

Effects of functional training on pain and functional capacity in elderly women

Efeito do treinamento funcional na dor e capacidade funcional de mulheres idosas

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Abstract

Introduction: The growing rate of elderly people in the world can became a public health problem when they exhibit insufficient levels of physical activity, which can increase chronic pain and lead to functional disability. **Objective:** To analyze the effects of functional training on pain and functional capacity in elderly women. Methods: A non-randomized controlled clinical trial was conducted with 32 elderly women, divided into two groups: functional training (FT: n = 17) and control group (CG: n = 15). Functional capacity was analyzed using the Physical Fitness Test for the Elderly. Pain was assessed by reports of musculoskeletal discomfort symptoms and their characteristics using the Nordic Musculoskeletal Pain Questionnaire and pain visual analog scale (VAS). The functional training program was applied for 12 weeks at a frequency of three times a week. Results: Significant effects after the intervention in the FT group were observed, with pain reduction, increased flexibility and resistance for lower limbs, and cardiorespiratory capacity (p < 0.05). Conclusion: The functional training program in elderly women was effective in improving the variables of lower limb flexibility, pain perception, lower limb strength resistance and cardiorespiratory capacity.

Keywords: Aged. Circuit-based exercise. Pain. Physical fitness.

Resumo

Introdução: O crescimento da taxa de idosos no mundo pode tornar-se um problema de saúde pública quando estes exibem níveis insuficientes de atividade física, que têm o potencial de aumentar dores crônicas e causar incapacidade funcional. Objetivo: Analisar os efeitos do treinamento funcional na dor e capacidade funcional de mulheres idosas. Métodos: Desenvolveu-se um ensaio clínico controlado não randomizado com 32 idosas, divididas em dois grupos: treino funcional (TF: n = 17) e grupo controle (GC: n = 15). Como indicador da capacidade funcional foi utilizado o Teste de Aptidão Física para Idosos. A dor foi avaliada pelos relatos de sintomas de desconforto musculoesquelético e suas características por meio do Questionário Nórdico de Sintomas Osteomusculares de Dor e Escala visual Analógica de Dor (EVA). O programa de treinamento funcional foi aplicado por 12 semanas em uma frequên-cia de três vezes semanais. **Resultados:** Verificaramse efeitos significativos após a intervenção no grupo TF, com redução da dor e aumento da flexibilidade e resistência para membros inferiores e capacidade cardiorrespiratória (p < 0,05). Conclusão: O programa de treinamento funcional em idosas foi efetivo para a melhoria das variáveis de flexibilidade de membros inferiores, percepção de dor, resistência de força de membros inferiores e capacidade cardiorrespiratória.

Palavras-chave: Idoso. Exercícios em circuitos. Dor. Aptidão física.

Introduction

The aging of the world population can be a major public health problem when situations that make the aging process worse, such as lack of healthy eating, low social interaction and reduced physical activity, increasing the incidence of diseases and chronic pain, musculoskeletal disorders and functional disability.¹⁻³ These situations can contribute to decreased physical function and consequently increase expenses related to health, dependence and fragility of this population.⁴

In addition, there is a high prevalence of chronic pain in the elderly, due to the low ability to suppress pain and greater sensitivity to it when compared to younger people.⁵ It is not entirely clear in the literature whether this perception increases or decreases in old age, but it is known that physical inactivity and pain are major villains for the autonomy and functional capacity of this population.⁶The increase in pain associated with mobility restriction promotes a deterioration in the functional capacity of the elderly, often presenting a marked loss of strength and agility.⁷ This process can become a vicious cycle, in which the greater the pain, the lower the functional capacity. This cycle must be interrupted or even prevented through physical exercise.^{8,9}

Therefore, non-systematized physical activity and exercise improve quality of life, functionality, independence and psychological well-being, and reduce non-communicable chronic diseases and mortality for all elderly, fit or frail, and are more useful than pharmacological interventions. that target single systems to control fragility. When considering the accumulating evidence of the benefits of exercise in the elderly, it is unjustifiable not to prescribe physical exercise, and one of the main challenges is to integrate exercise programs as a mandatory part of the care of frail elderly patients in all hospitals, clinics and elderly care settings.¹⁰

