



## Review

# Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials

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Functional electrical stimulation (FES) produces beneficial effects in the treatment of patients with chronic heart failure (CHF), but studies carried out in these patients show small sample sizes and conflicting results. The aim of this meta-analysis was to systematically review the effect of treatment with FES compared with conventional aerobic exercise training (CA) or control group in patients with CHF. The search strategy included MEDLINE, LILACS, Physiotherapy Evidence Database and Cochrane Library. Randomized trials comparing FES versus CA or control group in the treatment of patients with CHF were included. Two reviewers independently extracted the data. Main analysis used a fixed-effects model. The search retrieved 794 articles, from which seven studies were included. Treatment with FES provided a smaller gain in peak  $\text{VO}_2$  compared with CA [−0.74 ml/kg/min (95% confidence interval (CI): −1.38 to −0.10)]. There was no difference in the muscle strength [−0.33 Nm (95% CI: −4.56 to 3.90)] and in the distance of the 6-min walk test [2.73 m (95% CI: −15.39 to 20.85)] on comparing FES with CA. An increase in peak  $\text{VO}_2$  of 2.78 ml/kg/min (95% CI: 1.44–4.13) was observed in FES versus the control group. Treatment with FES provides a similar gain in the distance of the 6-min walk test and in the muscle strength when compared with CA, but a small gain in the peak  $\text{VO}_2$ . An increase in the peak  $\text{VO}_2$  can be obtained with FES as compared with the control group. Thus, FES may be an alternative in relation with CA for patients with CHF and with those who are unable to perform this kind of exercise. *Eur J Cardiovasc Prev Rehabil* 00:000–000 © 2010 The European Society of Cardiology

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## Introduction

An increase in heart failure prevalence has brought about high social and economic costs and high morbidity and mortality for the patients. Functional capacity limitation, commonly associated with reduced quality of life and poor prognosis, is a hallmark of this syndrome [1]. Several useful parameters can estimate functional capacity and prognosis of the patients with heart failure in clinical practice. Peak oxygen consumption (peak  $\text{VO}_2$ ) is also an

independent predictor of survival in patients with heart failure [2,3]. The distance of the 6-min walk test is also an independent predictor of survival for these patients [4,5]. Finally, reduction in the cross-sectional area of skeletal muscular fibres and in muscular strength are predictors of exercise intolerance in heart failure patients [6,7].

There is evidence that aerobic and resistance training are beneficial for patients with chronic heart failure (CHF). Thus, physical training has been recommended as part of the therapy for these patients [8]. However, some patients do not adapt or drop out of conventional physical

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training, and others are unable to support even low levels of physical effort. Functional electrical stimulation (FES) was used in CHF patients and has shown potential beneficial effects, such as increase in muscular mass (type I fibres), oxidative enzyme levels [9] and peak  $\text{VO}_2$  [10], muscular atrophy prevention [9], endothelial function improvement [11], better performance in functional tests [12], and improvement in the quality of life [13]. This therapy seems to be an alternative treatment for patients who cannot engage in conventional exercise training programs.

Earlier randomized trials have shown the beneficial effects of FES in the treatment of patients with CHF as compared with conventional aerobic exercise training (CA) [9–15]. However, studies comparing these benefits with those obtained from CA or placebo in these patients show small sample sizes and conflicting results. A systematic review of the evidence would allow a more precise evaluation of its effectiveness, and, if the benefits are proven, aid in the dissemination of FES use. Therefore, the aim of our study was to systematically review the effect of CHF treatment with FES on peak  $\text{VO}_2$ , distance of the 6-min walk test, and muscle strength compared with CA or control group in patients with CHF.

## Methods

### Search strategy

We searched the following electronic databases (from inception to January 2009): MEDLINE (accessed by PubMed), LILACS, Physiotherapy Evidence Database (PEDro), and Cochrane Library. Search terms used included ‘electric stimulation therapy’, ‘electric stimulation’, ‘electrical stimulation’, ‘neuromuscular electrical stimulation’, ‘electrostimulation’, ‘heart failure’, and a string of words proposed by Robinson and Dickersin [16], which yields a high sensitivity in the search for randomized controlled trials. We did not include words related to the outcomes of interest to enhance the sensitivity of our search. There were no language restrictions.

