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PHYSICAL EXERCISE, SYMPTOMS OF CHRONIC PAIN AND INFLAMMATORY MARKERS IN POSTMENOPAUSAL OBESE WOMEN

EXERCÍCIO FÍSICIO, SINTOMAS DE DOR CRÔNICA E MARCADORES INFLAMATÓRIOS EM MULHERES OBESAS PÓS-MENOPAUSA

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ABSTRACT - The aim of the study was to analyze the effect of 20 weeks of physical exercise on pain symptoms in obese postmenopausal women, as well as the relationship between pain symptoms and body composition and inflammatory markers. A clinical trial was carried out on 66 randomized women into an exercise group (EG = 33) and a control group without exercise (CG = 33). The physical exercise intervention lasted 20 weeks and was based on the recommendations of American College Sports and Medicine (ACSM). Nine regions of the body were considered to assess the presence and intensity of pain symptoms. The EG showed reductions in pain symptoms, both in the presence and in the intensity, for most of the anatomical regions analyzed. In addition, the EG showed reductions in waist circumference (WC), BMI, fat percentage and pro-inflammatory markers IL-6 and TNF-α, which demonstrate a significant correlation with the reduction of pain symptoms, with the exception of IL-6. Exercise program based on general ACSM recommendations has a significant effect on reducing pain symptoms in obese postmenopausal women. Although a reduction in IL-6 was observed in the EG, this pro-inflammatory marker did not show a significant correlation with the reduction in pain symptoms. However, reductions in WC, BMI, fat percentage, fasting blood glucose and TNF-α are related to the reduction of pain symptoms.

Keywords: Physical activity; Menopause; Pain; Obesity; Cytokines.

RESUMO - O objetivo do estudo foi analisar o efeito de 20 semanas de exercícios físicos sobre os sintomas de dor em mulheres obesas na pós-menopausa, bem como a relação entre os sintomas de dor e a composição corporal e marcadores inflamatórios. Um ensaio clínico foi realizado em 66 mulheres randomizadas em um grupo de exercício (GE = 33) e um grupo controle sem exercício (GC = 33). A intervenção de exercícios físicos durou 20 semanas e foi baseada nas recomendações do American College Sports and Medicine (ACSM). Nove regiões do corpo foram consideradas para avaliar a presença e intensidade dos sintomas álgicos. O GE apresentou redução dos

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sintomas dolorosos, tanto na presença quanto na intensidade, para a maioria das regiões anatômicas analisadas. Além disso, o GE apresentou reduções na circunferência da cintura (CC), IMC, percentual de gordura e marcadores pró-inflamatórios IL-6 e TNF-α, que demonstram correlação significativa com a redução dos sintomas de dor, com exceção da IL-6. O programa de exercícios baseado nas recomendações gerais do ACSM tem um efeito significativo na redução dos sintomas de dor em mulheres obesas na pós-menopausa. Embora tenha sido observada redução da IL-6 no GE, esse marcador pró-inflamatório não apresentou correlação significativa com a redução dos sintomas álgicos. No entanto, as reduções na CC, IMC, percentual de gordura, glicemia de jejum e TNF-α estão relacionadas à redução dos sintomas álgicos.

Palavras-chave: Atividade física; Menopausa; Dor; Obesidade; Citocinas.

INTRODUCTION

It is estimated that most medical consultations are related to pain symptoms (DA OLIVEIRA; FERNANDES; DAHER, 2014). Pain is considered by the International Association for the Study of Pain (IASP) as an unpleasant, sensitive and emotional experience, associated or not with real or potential damage to tissue injuries and related to individual memory, with the expectations and emotions of each person, which can be acute or chronic (DESANTANA et al., 2020).

Chronic pain is characterized when the symptom or set of symptoms remains beyond the physiological healing time or the symptoms remain for more than three months continuously, persistent or recurrent. Its cause is not always evident and can even be undefined (CARVALHO et al., 2018). Pain complaints are common in postmenopausal women, which can have significant effects on health-related quality of life (BRADEN et al., 2012).