In addition, falls are the main cause of hospitalization and fatal injuries among the elderly.⁴ Physical activity programs such as functional training (FT), which emphasize combinations of balance, strength, endurance, gait and physical function training, are shown to be more effective in reducing the risk of injuries and fractures related to falls in the elderly.⁴

For these reasons, FT has become a worldwide trend for this population, being a promising resource for improving functional capacity, decreasing pain perception and promoting physical fitness.^{11,12} Therefore, the objective of this study was to determine the effect of 12 weeks of FT on pain perception and functional capacity in elderly women.

Methods

This was a non-randomized controlled clinical trial, with elderly women who attended two parishes in the city of Ourinhos/SP in 2018. After approval by the Ethics Committee at Universidade do Sagrado Coração, Bauru, SP (number: 2,285,538), the project was submitted to the Brazilian Clinical Trials Registry platform (ReBEC registry: RBR-9kr2jb).

Sample

Elderly women were chosen by non-probabilistic sampling. Sample size was calculated using the G*Power 3.1.9.2 program. The values found in the study by Miranda et al.¹³ for strength endurance of the lower limbs (sit-to-stand test) were used as a parameter. For a test power of 0.95, effect size of 1.60 and alpha of 5%, a sample of 16 elderly women was suggested for each group: FT group and control group (CG). Considering a possible sample loss of 40%, 41 women were recruited (FT = 19; CG = 22).

As inclusion criteria, the volunteers had to be female, aged between 60 and 69 years old (meeting the criteria of the Senior Fitness Test - SFT), and present a medical referral for physical exercises and could not be practicing systematic physical activity in the last three months. The women excluded from the study were those with: loss of strength and aphasia caused by a previous cerebrovascular accident; impaired gait, using devices for ambulation (canes, crutches and wheelchair) and also using orthoses and orthopedic prostheses; more than three consecutive absences in the proposed protocol; and cognitive deficits such as problems with memory, attention, communication, impaired temporal and spatial orientations and difficulties in communication due to hearing and vision deficits.

To help with the exclusion criteria, the Mini Mental State Examination (MMSE) was applied, considering for participation: a score below 17 for the illiterate; 22 for elderly people with between one and four years of schooling; 24 for those with between five and eight years of schooling; 26 for those with nine or more years of schooling.^{14,15}

According to the inclusion and exclusion criteria, independent elderly women were selected for both groups, without the presence of functional disabilities or any chronic condition associated with greater vulnerability; that is, the elderly women were in good condition to carry out their activities, with adequate mental and motor health, which characterizes the condition of a robust elderly person.¹⁶

The division of the groups was made for convenience according to the availability to practice physical exercises. Thus, the CG was composed of elderly women who did not perform any type of training.

Procedures

The women were informed about the voluntary nature of their participation in the study, the possibility of quitting the study at any time and the right to confidentiality of the individual's data. Those who agreed to participate in the study signed an informed consent form.

Before the intervention, anamnesis questionnaires with sociodemographic information were administered to all the women in both groups, in the form of an interview by the same evaluators, who were previously trained for such procedures. In addition, functional capacity and pain variables were evaluated before and after the intervention for both groups.

Instruments

Characterization of subjects

Demographic aspects were assessed using closedended questions that included age (in complete years), marital status (married or in a consensual union, single, separated, widowed and did not respond), skin color (white, black, brown, yellow and indigenous). Socioeconomic aspects were investigated by schooling (in years of study) and income, defined based on the Brazil's Economic Classification Criteria (National Association of Research Companies) which estimate the purchasing power of urban people and families.¹⁷

Functional capacity

As an indicator of functional capacity, the battery of tests STF or Physical Fitness Test for the Elderly (TAFI) was used, proposed by Rikli and Jones¹⁸ for American elderly aged 60 to 94 years and validated in Brazil by Marzo et al.,¹⁹ for the elderly public from 60 to 69 years old.