### Study eligibility

We included any randomized trials evaluating FES in the treatment of CHF patients with New York Heart Association functional class II, III, or IV. We included studies that compared FES with CA or control group (the same regimen as the FES group, except that the intensity of stimulation did not lead to visible or palpable contractions), where the objective was the assessment of the peak  $\text{VO}_2$ , the distance of the 6-min walk test, and/or the muscle strength. Exclusion criteria were summarized as follows: (i) inclusion of patients other than CHF patients; (ii) failure, on the part of the investigators, to provide a reliable definition of what was considered as CHF; (iii) nonapplication of FES in the quadriceps femoral muscle, and (iv) the follow-up was shorter than 5 weeks.

### Study selection and data extraction

Titles and abstracts of all articles identified by the search strategy were evaluated by the investigators. All abstracts that did not provide enough information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the full-text stage, two reviewers independently evaluated the complete articles and did their selection in accordance with the eligibility criteria. Disagreements between reviewers were solved by consensus.

The main outcome extracted was functional capacity, measured by peak  $\text{VO}_2$  in ml/kg/min. Other outcomes of interest were the distance of the 6-min walk test [in meters (m)] and muscle strength [in Newton-meter (Nm)].

### Quality assessment

The major quality issues assessed were the following: concealment of the allocation list, intention to treat analysis, baseline comparability, outcomes assessment blinding, and description of losses and exclusions. Studies without a clear description of the use of an intention to treat analysis were considered as not fulfilling this criterion. The lack of a description of how the allocation list was concealed was judged as absence of allocation concealment. The only possible blinding in this type of study is that of the outcomes assessment; lack of description of this kind of blinding was judged as an open study. The quality was also evaluated globally through the use of two commonly used scales (PEDro [17] and Jadad *et al.* [18]). This appraisal was independently performed by two reviewers.

### Analyses

Pooled-effect estimates were obtained by comparing the least square mean percentage change from baseline to study end for each group, and were expressed as the weighted mean difference between groups. Calculations were done using a fixed-effects model. Two comparisons were made: FES versus CA and FES versus control group. An  $\alpha$  value of 0.05 was considered significant. Statistical heterogeneity of the treatment effect among studies was assessed using Cochran’s  $Q$ -test and the inconsistency  $I^2$  test, in which values above 25 and 50% were considered indicative of moderate and high heterogeneity, respectively [19]. All analyses were conducted using Review Manager Version 5.0 (Cochrane Collaboration) [20].

Sensitivity analyses were carried out by taking into account the methodological characteristics of the studies (blinding, intention to treat, and allocation concealment), where meta-analysis calculations were redone including those studies that meet the quality criteria. Separate calculations were done by considering each characteristic. Finally, a sensitivity analysis with all studies using the random-effects model was also carried out.

## Results

### Description of selected studies

The initial search led to the identification of 794 abstracts, from which 56 studies were considered as potentially relevant and were retrieved for detailed analysis. Only seven articles met the eligibility criteria. Figure 1 shows the flow diagram of studies in this review.

The seven studies included had a total of 224 patients. Table 1 summarizes the characteristics of these studies. Five trials [10,12,14,15,21] of the seven studies compared FES with CA (total  $n = 168$ , of which 83 were on FES) whereas two trials [9,11] compared FES with a control group (total  $n = 56$ ,  $n$  in FES group = 31). All patients were on optimal medical therapy for heart failure before enrollment, which included  $\beta$ -blockade, angiotensin inhibition, and the use of diuretics.

The quality of most of the included studies was poor. Observing the Jadad scale, all articles (100%) presented a score lower than or equal to 3 (out of 5) points; in the PEDro scale, five studies (71%) scored less than or equal to 5 (out of 10) points.

### Functional electrical stimulation versus conventional aerobic exercise training

The five articles that compared FES with CA evaluated the peak  $\text{VO}_2$  and the distance of the 6-min walk test. Two of these articles also evaluated isometric muscle strength of the right femoral quadriceps. Separate meta-analyses were carried out for each outcome.

