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The Effectiveness of Therapeutic Physical Exercise in Patients with Amyotrophic Lateral Sclerosis in Relation to the Alsfrs-R Functionality Scale: A Systematic Review

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Abstract

Background: to analyze the changes that a therapeutic physical exercise program is capable of causing in the functionality of patients suffering from ALS and in addition, to analyze the respiratory capacity. Methods: a systematic review of the PubMed, SCOPUS, Cochrane, SciELO, PEDro, CINAHL and MEDline databases is carried out. The information was filtered using the following MeSH terms: "Amyotrophic lateral sclerosis", "Physical Therapy", "Physical and Rehabilitation Medicine". Clinical trials published in the last 5 years were included in which one of the interventions was therapeutic physical exercise in patients with ALS, which included the ALSFRS-R as a result variable. Results: 10 clinical trials with a total of 421 patients were analyzed, of which 183 underwent rehabilitation with physical exercise and were part of the case group; the rest belong to the control group and their treatment was mostly passive. The observed trend is of a decrease of approximately 6 points in the ALSFRS-R scale at 6 months in the case groups; however, no behavior pattern was met in the controls. Conclusions: Therapeutic physical exercise could contribute to slow down the deterioration of the musculature of people with ALS, thus facilitating the performance of their daily activities.

Keywords: Amyotrophic lateral sclerosis, physical therapy, rehabilitation, exercise.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a disease of the central nervous system (CNS) and is characterized by a progressive involution of motor neurons in the cortex of the brain (upper motor neurons) [1]. As a consequence, muscle weakness occurs that causes paralysis, spreading from different body regions. It compromises motor autonomy, written and oral communication, swallowing and breathing; however, the ocular muscles, sensitivity or intellect are not altered [2]. The clinical manifestations of ALS are due to the abnormal behaviour of the nervous system [3].

The Revised Amyotrophic Lateral Sclerosis Functional Scale (ALSFRS-R) is a measure used to assess the status and progression of patients with ALS. It is one of the most widely used scales to assess the functionality of these patients. The main components of this scale are [4]: bulbar function: language, salivation and swallow; fine motor: writing, use of cutlery, dress and hygiene; gross motricity: rolling over in bed, walking and climbing stairs; and respiratory function: dyspnoea, orthopnoea and respiratory insufficiency. It is common for people with ALS to obtain their diagnosis 1 year after the onset of the disease and with a score greater than 39 on the ALSFRS-R scale [5].

The treatment of this disease must be comprehensive and must be approached from a multidisciplinary point of view, from the moment it is diagnosed until its terminal phase. It includes pharmacological, neurorehabilitation and symptomatic treatments [6]. Physical therapy consists of planned therapeutic physical exercise to correct postural abnormalities, combat pain and reduce muscle stiffness. In addition, it promotes functional independence, trains the patient to prevent falls, and re-educates walking, if necessary with certain technical aids [7]. The role of physical exercise begins prior to significant loss of strength and continues throughout the course of the disease, up to the last days of the person's life.

Stretching and range-of-motion exercises are commonly accepted therapies for patients with ALS [2]. However, controversy still exists when it comes to exercise intensity. Resistance exercises for unaffected muscles (with strength of at least grade 3) using low to moderate load and intensity and aerobic activities, such as swimming, walking, and cycling, at levels between 50% and 65% of the heart rate reserve can be safe and help to achieve therapeutic goals.

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Everything indicates that exercise can be physically and psychologically important for people with ALS; however, although recent studies focus on what type of exercise is most indicated for these patients, there is still no evidence of this or at what frequency or intensity should exercise be performed in training sessions or to what extent it helps patients maintain functionality. Therefore, the main objective of this study is to analyse the changes that a therapeutic physical exercise programme is capable of causing in the functionality of patients suffering from ALS, measured with the ALSFRS-R scale. In addition, secondarily, to analyse the changes that a therapeutic physical exercise programme is capable of causing in the respiratory capacity of patients with ALS through the forced vital capacity (FVC) test, in addition to seeing how this rehabilitation influenced the fatigue of patients with the Fatigue Severity Scale (FSS) and with the 6-minute walk test (6MWT).