Composed of six motor tests, the STF battery assesses the level of physical fitness, which represents the level of functional capacity of the elderly, in which each item has scores above average, average, below average and risk of loss of mobility.

STF assesses the level of strength endurance of the lower limbs through the "sit-to-stand" test, in which a chair without armrests is used, leaning against the wall, and the subject remains in a sitting position, standing up fully and sitting, as many times as possible in 30 seconds. For the strength endurance level of the upper limbs, the subject remains seated, with the arm of his choice in extension at their side, holding a 2-kg dumbbell, indicated for women. Soon after, the elbow is fully flexed and extended for 30 seconds.

To assess the level of flexibility of the lower limbs, the "sit-and-reach" test was used, which uses a chair for the subject to sit with one leg flexed and the other extended with the foot flexed. Next, with the spine erect, they are asked to flex the trunk, with the hands towards the feet, using a 45-cm ruler for measurement. Thus, the greater the distance reached with the tips of the middle fingers in relation to the feet, the greater the level of flexibility.

For upper limb flexibility, the literature,¹⁹ points to the use of the "behind-the-back reach" test, in which, the subject in the standing position, places the arm of his choice over the ipsilateral shoulder, bringing the hand towards the back. The other arm should be directed towards the back, with the hand towards the other positioned earlier. The measurement is similar to the lower limb test; that is, the greater the distance, the worse the level of flexibility is, and the greater the approximation, the better the level is.

To assess speed, agility and dynamic balance, the "sitting, walking 2.44 m and coming back and sitting" test was used. To do this, the subject sits on a chair and, upon verbal command, walks away quickly (without running) and walks the distance marked by a cone (2.44 m), goes around it, returning and sitting down again. The time for this route is marked with a stopwatch. To assess aerobic endurance, the "6-minute walking test" was used, marking a distance of 46 m, with a cone placed at every 4.57 m to facilitate the measurement of the distance covered quickly, but without running, for six minutes. Physical fitness tests in the elderly show a direct integration with everyday tasks, where the worse the physical fitness, the greater the degree of dependence of the elderly to perform activities of daily living.²⁰

Pain

Pain was analyzed by reports of musculoskeletal discomfort symptoms and their characteristics (frequency, duration and severity) using the Nordic Musculoskeletal Pain Questionnaire²¹ eand the pain visual analog scale (VAS).²²

Pain intensity was also assessed by VAS, which grades pain intensity at levels from 0 to 10, where 0 indicates no

pain and ten indicates the worst possible pain. If the pain is moderate, its reference level is five; if it is intense, then ten.

Functional training program (FT)

FT was applied for 12 weeks, in 36 classes, lasting 50 minutes, three times a week. Each class was structured in the following sequence: warm-up, specific part and cooldown. The application strategy selected was in a circuit, which allows it to be a dynamic class, with few pauses between changing stations (each exercise).

Warm-up: The warm-up was performed through dances with choreographies of light to moderate intensity and maximum duration of 15 minutes.

Specific part: Eight functional exercise stations were applied with a duration of one minute at each station and a rest of approximately 30 seconds, enough to change the station and adequate positioning to start the next exercise. Each participant performed two complete passes at the 8 stations of the circuit, with an interval of 2 to 3 minutes between each complete pass. The detailed exercises with their variations, objectives and intensities are presented in Chart 1

Cool-down: Ten minutes of stretching were performed, prioritizing the muscles worked, such as quadriceps, hamstrings, deltoids and dorsal, among others.

Data analyses

All numerical variables were submitted to data distribution testing using the Kolmogorov-Smirnov test. For descriptive statistics, categorical data were presented in absolute and relative frequency and numerical data were expressed as mean and standard deviation.