The body weight gain that accompanies the climacteric period is accentuated in the post-menopausal years, having an additional effect on the decrease in functional fitness and vitality, in addition to being associated with a greater occurrence of bodily pain, especially in the lumbar spine, knees and ankles (ORSI et al., 2008). In addition, an increase in pro-inflammatory cytokines, such as IL-6 and TNF-α (NIMROUZI et al.,

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2020; ORÓSTICA et al., 2020), is observed in postmenopausal women, which has shown a possible relationship with increased chronic pain (MORRIS et al., 2020).

Pain treatment comprises a range of different intervention strategies, including surgery, drug therapy and non-medical interventions (PRUDENTE et al., 2020). Although physical exercise is widely recommended for the pain treatment, its effect is still contradictory, especially with regard to the use of general exercise programs described in the recommendations for healthy adults (BORISOVSKAYA; CHMELIK; KARNIK, 2020). However, the practice of supervised physical exercises has been suggested to minimize pain symptoms (GENEEN et al., 2017), as well as on the inflammatory state (CHAGAS et al., 2017).

Considering the repercussion that pain symptoms have on the population's health condition, this study aimed to analyze the effect of a physical exercise program, based on the recommendations for physical exercise by American College Sport and Medicine (CHODZKO-ZAJKO et al., 2009; GARBER et al., 2011), on the pain symptoms of obese women in the post-menopausal period, as well as the relationship between the variation in pain symptoms and the pro-inflammatory markers IL-6 and TNF-α.

METHOD

Population of Study and Casuistic

The study is characterized by a randomized controlled clinical trial and followed the recommendations of CONSORT (Consolidated Standards of Reporting Trials) (MOHER et al., 2010). This study was approved by the Research Ethics Committee of the University of Marília (protocol number 364/2011), by the Municipal Evaluation and Research Committee (COMAP) (process number 476/11-SS) and by the Brazilian Registry of Clinical Trials (REBEC) (case number RBR-8fdmb8).

The sample consisted of women using the Family Health Unit (USF) of the Unified Health System (SUS) who: reported pain symptoms in the last three months; age between 50 to 79 years; absence of menstruation for at least five years; percentage of body fat (% BF) ≥ 35% (diagnosis of obesity); having performed less than 150 minutes a week of moderate to vigorous exercise for the past 6 months; not being on

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hormone replacement therapy; and, not having physical limitations and medical restrictions to participate in the exercise intervention program.

From the USF database, 140 women were randomly selected to home visit and invited to participate in the research. Initially 82 met the inclusion criteria, however, after the initial interview, 16 women were excluded for having health problems that limit their ability to carry out the exercise program or the inability to participate in the assessment and intervention routines due to personal issues. At the end of the screening process and verification of the inclusion criteria, 66 women were selected and randomized into an intervention group with exercise (EG = 33) and a control group without exercise (CG = 33). Figure 1 shows the test flow diagram.

<insert figure 1>

Study Variables

To avoid bias in the results, data collection was performed by a single evaluator, who was unaware of the study group in which the evaluated was participating. Data on the presence of noncommunicable diseases and time without menstruation were obtained by a questionnaire structured for the purposes of the study. Information on the pattern of physical activity in the last six months was carried out through anamnesis.

Body composition was determined by Bioelectrical Impedance Analysis (BIA) method, to estimate the percentage of body fat. Fat percentage (FP) values ≥ 35% were interpreted as confirming the diagnosis of obesity (VAN DIJK et al., 2012). Body weight and height measurements were used to calculate the body mass index (BMI) and waist circumference (WC) to quantify abdominal obesity.

For the biochemical variables examination, the study participants were instructed to fast for at least 12 hours, not to practice physical activity in the previous 24 hours, and not to drink alcoholic beverages 72 hours before blood collection. Blood collection after the study period occurred seven days after the end of the intervention period. Biochemical assessments included fasting blood glucose (FBG), IL-6 and TNF-α. Cytokine levels were performed using an ELISA immunoenzymatic technique (BD Biosciences) with a detection limit of 2.0 pg / mL for TNF-α and 2.2 pg / mL for IL-6.