Figure 2 shows the comparison between FES and CA effects on peak  $\text{VO}_2$ . We observed that FES treatment provides smaller gain in peak  $\text{VO}_2$  as compared with CA [ $-0.74$  ml/kg/min (95% confidence interval (CI):  $-1.38$  to  $-0.10$ ,  $I^2 = 0\%$ )]. There was no difference observed in the muscle strength [ $-0.33$  Nm (95% CI:  $-4.56$  to  $3.90$ ,  $I^2 = 0\%$ )] when FES treatment was compared with CA (Fig. 3). In relation to the distance of the 6-min walk test, we could observe that the treatment with FES caused a nonsignificant increase of 2.73 m (95% CI:  $-15.39$  to  $20.85$ ,  $I^2 = 41\%$ ) as compared with CA (Fig. 4).

### Functional electrical stimulation versus control group

Two articles compared FES with a control group. FES treatment significantly enhanced the peak  $\text{VO}_2$  (2.78 ml/kg/min, 95% CI: 1.44–4.13,  $I^2 = 52\%$ ) when compared with the control group (Fig. 5).

With regard to the 6-min walk test, an increase in the distance, comparing before and after treatment measurements, occurred in the FES group ( $227 \pm 138$  to  $299 \pm 137$  m,  $P < 0.001$ ), but not in the control group ( $237 \pm 132$  to  $243 \pm 145$  m,  $P = \text{NS}$ ) as observed in the study carried out by Nuhr *et al.* [9]. Karavidas *et al.* [11] observed similar results:  $454 \pm 85$  to  $487 \pm 91$  m, ( $P = 0.003$ ) in the FES and  $452 \pm 71$  to  $454 \pm 79$  m, ( $P = 0.621$ ) in the control group. We were unable to carry out the meta-analysis of these values, as the articles did not provide sufficient data for the calculation (no exact  $P$  values or standard deviations for change from baseline in each group were available). We did not consider the option of meta-analyzing the ending walked distance found in each group, as a baseline imbalance of the distance walked was significant in the study carried out by Nuhr *et al.* [9]. We contacted the authors of the original study to obtain the missing data, but we did not receive any feedback.

None of these articles assessed the muscle strength.

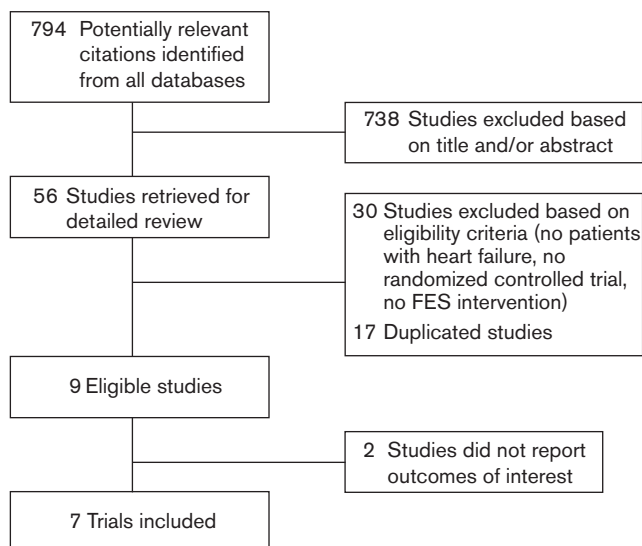
The prespecified sensitivity analyses were impaired by the low quality presented by the studies. It was not possible to conduct analyses excluding studies without clearly stated allocation concealment, because only one study met this criterion [9]. None of the studies reported outcome assessment blinding or intention to treat this analysis.

With regard to the sensitivity analysis and the use of the random-effects model, results were mostly unchanged, with little difference in the estimates, but  $P$  values were similar to those seen in the fixed-effects models.

## Discussion

In this systematic review of randomized controlled trials, we wanted to evaluate the performance of FES when compared with both CA and control group in patients with CHF. Guidelines have recommended an

Fig. 1



The flow diagram of the studies included in the review.