For comparisons of functional capacity and pain between pre- and post-intervention groups, analysis of variance (mixed ANOVA) was applied. To identify the magnitude of the effects, the delta percentage of the differences was calculated using the equation: [(postmeasurement - pre-measurement)/pre-measurement] *100. In addition, to determine the correlation of positive and negative changes in physical capacity variables with pain alterations, Spearman's correlation was used between post-pre differences in functional capacity and pain variables. The analyses were performed in the program SPSS 26.0, using a significance of 5%.

Station	Objective	Variations	Intensity or overload		
Agility ladder	Agility and motor coordination.	Jump or place feet together and then apart to the sides of the ladder.	Maximum speed		
Isometric plank	Strength endurance of abdominal, dorsal, erector spinae, gluteus and deltoid muscles.	With and without knee on the floor.	Body weight		
Development with dumbbells	Motor coordination, strength and strength endurance for the upper limbs.	Use of baton adequacy of the exercise by doing flexion and extension or abduction and adduction of the shoulder joint or performing the exercise in sitting position.	Moderate intensity SPE 3-5		
Running	Cardiorespiratory capacity.	Stationary running (in place), running with lateral displacement and walking.	Moderate intensity SPE 3-5		
Squat with simultaneous curl	Motor coordination, strength and endurance of lower and upper limbs.	Use pf resources such as baton and balance disk, always with the help of the performer, whether dynamic or isometric.	Moderate intensity SPE 3-5		
Jump rope	Motor coordination, agility, aerobic endurance, strength and endurance of lower limbs.	Exploration of glenohumeral mobility.	Moderate intensity SPE 3-5		
Deadlift	Strength and power of upper and lower limbs.	Use of equipment such as Swiss ball, dumbbells or your own body weight.	Moderate intensity SPE 3-5		
Hip abduction with elastic Lower limb strength and endurance.		Adduction and abduction of thigh in the standing position in lateral recumbency, flexion and extension of the hip joint in the standing position. The materials varied between shin guards and elastics.	Moderate intensity SPE 3-5		

Note: SPE = subjective perception of effort.

Results

A total of 128 elderly women who attended the Santo Antônio and São João Batista Parishes in the municipality of Ourinhos/SP were approached from May to October 2018. Of these, 78 were considered elderly, according to the literature, but 37 were not included in the study (eight older than 69 years and 29 who participated in training programs). Therefore, for this study, the sample consisted of 41 women allocated to the groups FT (n = 19) and CG (= 22). During the study, two women from FT were excluded because they did not show up for the collection of data regarding the physical evaluation (application of the tests), leaving a total of 17 women.

Of the 22 women in CG, seven were excluded (one for using an endogenous prosthesis, one for performing

structured exercises and five for not having time available), leaving a total of 15 women (Figure 1).

The characteristics of the sample are presented in Table 1, where similarities are observed between the groups for age, family income, race, schooling and marital status.

Table 2 presents the effects of the intervention. Significant effects are observed after the intervention in the FT, with the reduction of pain, increase in lower limb flexibility and endurance and improvement of cardiorespiratory capacity. These positive results were observed both by the statistical significance of the interaction (p < 0.05) and by the percentage deltas (Figure 2).

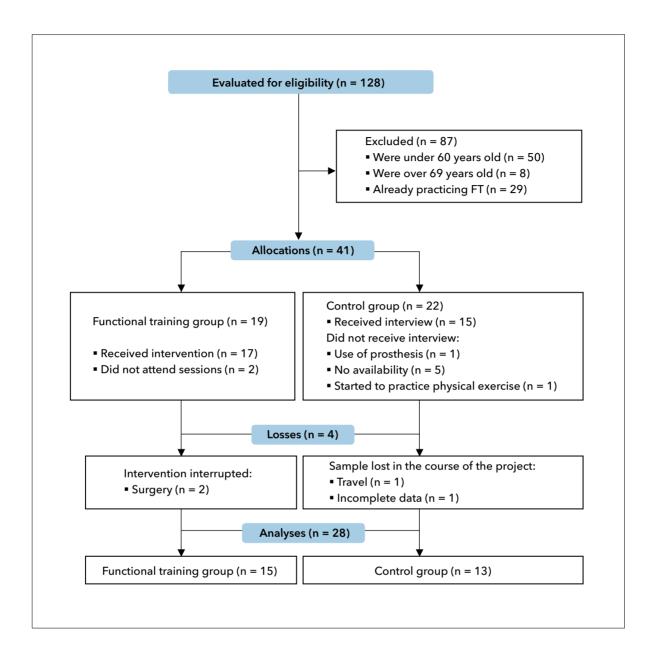


Figure 1 - Consortium 2010 - Flowchart: Experimental sequence.