Pain symptoms were collected by interview considering nine regions of the body (neck (NE), shoulder (SH), wrist / hands (WH), upper back (UB), lower back (LB), elbow (EL), hip / thigh (HT), knee (KN) and ankle / foot (AF)). Chronic pain was

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confirmed by the presence of pain symptoms for more than three months (MONTEIRO; REIS-PINA, 2017). The register of the intensity of pain symptoms was carried out by visual analogue scale (VAS) (PINCUS; BERGMAN; YAZICI, 2009) considering the last seven days. For the analysis of pain symptoms, two situations were considered: i) Sum of pain points (SPP) considering nine anatomical regions (0 to 9); and ii) the sum of VAS (SVAS) (0 to 10 per region) reported for all anatomical regions evaluated, producing a score from 0 to 90 points.

Intervention program with physical exercise

The exercise program was carried out for 20 weeks, divided into three sessions / week of 75 minutes each, accumulating 225 minutes / week. The content of the training sessions was divided into four parts: i) initial, lasting 10 minutes (including blood pressure measurements and warm-up activities); ii) main 1, lasting 25 minutes of neuromuscular / strength and flexibility training; main 2, lasting 50 minutes of aerobic training performed with moderate intensity walking; and, iii) final, lasting 5 minutes, composed of relaxation activities. The exercise program followed the recommendations proposed by the ACSM (CHODZKO-ZAJKO et al., 2009; GARBER et al., 2011).

Neuromuscular training consisted of isometric and dynamic strength exercises and stretching. Aerobic training consisted of a 50-minute walk on a flat surface with an intensity of 50% to 60% of the heart rate reserve (% reserve HR) (12). The maximum heart rate (HRmax) was estimated by the equation for asymptomatic women between 35 and 85 years old (GULATI et al., 2010). For participants using beta-blocking medication, heart rate (HR) was adjusted according to the dosage and type of medication.

Statistical analysis

The effect size ($r = z\text{-score} / \sqrt{N}$) was calculated considering the sum of the VAS values for the nine anatomical regions (SVAS) of the EG between the pre and post-intervention moments, which indicates a large effect size ($r = 0.87$) and a study power of 92%. The results were organized in descriptive statistics, with the values of mean and standard deviation (SD) or by the distribution of relative frequency (%) and absolute (f). The distribution of normality was verified with the Kolmogorov-Smirnov test. To

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analyze the association between group and presence of morbidity, the Chi-square association test was performed. To analyze the variation in the distribution of the proportion of pain symptoms between the moments within each group, the McNemar test was performed. To analyze the effect of the intervention period, the delta value (Δ) was calculated considering the difference between the pre and post-intervention moments (Δ = post-pre). Student t test or Mann-Whitney non-parametric test was used to compare Δ values between groups. To analyze the effect of the intervention within each group, Wilcoxon's non-parametric test was performed. The effect (Δ) of the covariables (body composition and biochemistry) on the Δ of pain symptoms for SVAS was analyzed by Spearman's correlation test. SPSS software version 19.0 for Windows was used for all analyzes, with a significance level of 5%.

RESULTS

Initially, the sample showed a mean weekly exercise of moderate to vigorous intensity of 41 ± 58 minutes / week. No significant differences were observed between the groups regarding the distribution of morbidities, especially in relation to the presence of osteoarthritis (OST) (Table 1). There were no significant differences between groups for age (CG = 59.5 ± 6.8 versus EG = 61.8 ± 6.7 years) and time without menstruation (CG = 152.0 ± 18.2 versus EG = 163,6 ± 16.8 months).

<insert table 1>

When comparing the delta (Δ) variation of body composition and biochemistry between groups, significant differences were observed. The EG presented, in relation to the CG, reductions in the BMI, WC, FP, FBG, IL-6 and TNF-α (table 2).

<insert table 2>

Regarding the reports of pain symptoms by study group and anatomical region, the CG did not show significant variation in the proportion of pain symptoms between the pre and post-intervention moments. In the CG, the anatomical region with the highest prevalence of pain symptoms was the LB, WH, HT and KN region. In the EG, the anatomical region with the highest prevalence of pain was the region of NE, SH, WH and LB. After the intervention period, the EG showed a significant reduction in the proportion of patients who reported pain symptoms in the regions of NE, SH, UB, WH and LB (table 3).

