were analyzed, while four presented items to be questioned by blinding, in which some of the interventions applied, notably, was not possible to be performed. However, two studies suggested high risk[34,36], as both the participants and the evaluators were aware of the conduct used, in addition to the fact that it was not related to the context of the study.

Among the 11 studies, one was classified as high risk[36] in the domain "Bias due to missing outcome data", as it did not understand all the information from the participants' data, and another with "some concerns" [34] due to the loss of these data that could probably depend on the true values. Within the domain "Bias in outcome measurement", most studies responded positively regarding the instruments used to assess the outcome. However, in three articles, the evaluators were probably aware of the intervention received by the participants, which may have evidenced biases during the evaluation. One article showed multiple comparisons, both in measurements and in data analysis, and there was not enough information for this assessment, raising some concerns such as domain judgment[35,36,39].

At the end of the bias analysis using the Rob 2 tool, six articles were classified as high risk, one with "some concerns" and four articles were judged as low risk, as all domains were judged with this algorithm.

For the pain intensity outcome, it was possible to include 7 studies for this meta-analysis that evaluated the effect of physical exercise in individuals with chronic pain after viral infections, with a total of 395 participants[24,25,27,38-41]. Overall, there was no significant difference between the groups, despite the trend in favor of the intervention; in the HIV and HTLV subgroups there was no difference; and in the Chikungunya subgroup both studies were positive, demonstrating significant pain reduction[40,41]. Regarding the general analysis of heterogeneity, this was substantial among the analyzed studies (I^2: 68%), mainly in the HTLV subgroup (I^2: 71%) (Figure 4).

According to the GRADE system, studies with the fatigue outcome were classified as very low evidence both with the intervention of aerobic exercise and when resistance training was performed. For the pain outcome, aerobic exercise or it combined with resistance training were found to be of low evidence, as is the control exercise performed with the virtual reality method. However, resistance training showed moderate evidence for pain control after viral infections (Table 2).