Note: FT = functional training.

When analyzing the magnitude of the differences through the percentage delta, which is an excellent clinical indicator, it can be observed that the lower limb flexibility, lower limb endurance and cardiorespiratory capacity showed relevant values, above 10% and reaching up to 140% improvement. Pain reduction was more than 60%, being very beneficial. In Table 3, a consistent behavior is observed between the correlations of changes in pain and functional capacity. All abilities, regardless of their significance, showed a negative correlation with pain; however, only upper limb flexibility, agility and cardiorespiratory capacity effectively showed significant results.

Variable	Functional training group n (%)	Control group n (%)		
Age (years)				
61 - 65	10 (66.5)	11 (73.1)		
66 - 69	5 (33.5)	4 (26.9)		
Family income (MS)				
1 - 5	14 (93.2)	13 (86.6)		
5.1 - 10	1 (6.8)	2 (13.4)		
Race	·			
White	13 (86.6)	12 (80.0)		
Black and brown	2 (13.3)	3 (20.0)		
Schooling				
Up to 8 years	11 (72.9)	10 (66.4)		
9 to 14 years	4 (27.1)	5 (33.6)		
Marital status				
With partner	8 (53.3)	7 (46.7)		
Without partner	7 (46.7)	8 (53.3)		

Table 1 - Distribution of elderly women regarding sociodemographic aspects

Note: MS = minimum salary in force in 2018.

Table 2 - Mean (standard deviation) of pain and functional capacity in elderly women in both groups, pre- and postintervention

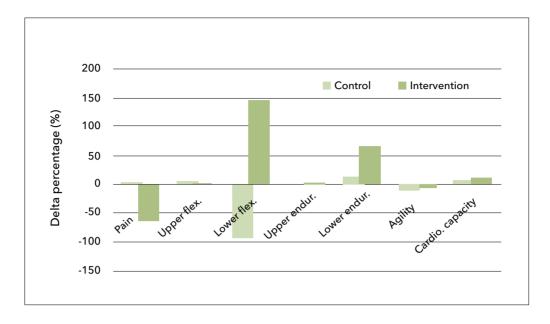
	Control group		Functional training group		p-value		
	Pre	Post	Pre	Post	Group	Moment	Interaction
Pain (VAS) (AU)	5.0 (3.2)	5.2 (3.5)	3.2 (2.7)	1.2 (2.9)	0.011	0.028	0.014
Upper limb flexibility (cm)	-10.8 (9.7)	-10.2 (8.7)	-6.14 (11.5)	-6.0 (8.3)	0.194	0.781	0.864
Lower limb flexibility (cm)	-8.8 (12.7)	-16.9 (14.0)	-3.0 (13.4)	1.4 (7.9)	0.006	0.331	0.002
Upper limb endurance (Rp)	12.9 (1.9)	12.7 (1.7)	21.1 (4.1)	21.9 (3.8)	<0.001	0.637	0.429
Lower limb endurance (Rp)	15.0 (2.1)	17.1 (3.0)	10.2 (1.7)	17.1 (3.0)	<0.001	0.054	0.015
Agility (s)	8.6 (1.9)	7.6 (1.4)	6.0 (1.1)	5.6 (0.6)	<0.001	0.003	0.160
Cardiorespiratory capacity (m)	345.3 (49.9)	369.0 (48.2)	432.8 (53.2)	484.3 (43.3)	<0.001	<0.001	0.017

Note: VAS = pain visual analog scale; AU = arbitrary unit; cm = centimeters; Rp = repetitions; s = seconds; m = meters. Values in bold indicate statistically significant.