Table 1 Characteristics of studies included in this review

Study, year	Patients (n)	Age (mean $\pm$ SD)	Male sex (n)	NYHA II-III-IV (n)	Features	PEDro score	Jadad score
FES versus conventional training							
Harris <i>et al.</i> [12]	22/24	63 $\pm$ 10/ 62 $\pm$ 11	17/21	17-5-0/ 18-6-0	FES=quadriceps and gastrocnemius muscles of both legs; F=25 Hz; TON=5 s; TOFF=5 s; 30 min daily, 5 days per week for 6 weeks; Conventional=30 min daily, 5 days per week for 6 weeks; 70% of the HR max	4	2
Eicher <i>et al.</i> [21]	12/12	54 $\pm$ 9 <sup>a</sup>	19 <sup>a</sup>	4-20-0 <sup>a</sup>	FES=quadriceps and calf muscles of both legs; F=10 Hz; TON=20 s; TOFF=20 s; 25 daily sessions of 60 min; Conventional=20 min daily, 25 daily sessions; 60-80% of the HR max	2	1
Deley <i>et al.</i> [14]	12/12	56 $\pm$ 8/57 $\pm$ 6	9/11	9-3-0/9-3-0	FES=quadriceps and calf muscles of both legs; F=10 Hz; pulse=200 $\mu$ s; TON=12 s; TOFF=8 s; 60 min/day; 5 days per week for 5 weeks; Conventional=60 min sessions, 5 days a week for 5 weeks; 60-70% of the HR max	5	2
Dobsak <i>et al.</i> [10]	15/15	56 $\pm$ 6 <sup>a</sup>	23 <sup>a</sup>	22-8-0 <sup>a</sup>	FES=quadriceps and calf muscles of both legs; F=10 Hz; pulse=200 $\mu$ s; TON=20 s; TOFF=20 s; 60 min daily for 7 days per week for 8 weeks; Conventional=40 min daily, 3 days a week for 8 weeks; exercise workload was adjusted individually at the level of the anaerobic threshold determined by spiroergometry	4	1
Deley <i>et al.</i> [15]	22/22	55 $\pm$ 10/ 56 $\pm$ 7	16/19	9-12-1/ 11-11-0	FES=quadriceps and calf muscles; F=10 Hz; pulse=0.2 ms; TON=12 s; TOFF=8 s; 60 min per day, 5 days per week, 5 weeks; Conventional=60 min sessions, 5 days a week for 5 weeks; exercise workload was adjusted individually at the HR at ventilatory threshold determined by spiroergometry	5	2
FES versus control							
Nuhr <i>et al.</i> [9]	15\17	53 $\pm$ 7\53 $\pm$ 13	14\14	5-8-2\2-13-2	FES=knee extensor and hamstring muscles of both legs; F=15 Hz; pulse=0.5 ms; TON=2 s; TOFF=4 s; intensity=25-30% of the MVC; 240 min/day, for 10 weeks (7 days/week); Control=same regimen of the FES group, except that the intensity of stimulation did not lead to visible or palpable contractions	6	3
Karavidas <i>et al.</i> [11]	16\8	57 $\pm$ 15\64 $\pm$ 8	14\7	12-4-0\6-2-0	FES=quadriceps and gastrocnemius muscles of both legs; F=25 Hz; TON=5 s; TOFF=5 s; 30 min daily, 5 days per week for 6 weeks; Control=same regimen of the FES group, except that the intensity of stimulation did not lead to visible or palpable contractions	6	2

6 MWT, 6-min walking distance; F, frequency; FES, functional electrical stimulation; HR max, maximum heart rate; MVC, maximal voluntary contraction; NYHA, New York Heart Association; TOFF, time of rest; TON, time of followed. <sup>a</sup>Trials did not report separate mean  $\pm$  SD age, number of male patients or functional class for FES versus conventional training, FES versus the control group.