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<insert table 3>

Regarding the intensity of pain symptoms measured by the visual analogue scale considering the last seven days, the EG showed a significant reduction for the anatomical regions of the NE, SH, UB, LB, HT, KN and AF, as well as for the sum of the points with the presence of pain symptoms considering the nine anatomical regions analyzed and for the sum of the visual analog scale considering the nine anatomical regions analyzed. The control group did not show significant variations in pain symptoms due to VAS or to the sum of the anatomical regions analyzed (table 4).

<insert table 4>

When analyzing the effect of the variables of the delta variation of the body composition and biochemical variables on the delta variation of SVAS, no significant correlation was found only for IL-6 (table 5). The increase in BMI, WC, FP, FBG and TNF-α are related to the increase in pain symptoms considering the sum of the VAS values for the nine anatomical regions investigated. However, the values of R2 indicate a small effect size.

<insert table 5>

DISCUSSION

The sedentary lifestyle has been shown to be associated with a higher prevalence and intensity of chronic pain (NIJS et al., 2019), especially in the elderly population. Considering that the sample of the present study was composed of women with a low profile of active or sedentary physical activity, the observed proportion of chronic pain symptoms has a frequency distribution similar to that of the previous study (DEDICAÇÃO et al., 2017), but with differences by anatomical region. The anatomical region with the highest prevalence of pain symptoms was the lumbar region, which has been identified as the region with the highest prevalence of pain symptoms in the elderly population (KANWAL et al., 2021).

The presence of comorbidities has also been associated with a higher prevalence and intensity of symptoms of chronic pain. Hypertension, which had a high prevalence in this study in both groups, has also been associated with a higher prevalence and intensity of pain symptoms (ID et al., 2020). The relationship between type 2 diabetes mellitus (T2DM) and pain in the elderly is still under investigation, but although pain

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symptoms are highly prevalent in the elderly with T2DM, this may be more strongly related to depressive symptoms, the number of comorbidities and neuropathy (KARJALAINEN et al., 2018).

The EG showed significant reductions in pain symptoms for the NE, SH, UB, WH and LB region. The significant reduction in BMI, WC and fat percentage in the EG, as well as the change in lifestyle with participation in the physical exercise program, are factors that may have contributed to the reduction of pain symptoms (GENEEN et al., 2017).

The reduction in the values of the pro-inflammatory markers IL-6 and TNF-α observed in the EG can also be related to the reduction of pain symptoms. However, it is not possible to determine the real cause and effect relationship between the reduction of the pro-inflammatory markers IL-6 and TNF-α and the reduction of pain symptoms (YAO et al., 2019; ZHOU et al., 2016).

However, there is evidence that the most severe pain symptoms are related to increases in IL-6. In the joint structure, the increase in IL-6 results in the development of chronic synovitis, fibroblast-like proliferation through signaling, promotion of angiogenesis and degradation of cartilage in the synovial. In muscle tissue, the chronic increase in IL-6 is associated with increased production of nuclear factor-κB activating receptor (RANKL) and activation of osteoclasts through signaling, leading to bone loss and osteoporosis (FAVALLI, 2020), which are associated to the symptomatology of pain.

TNF-α has been related to neuropathic pain, and possible mechanisms are most related to peripheral sensitization and central sensitization of the nervous system in response to nociceptive stimuli (LEUNG; CAHILL, 2010). In intervention study of diet and exercise in patients with knee osteoarthritis were observed reduction of pain symptoms which was associated with reduction of inflammation markers IL-6 and TNF-α (RUNHAAR et al., 2019).

In addition to the effect on improving body composition, fasting blood glucose and inflammatory markers (IL-6 and TNF-α), the moderate-intensity exercise program, combining aerobic and strength exercise, produced improvement in the pain symptoms in the EG, when compared to the control group (CG), for different anatomical regions.