Table 3 - Correlation between changes in pain status and functional capacities investigated

	Upper limb flexibility	Lower limb flexibility	Upper limb endurance	Lower limb endurance	Agility	Cardiorespiratory capacity
Correlation with pain	-0.56	-0.19	-0.16	-0.29	-0.38	-0.54
p-value	0.001	0.300	0.380	0.108	0.039	0.002

Note: Values in bold indicate statistically significant.





Note: flex. = flexibility; endur. = endurance; cardio = cardiorespiratory.

Discussion

As main results, it was observed that FT in elderly women improved some indicators of functional capacity, such as upper limb flexibility, agility and cardiorespiratory capacity, which correlated with pain reduction. In addition, improvements in lower limb strength and flexibility were also observed. These findings corroborate the literature, demonstrating that multicomponent exercise programs for the elderly, such as FT, are able to provide improvements in physical performance, delay frailty and decrease inflammation, including those who are frail.²³ This evidence helps to explain the reduction of pain and its association with the improvement in physical capacity observed in the present study.

According to Gallagher et al.²⁴ and Morcelli et al.,²⁵ after 65 years of age, 80% of the elderly will experience pain due to decreased functional capacities. In addition, women are more susceptible to pain, especially joint pain, due to some intrinsic factors such as loss of muscle and bone mass and hormonal decrease, characterized by menopause.^{24,25} In the present study, it was possible to observe that FT women exhibited a 60% reduction in pain compared to CG. In addition, in the correlation

analyses, it is evident that this variable is moderately correlated in the behavior of some capacities such as cardiorespiratory capacity, flexibility and agility.

Pain is subjective, and only the individual can assess its intensity. The fact is that physical exercises and social interaction are responsible for reducing this sensation.²⁶ Modalities such as stretching and strengthening reduce pain; however, the literature proposes aerobic exercises as the most indicated for the population that feels pain.²⁶ In the present study, we opted for the circuit class strategy for FT, presenting a more aerobic profile, which led to a reduction in the perception of pain in the elderly. However, Laredo-Aguilera et al.,²⁷ observed that healthy elderly women who underwent FT did not see significant improvements in pain, while CG worsened.

The results of the present study can be explained by the improvement of the other variables, having an impact on the reduction of pain, because Román et al.²⁸ demonstrated that women with fibromyalgia who underwent FT increased their general quality of life because of improvement in physical functioning, reducing the impact of the disease and pain compared to sedentary women, where medication could be reduced or eliminated completely. Another item that influences the functional capacity of the elderly is cardiorespiratory health, as intrinsic conditions are not enough to justify the health problems that cause aging, but multiple domains of physical fitness such as strength and aerobic capacity are responsible for maintaining this function. VO_{2max} decreases in the elderly population, and a sedentary lifestyle aggravates this condition.²⁹ In this study, both groups showed an increase in cardiorespiratory capacity, but FT individuals showed a greater magnitude of improvement (10%) compared to CG.

Asystematic review showed that FT can have beneficial effects on cardiorespiratory fitness in the elderly, where it is recommended elderly for this purpose.³⁰ Another systematic review, however, pointed out that it is not possible to say that FT is a better alternative than other interventions to increase cardiorespiratory fitness and emphasizes the importance of new studies with greater methodological rigor.³¹

Regarding strength endurance, FT improved over 60% compared to CG. Our results are in line with those of Aragão-Santos et al.³² who found that FT, when compared to traditional strength training, was effective in improving maximum dynamic strength, muscle power, muscle endurance and isometric strength in the elderly. Thus, both methods can be used safely and effectively in this population. However, since it presents a series of benefits related to independence and autonomy in the elderly because of the specificity of their tasks, FT tends to be more transferable to activities of daily living, and can be associated with traditional endurance training in the long term.³² In addition, in a multicomponent training such as FT, improvements in physical functioning were observed in elderly women with dynapenia.³³ Romero-García et al.³³ reported a significant decrease in the risk of falls, which leads us to consider that this type of intervention can have a preventive effect on the development of frailty in the elderly.