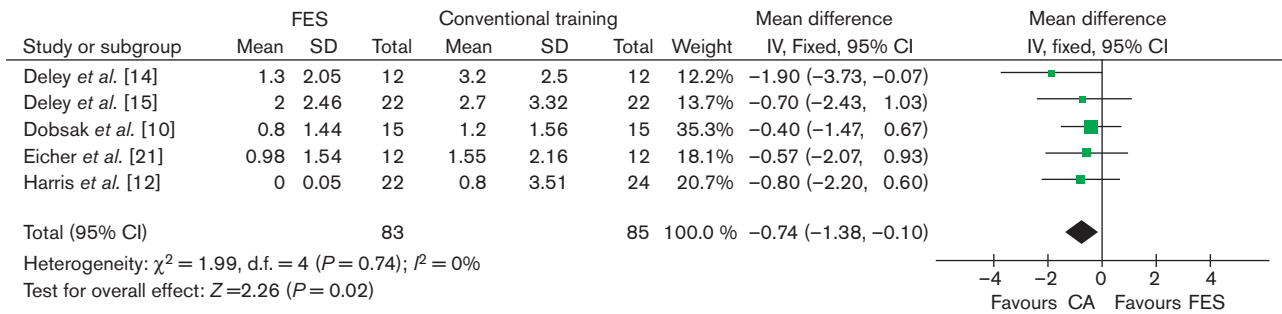
exercise-training program as a part of the treatment in these patients [22,23], but not all patients adhere to the CA programs. Treatment of the patients with CHF through FES training has been proposed as an interesting alternative to CA. The proposed mechanisms by which FES provides its benefits involve improvements in peripheral factors, including modifications of myotology and in skeletal muscle oxidative capacity [14]. The first relevant study in the field was conducted by Harris *et al.* [12], who compared conventional training with FES. In this study, the performance of FES had similar effects on functional capacity when compared with conventional training. Other studies were published in the following years, but generally lacked sufficient power to provide a conclusive answer [10,14,15,21]. In addition, two other research studies showed beneficial effects of FES when compared with no intervention, but the number of studied patients was small [9,11]. This meta-analysis was carried out to evaluate if enough evidence was available to provide a definite appraisal of FES.

In this meta-analysis, we observed that treatment with FES causes an increase in the peak  $VO_2$  and in the distance of the 6-min walk test in CHF patients as compared with the control groups without any intervention. Further-

more, FES treatment provides similar gains in the distance of the 6-min walk test and a similar gain in muscle strength when compared with CA, and a small improvement in the peak  $VO_2$ , which has little clinical significance.

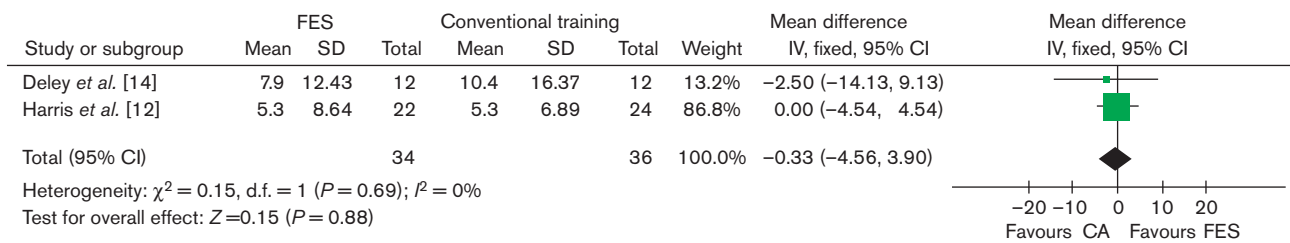
A limitation of the studies included in this meta-analysis is that most of them presented low methodological quality, only one of them being a study with a description of the sample calculation [9] and description of the confidentiality of the allocation list [9], and no study describing blinding. Therefore, it was impossible to perform sensitivity analyses stratified by methodological quality. Despite the impossibility of blinding patients and therapists in FES studies, it is possible to blind the evaluation of outcome, which occurred in only three studies [11,14,15]. Another reason for the low methodological quality was that the authors did not describe how confidentiality of the allocation list was maintained, and, reading the articles, it was impossible to conclude whether this methodological item was obeyed. Only the study carried out by Nuhr *et al.* [9] described randomization to be based on a sealed envelope randomization list. Moreover, two studies [10,21] also failed to describe the losses and exclusions that occurred during the treatment period [18,24].