Among the mechanisms that explain the analgesia associated with physical exercise are: psychological aspect (action and in the limbic dopamine system); Autonomic Nervous System (sympathetic / parasympathetic balance); Opioid System

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(release of endogenous opioids); diffuse nociceptive inhibitory control (indirectly by rebalancing the concentration of opioids, serotonin and noradrenaline); release of opioids stimulated by neuromotor fibers; and, increased fiber excitability threshold by increasing the release of opioids, β-endorphin and met-enkephalins) (GENEEN et al., 2017).

Despite the recommendations for physical exercise (CHODZKO-ZAJKO et al., 2009; GARBER et al., 2011) have the main focus on hemodynamic and metabolic changes, analyzing the effects of general physical exercise programs on the symptoms of pain is of great relevance in clinical practice. Especially in generalized exercise programs carried out in primary care in health units, whose main public is composed by women in the post-menopausal period, with overweight or obesity, who have a high prevalence of symptoms of chronic pain.

The physical exercise program based on the recommendations for the elderly had a clinically important effect in reducing pain symptoms after 24 weeks of intervention. Reductions in waist circumference, body mass index, fat percentage, fasting blood glucose, IL-6 and TNF-α in the group that performed the intervention with physical exercise, indicate an important effect in reducing obesity, metabolic control and reduction of the inflammatory state, which may be related to the reduction of pain symptoms and general health condition.

Conflict of interest

The authors declare there is no conflict of interest.

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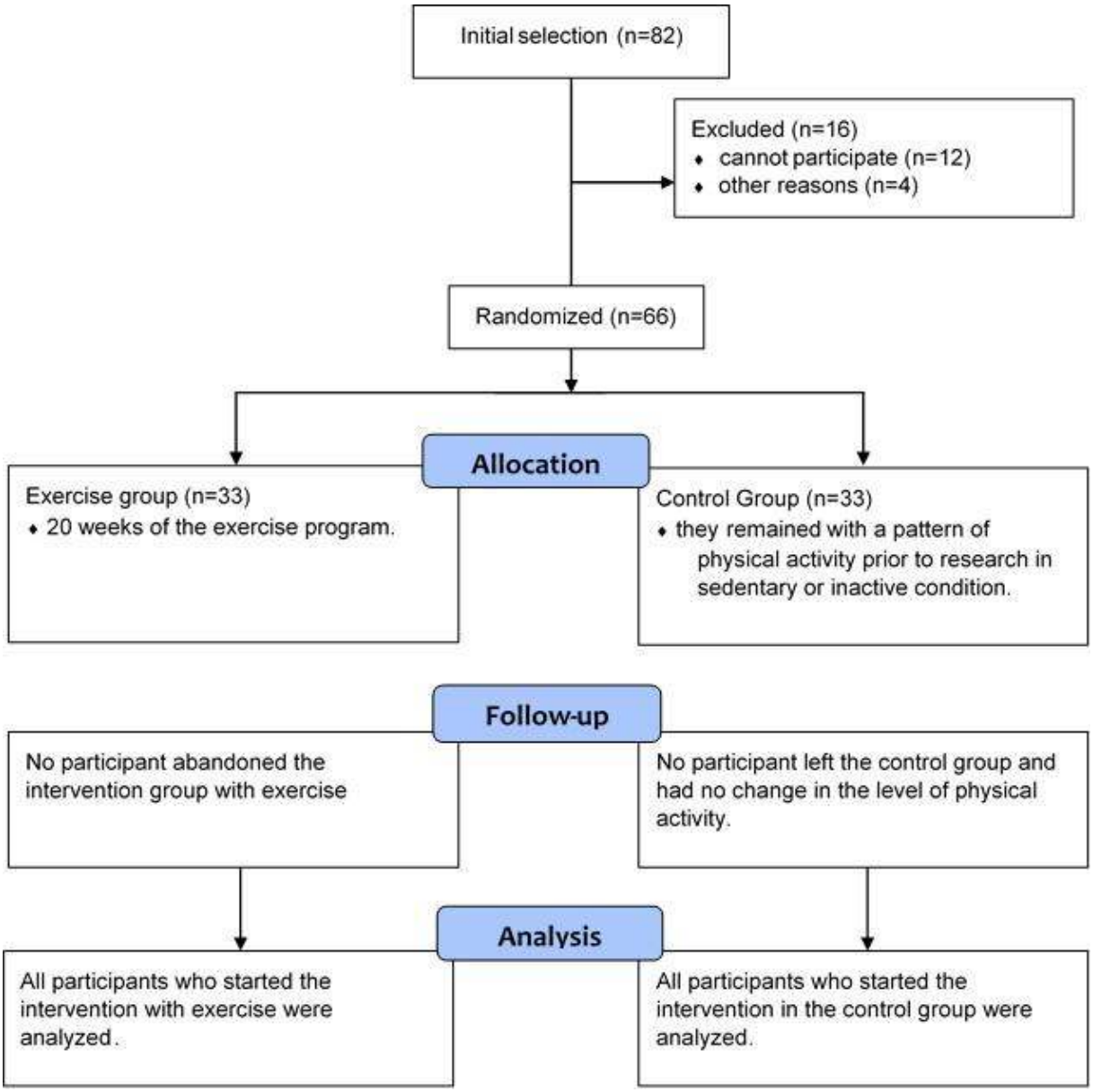