It is suggested that strength training should be considered to increase muscle function and dynamic balance in older women, while FT should be considered for increasing functional capacity and improving gait, which are variables strongly related to the risk of falling.³⁴

Regarding lower limb flexibility, an improvement of over 140% was observed in FT in relation to CG. Similarly, Matos et al.,³⁵ found that FT was sufficient to produce improvements in the autonomy of elderly women and

that with just 10 sessions it was possible to observe improvements in the power of the lower limbs, speed in getting up from a lying position, agility, and strength and mobility of the upper limbs. Thus, the development of lower limbs can be explained by improvements in general functionality. In addition, a core strength stability training, which was also performed in the present study, was able to promote a significant increase in functional mobility during the training period, while the CG participants did not show significant changes.³⁶ According to Resende-Neto et al.,³⁷ traditional training and FT are equally effective in improving joint mobility and strength components in older women, with maintenance of these adaptations even after detraining.

On the other hand, in the present study, some components of physical fitness did not show improvement as a result of the proposed intervention; they are: upper limb flexibility, upper limb endurance and agility. The main reason for this would be that the exercises were not sufficient and specific to these capacities.

In relation to upper body flexibility, Kang et al.³⁸ also did not observe significant changes between a multicomponent training similar to FT compared to CG, with changes only in the lower part. Regarding the exercises proposed in the present study, it is believed that they were not so specific for these variables when compared to the exercises proposed by Nogueira et al.,³⁹ who did their own exercises for flexibility within the specific part of the FT.

Regarding strength/endurance, effective improvements were expected for both upper and lower limbs, as FT promotes improvements in these capacities, even equaling strength training for this population.^{37,39,40} This suggests that the protocol used in this study was not enough to also cause adaptations in the strength of the upper limbs, making it necessary to have a program with an extra strength training session focused on muscle mass that results in greater improvements in arm strength.⁴¹ Another explanation, as pointed out by Sousa Jr et al.,⁴² would be that if the elderly women spend a lot of time developing manual activities, they will have more difficulty evolving in a training that does not stipulate a load.

In the present study, there were also no changes in agility, but other studies showed significant differences in agility/dynamic balance of the FT group compared to control.^{35,38-40} Interventions that resulted improvements in agility parameters had exercises of balance together

for its improvement,^{35,38} which may explain the lack of improvements in agility in the present study.

It is important to highlight the indication of FT for the elderly public, being safe, low cost and easy to apply in community environments when compared to exercises such as aerobic and endurance training. FT is able to improve health-related physical fitness, producing variable stimuli and greater demands on coordination and posture, allows a progressive increase in volume, intensity and density, improves body composition and can be a public health alternative in the management of compromise in mobility and blood pressure in the elderly.^{4,35-37}

As the main limitations of the present study, the small sample size and the presence of only robust elderly women stand out. In addition, the investigated sample had only elderly women aged between 61 and 69 years and a 12-week intervention, which limits the practical application to periods of approximately 12 weeks of training and in elderly women in this age group.

As a recommendation for future studies, we suggest the use of a larger sample and the relationship between frail and robust elderly women, rarely seen in the literature. In addition, the use of new dynamics and exercises of FT and their comparison with other training modalities can help in the decision-making of professionals whose objective is to serve this population.

Conclusion

FT applied to elderly women for 12 weeks was effective in improving the variables of lower limb flexibility, pain perception, strength endurance and cardiorespiratory capacity. In some aspects of functional capacity there was no improvement. The literature still has scarce studies that use FT, making further studies necessary for comparing FT with other types of training.

Authors' contributions

LPC, TPFB and MHSC contributed to the conception and design of the study and analysis and interpretation of the data. LPC, DAG, GFR and MHSC were responsible for writing the manuscript and reviewing its content.

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