**Fig. 2**



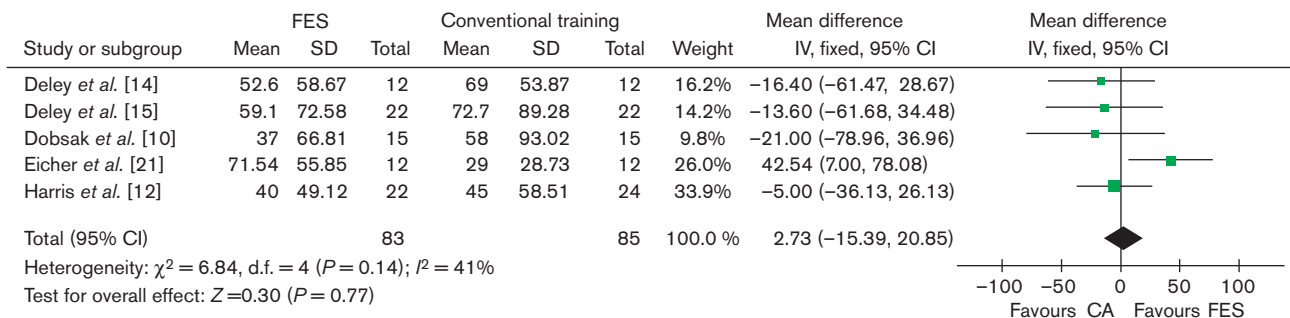
The mean weighted difference and 95% confidence interval (CI) in the peak  $VO_2$ , for treatment with the functional electrical stimulation (FES) versus the conventional aerobic exercise training (CA).

**Fig. 3**



The mean weighted difference and 95% confidence interval (CI) in the muscle strength for treatment with the functional electrical stimulation (FES) versus the conventional aerobic exercise training (CA).

**Fig. 4**



The mean weighted difference and 95% confidence interval (CI) in the distance of the 6-min walk test for treatment with the functional electrical stimulation (FES) versus the conventional aerobic exercise training (CA).

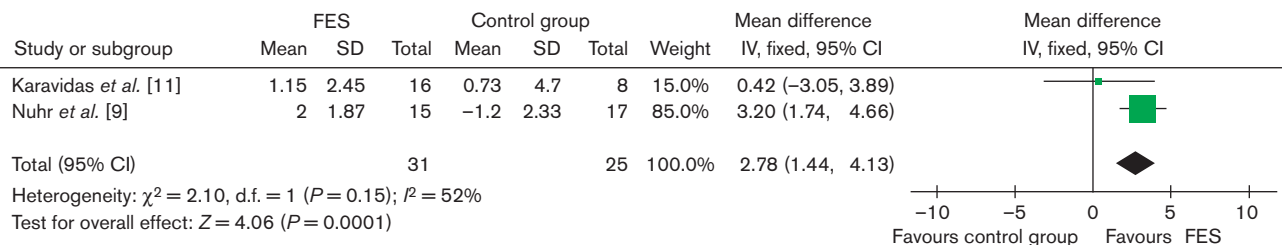
Another important fact observed was the short follow-up time of the patients included in the studies, which leads to the report of only substitute outcomes. Besides, the studies included do not have sufficient power, as even performing meta-analysis, the 95% CIs remained broad, suggesting that new studies should be carried out with a larger number of patients.

Meta-analysis comparing the distance of the 6-min walk test between the FES and CA groups showed a hetero-

geneity of 41% in the  $I^2$  test, which may be partly justified by the study of Eicher *et al.* [21], which presented a lower methodological quality when compared with the other included studies.

In the meta-analysis comparing the peak  $VO_2$  between the FES and the control group, significant heterogeneity was also observed ( $I^2$  test = 52%), which can be accounted for in part as a function of the study carried out by Nuhr *et al.* [9], which presented the longest time of

Fig. 5



The mean weighted difference and 95% confidence interval (CI) in the peak  $VO_2$  for treatment with the functional electrical stimulation (FES) versus the control group.

stimulation per day (240 min/day). Besides this, Nuhr *et al.* [9] had a longer duration of patient training (7 days per week for 10 weeks), as compared with the duration of 5 days per week for 6 weeks in a study carried out by Karavidas *et al.* [11]; these facts may justify better results for the study carried out by Nuhr *et al.* [9].

In summary, this systematic review suggests that treatment with FES increases the peak  $VO_2$  and the distance of the 6-min walk test as compared with the control group. Furthermore, the treatment with FES provides similar gain for the distance of the 6-min walk test and muscle strength when compared with CA, and a small gain for the peak  $VO_2$ , of little clinical significance. Our results show that FES may be an alternative to CA for patients with CHF and for those who are unable to perform this kind of exercise. However, the low methodological quality of the studies included in this systematic review and the small number of samples suggest that new randomized clinical trials on this patients are needed, and must be planned with greater methodological strictness, along with a larger number of patients and longer periods of intervention and follow up of the hard outcomes.

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