Figure 1: Flowchart tracking of volunteers.

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Table 1: Distribution of absolute and relative frequency of the presence of morbidities between the exercise (EG) and control (CG) groups.

	Group			
Morbidity	**CG (n=33)**	**EG (n=33)**	**Total (n=66)**	**p-value**
SAH	21 (63.6%)	24 (72.7%)	45 (68.2%)	0.431
T2DM	9 (27.3%)	6 (18.2%)	15 (22.7%)	0.382
DYS	17 (51.6%)	20 (60.6%)	37 (56.1%)	0.460
OST	17 (51.5%)	17 (51.5%)	34 (51.5%)	1

Note: p-value for association between group and morbidity by the Chi-square test. Systemic arterial hypertension (SAH). Type 2 Diabetes Mellitus (T2DM). Dyslipidemia (DYS). Osteoarthritis (OST).

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Table 2: Comparison of the mean and standard deviation (SD) of the delta variation (Δ) of the sample's quantitative variables in relation to the control (CG) and exercise (EG) groups between the pre and post-intervention moments.

	CG (n=33)						EG (n=33)						
	Pre		Post		Δ		Pre		Post		Δ		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-valor
BMI (kg/m)	33.5	6.2	33.8	6.4	0.28	1.41	30.0	3.7	29.3	3.8	-0.68	0.95	0.002*
WC (cm)	98.7	14.3	97.8	14.1	-0.89	5.95	93.0	10.2	88.7	10.0	-4.37	4.47	0.009*
FP (%)	55.0	5.0	56.9	5.5	1.88	2.24	54.4	2.9	53.2	3.4	-1.24	2.27	<0.001*
FBG (ml/dL)	97.2	18.6	114.2	24.1	16.97	17.96	95.5	16.2	93.8	13.3	-1.70	16.44	<0.001*
IL6 (pg/ml)	3.45	1.82	3.20	1.88	-0.25	1.12	4.77	3.35	2.71	0.97	-2.06	3.54	0.007*
TNF-α (pg/ml)	5.86	4.24	5.81	5.43	-0.05	3.96	8.21	5.42	4.61	3.47	-3.60	4.82	0.002*

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Note: * indicates a significant difference between the groups in relation to the values of Δ by Student's t test for p-value ≤0.05. Body mass index (BMI). Waist circumference (WC). Fat percentage (FP). Fasting blood glucose (FBG).

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Table 3: Distribution of the absolute (N) and relative (%) frequency of the presence of pain symptoms in the last three months in relation to the control (CG) and exercise (EG) groups between the pre and post-intervention moments for the anatomical regions neck (NE), shoulder (SH), upper back (UB), elbow (EL), wrist / hands (WH), lower back (LB), hip / thigh (HT), knee (KN) and ankle / foot (AF).