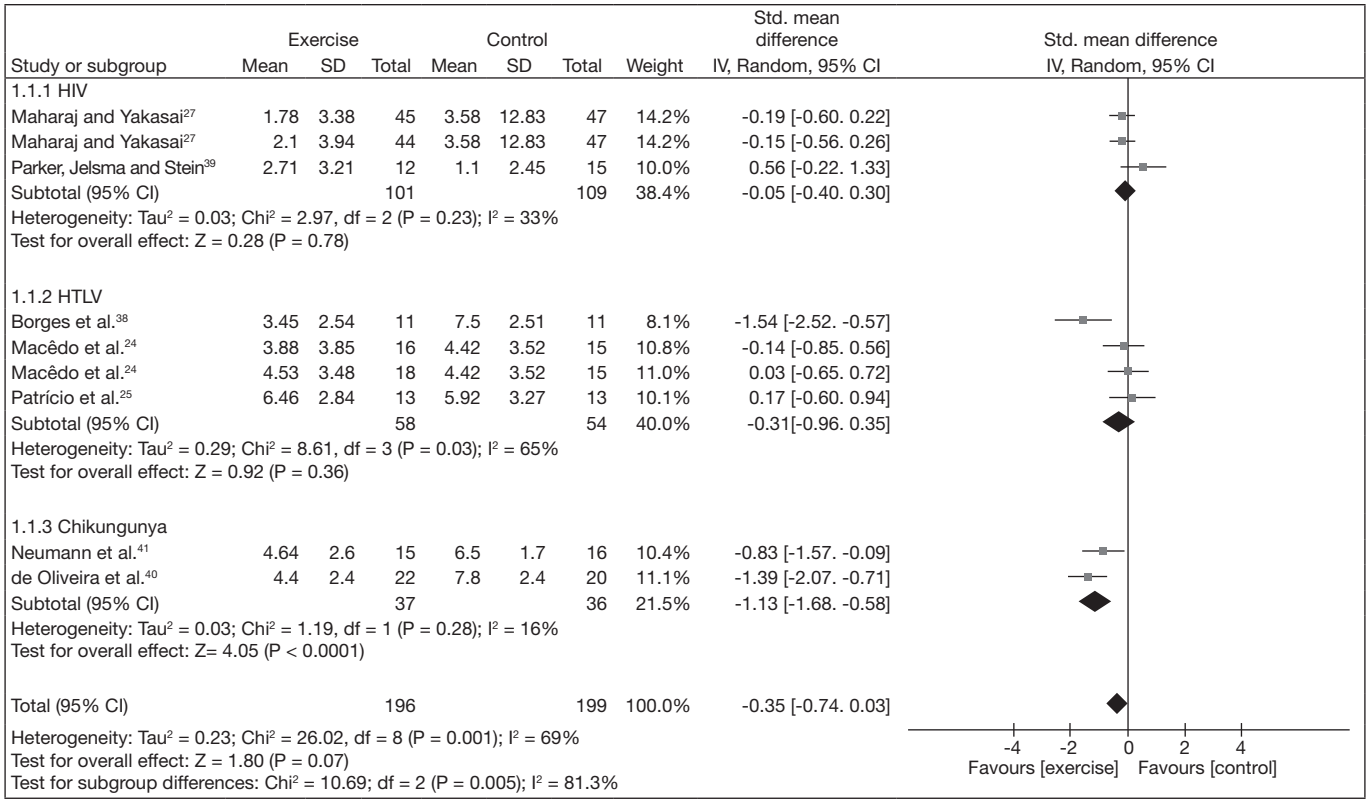

Figure 4. Forest-plot comparing the effect of physical exercises with a control group.

SD = standard deviation; CI = confidence interval

Table 2. Quality of exercise evidence for pain and fatigue after viral infections

	Summary of findings					Summary of findings
Nº of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty of evidence	Summary of findings
Fatigue 2 RCT Aerobic exercise group: n= 34 Control group n = 43	Serious[a]	Serious[b]	Not serious	Very serious[c]	⊕◯◯◯ VERY LOW	There is very low quality of evidence that aerobic exercise is effective in controlling fatigue after viral infection.
Fatigue 2 RCT Resistance exercise group: n = 46 Control group n = 42	Serious[a]	Serious[b]	Not serious	Very serious[c]	⊕◯◯◯ VERY LOW	There is very low quality of evidence that resistance exercise is effective in controlling fatigue after viral infection.
Pain 1 RCT Aerobic exercise group: n = 12 Control group n = 15	Serious[a]	Serious[b]	Not serious	Serious[c]	⊕⊕◯◯ LOW	There is low quality of evidence the aerobic exercise is effective in controlling pain after viral infection.
Pain 4 RCT Resistance exercise group: n = 82 Control group n = 61	Not serious	Serious[b]	Not serious	Serious[c]	⊕⊕⊕◯ MODERATE	There is moderate quality of evidence the resistance exercise is effective in controlling pain after viral infection.

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Table 2. Quality of exercise evidence for pain and fatigue after viral infections – continuation

Nº of participants (studies)	Summary of findings: Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty of evidence	Summary of findings: Summary of findings
Pain 1 RCT Aerobic + resistance exercise group: n = 89 Control group n = 47	Not serious	Serious[b]	Not serious	Serious[c]	⊕⊕◯◯ LOW	There is low quality of evidence the aerobic and resistance exercise is effective in controlling pain after viral infection.
Pain 1 RCT Exercise of control group: n = 13 Control group n = 13	Not serious	Serious[b]	Not serious	Serious[c]	⊕⊕◯◯ LOW	There is low-quality evidence that exercise control by the virtual reality method is effective in controlling pain after viral infection.

RTC = Randomized Clinical Trial
a. Study evaluated at high risk of bias in a domain of Rob2.
b. Without statistic difference between groups
c. Small sample size
⊕⊕◯◯ represents the classification obtained in the evaluated categories (risk of bias, inconsistency, indirectness, imprecision).

DISCUSSION

To the authors' knowledge, this was the first systematic review that sought to investigate the effect of exercise on pain or fatigue after viral infections. It was possible to reveal that progressive resistance exercises combined with aerobic training promote a decrease in the intensity of pain and fatigue. Through meta-analysis, it was shown that progressive resistance exercises are effective in reducing pain intensity in the population after Chikungunya[41] and the Pilates method is effective for pain control in the post-HTLV population (38) and Chikungunya[40]. For fatigue, however, it was not possible to perform a meta-analysis, due to the heterogeneity of the evaluated outcomes, although in each of the four selected clinical trials, the individual results are favorable to the exercise group.

Regarding the outcome of pain intensity, substantial heterogeneity was observed between studies. The samples are small and the protocols applied are very diverse, which may explain this phenomenon. In the risk of bias analysis, flaws are observed mainly in the domains related to the tested interventions, selection of reported outcomes and missing data in the applied methodology. The only population in which the metanalysis showed statistically significant results was that of Chikungunya, with a large effect size and low heterogeneity between the two included clinical trials. Strength and resistance exercise programs have demonstrated similar effects involving adults with chronic low back pain[42]. Therefore, the findings confirm that pain processing is modified through exercises, reducing the perception of intensity.

The Pilates method was applied both to the population with Chikungunya and to a group of people with HTLV-1. The results of both studies report high efficacy in reducing pain, with the largest effect sizes observed in the present meta-analysis[38,40]. The sessions were held twice a week, with exercises involving coordination, flexibility, control, strength and balance, performed in the rhythm of diaphragmatic breathing, respecting the principles of the method. The protocols used both the ground modality and exercises performed on equipment with springs, typical of the method.