	CG (n=33)					EG (n=33)				
	Pre		Post			Pre		Post		
	N	%	N	%	p-valor	N	%	N	%	p-valor
NE	14	42.4	16	48.5	0.625	22	66.7	13	39.4	0.004*
SH	17	51.5	16	48.5	0.500	22	66.7	14	42.4	0.029*
UB	14	42.4	16	48.5	0.804	17	51.5	4	12.1	0.001*
EL	4	12.1	10	30.3	0.070	9	27.3	5	15.2	0.125
WH	20	60.6	14	42.4	0.146	26	78.8	12	36.4	<0.001*
LB	26	78.8	20	60.6	0.109	28	84.8	18	54.5	0.002*
HT	20	60.6	16	48.5	0.289	19	57.6	17	51.5	0.727
KN	20	60.6	20	60.6	1.000	18	54.5	14	42.4	0.289
AF	13	39.4	14	42.4	0.500	19	57.6	15	45.5	0.145

Note: * p-value ≤0.05 significant difference between the pre and post-intervention moments using the McNemar non-parametric test.

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Table 4: Comparison of the mean and standard deviation (SD) of pain symptoms by the Visual Analogue Scale (VAS) of the last seven days in relation to the control (CG) and exercise (EG) groups between the pre and post-intervention moments for the anatomical regions of the neck (NE), shoulder (SH), upper back (UB), elbow (EL), wrist / hands (WH), lower back (LB), hip / thigh (HT), knee (KN) and ankle / foot (AF).

	CG (n=33)					EG (n=33)				
	Pre		Post			Pre		Post		
	Mean	SD	Mean	SD	p-valor	Mean	SD	Mean	SD	p-valor
NE (VAS)	1.7	2.8	1.8	2.8	0.681	2.6	2.6	1.0	1.6	<0.001*
SH (VAS)	3.1	3.7	3.3	3.4	0.688	2.9	3.3	1.4	2.4	0.002*
UB (VAS)	2.1	3.0	2.8	3.2	0.242	2.7	3.0	0.4	1.3	<0.001*
EL (VAS)	0.7	2.0	1.5	2.6	0.058	1.6	3.1	1.1	2.8	0.181
WH (VAS)	2.6	2.9	1.9	2.5	0.250	4.6	3.4	1.8	2.9	<0.001*
LB (VAS)	4.5	3.2	3.6	3.4	0.096	5.1	3.2	2.1	2.5	<0.001*
HT (VAS)	3.7	3.8	3.3	3.7	0.613	3.7	3.8	2.0	2.9	0.003*
KN (VAS)	4.1	4.2	3.7	3.7	0.407	3.3	3.7	1.9	3.1	0.008*
AF (VAS)	2.1	3.1	2.6	3.6	0.517	3.6	3.8	1.9	2.7	0.002*
SPP	4.5	2.5	4.4	2.5	0.835	5.5	2.3	3.4	2.4	<0.001*
SVAS	24.5	18.7	24.6	18.1	0.872	30.1	21.0	13.7	14.5	<0.001*

Note: * p-value ≤0.05 significant difference between the pre and post-intervention moments by the Wilcoxon non-parametric test. APP sum of points with presence of

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pain considering the nine anatomical regions analyzed. Sum of pain points (SPP). Sum of the Visual Analog Scale (VAS) considering the nine anatomical regions analyzed. (SVAS).

Table 5: Analysis of the correlation between the delta (post-pre) of the sum of pain symptoms in the nine anatomical regions using the visual analogue scale (SVAS) with the delta (post-pre) of the variables of body composition, glycemia and pro-markers inflammatory (IL-6 and TNF-α) independent of the group.

Delta (post-pre) (Independent variable)	Delta (post-pre)		
	SVAS (Independent variable)		
	r	p-valor	R^2
BMI (kg/m^2)	0.311	0.010*	0.097
Waist circumference (cm)	0.302	0.013*	0.091
Fat percentage (%)	0.364	0.002*	0.132
FBG (mg/dL)	0.379	0.001*	0.144
IL-6 (pg/ml)	0.103	0.408	0.011
TNF-α (pg/ml)	0.248	0.044*	0.062

Note: correlation coefficient (r); * significant p-value ≤0.05 by Spearman's nonparametric test; R^2 (percentage of variation of the dependent variable explained by the variation of the independent variable). Sum of Visual Analog Scale (SVAS) considering the nine anatomical regions analyzed. Body mass index (BMI). Fasting blood glucose (FBG).

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