A Pilates protocol was also compared to usual care and pharmacological treatment and showed significant improvement in chronic low back pain in adults without associated viruses. However, in this same study, when comparing Pilates with other types of exercises, a lower effectiveness was observed in the reduction of pain in the short term[43]. Therefore, even though clinical trials demonstrate the effectiveness of the Pilates method, it is not possible to claim superiority over other forms of exercise[44]. For this reason, more therapeutic exercise modalities should be tested for the treatment of pain associated with viruses, and a recommendation based on levels of evidence for their modality is not possible.

For the fatigue outcome, the high level of heterogeneity between studies made it impossible to carry out a meta-analysis. Fatigue, measured by time on the treadmill in minutes in HIV-infected people, was safely reduced after 12 weeks of aerobic training performed at 60-80% of maximum heart rate[34]. In a meta-analysis involving seven randomized controlled trials of subjects with chronic fatigue syndrome, compared to controls, the effect was relevant in aerobic exercise such as walking, swimming, cycling or dancing. The control groups of the aforementioned meta-analysis used, among others, were usual care, Cognitive-Behavioral Therapy (CBT) and pharmacological treatment; in which there was a significant reduction in fatigue after treatment with aerobic exercises[45]. In the present study, the outcomes were measured using different scales, and it was not possible to present conclusive data. However, this exercise modality seems to be promising in the treatment of chronic fatigue and, therefore, a greater number of clinical trials need to complement its evaluation.

Aerobic training combined with flexibility exercises was compared to home exercises guided by a booklet in the population

with post-polio syndrome. It was found that both possibilities improved fatigue after a regular exercise program[35]. In the same population, aerobic training was used combined with muscle strengthening and functional exercises. Compared to usual care, exercises were not superior to the control group in reducing fatigue in severely fatigued patients[37].

Similar to the post-polio syndrome, in the HIV population, the comparison of aerobic exercise with muscle strengthening of the upper limbs did not show efficacy[36]. A study that evaluated aerobic training on fatigue in people with multiple sclerosis found a small positive effect after the intervention, not leading to clinically significant improvements[46]. Another study showed that fatigue significantly decreased in subjects with cancer who performed exercise compared to the control group. The authors believe that the results may be due to the reduction of inflammation, gain in muscle mass or strength, improvement in functional capacity and mental health[47].

The present findings point to a greater effectiveness in the combination of aerobic and resistance exercises, mainly because patients after viral infection usually present both symptoms. It is worth mentioning that the neurofunctional differences in each of the populations in which the protocols were tested may justify the divergences in the results, opening a question about the effectiveness of exercises in COVID-19 that should also be tested in specific clinical trials for this population.

COVID-19 is a viral infection that has left people with persistent symptoms, such as pain and fatigue, even after three months of remission[12,13]; common symptoms in viral infections in the studies included in this systematic review. A task force has been published by the European leaders Respiratory Society (ERS) and the American Thoracic Society (ATS), which reiterate the importance of physical activity in patients who have been hospitalized with COVID-19.

Low to moderate intensity exercises, essentially between the sixth and eighth weeks after discharge, with monitoring of peripheral oxygen saturation were recommended[48]. A post-COVID-19 rehabilitation program, based on the Expert Consensus, was tested in a preliminary study, resulting in reduced fatigue in these individuals. Aerobic exercises such as walking or treadmill were performed, followed by muscle strength training in upper and lower limbs and educational discussions. Fatigue was assessed by the Chronic Disease Therapy Fatigue Scale (FACIT) with statistically significant symptom reduction in participants[33]. As the literature for the post-viral infection population is scarce and very new for COVID-19, this study is relevant and may inspire studies in this population, provided that therapeutic exercise protocols are tested in randomized clinical trials.

The limitation of this study lies in the databases that do not cover many studies in Chinese, a population that must already have interesting studies on exercises to treat pain and fatigue even in COVID-19. As future perspectives, more randomized clinical trials should be performed in this population for a higher level of evidence of this clinical response of improvement in pain and fatigue after physical exercises.

CONCLUSION

It can be concluded that exercises for the treatment of fatigue show very low evidence, while resistance exercises showed moderate evidence for the pain outcome. Although the safety and efficacy of the protocols cannot be guaranteed due to the lack of data in the literature that guarantee a high level of evidence for their recommendation, resistance exercises should be tested in clinical trials involving this population. Exercises are low-risk, low-cost interventions that can be helpful in treating the large number of people who may be affected by these conditions.

ACKNOWLEDGMENTS

The project has financial support from the Higher Education Personnel Improvement Coordination (CAPES), with a master's scholarship at the BAHIANA - School of Medicine and Public Health.

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