2. Materials and methods

Search strategy

To carry out this systematic review, information collected from the PubMed, SCOPUS, Cochrane, SciELO, PEDro, CINAHL and MEDLINE databases was used. For the selection of the information, descriptors were used that were obtained from Medical Subjects Heading (MeSH). The information was filtered using the following keywords: "Amyotrophic lateral sclerosis", "ALS", "Motor Neuron Disease", "Physical Therapy", "Exercise Therapy", "Physical and Rehabilitation Medicine", and "Exercise Training". A systematic review of the scientific literature was carried out following the PRISMA checklist system.

Selection method

Two researchers with more than 10 years in the selection of documents performed, in a blinded way, the selection of the different documents. After applying all the previously described criteria, those that were duplicated were eliminated and the selected articles were read in full by the authors. In the event of a discrepancy in any criteria, a third researcher (blinded) with more than 15 years of experience in document selection, decided if the paper was included.

Selection of documents

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The following inclusion criteria were established: clinical trials published in the last 5 years, with at least one of the interventions being therapeutic physical exercise in patients with ALS, which included the values of the ALSFRS-R as a result variable of patients who underwent study, in addition to obtaining a score ≥ 5 on the PEDro methodological quality scale.

The following exclusion criteria were assigned: score < 5 on the PEDro methodological quality scale; the absence of the result variable ALSFRS-R among the measurement values; trials with exclusively respiratory/bulbar rehabilitation programmes; or trials involving animals.

Evaluation of the internal validity of the selected documents

The PEDro methodological assessment scale was applied to estimate the quality of the studies analysed [8]. This scale consists of 10 points, including selection criteria; randomization of the sample; concealed allocation; initial comparability between groups; all subjects blinded; all therapists who administer therapy blinded; all evaluators measuring key outcomes blinded; adequacy of follow-up; analysis with intention to treat; statistical comparison of results between groups; and existence of specific measures and variability for at least one key result. Such items may or may not be given, so points were awarded based on compliance failure to comply with the requirements of each particular item [8].

Studies with a score ≥ 6 were considered high-quality studies.

3. Results

Initially, 753 documents were found in the PubMed, SCOPUS, Cochrane, SciELO, PEDro, CINAHL and MEDLINE databases. The following were excluded: 467 duplicates, 155 because they were older than 5 years, 84 that were not clinical trials, 11 because they were animal studies, nine because they only contained bulbar rehabilitation, and 17 because they did not include the main outcome variable of the ALSFRS-R. After this, 10 clinical trials were analysed in full-text and included (Figure 1).

The 10 selected clinical trials were evaluated with the PEDro scale. The score ranged from 5 to 7 points. Four of the studies scored a 5, three of them scored a 6 and the rest scored a 7. Furthermore, none of them were masked, and all included the results of the primary variable (Table 1).

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The characteristics of all the documents were analysed and are reflected in Table 2. It can be seen how a total of 421 patients were test subjects, of which 183 underwent rehabilitation with physical exercise and were part of the group of cases; the rest of the participants belonged to the control group and their treatment was mostly passive. The mean age of the patients was 60 years, and the mean time they suffered from the disease was 15 months.

Some of the therapeutic physical exercise interventions consisted of aerobic exercise [9, 10], moderate-high intensity strength and endurance exercises [5, 11–13], functional training or stretching [14, 15]. Frequencies ranged from highest to lowest [10] according to the study, and the intervention time was a minimum of 2 weeks and a maximum of 6 months. The exercises were performed around at 70% of the heart rate (HR), and the strength of each patient was measured so that it did not exceed 80% of their MR.

The outcome variables of each article were analysed. The main one was the ALSFRS-R functionality scale (Table 3), in which the score ranged between 32 and 43, the initial minimum and maximum respectively. In addition, these documents included secondary variables such as FVC, FSS and 6MWT. Scores were collected at the start of treatment and in the short, medium and long terms. They were divided into two tables: ALSFRS-R (all studies) (Table 3) and FVC, FSS, and 6MWT (7/10 studies were included) (Table 4). We chose these variables according to their relevance and the frequency with which they occurred in the analysed studies. Both tables show the evolutionary comparison of cases and controls, in addition to the standard deviation of each data.

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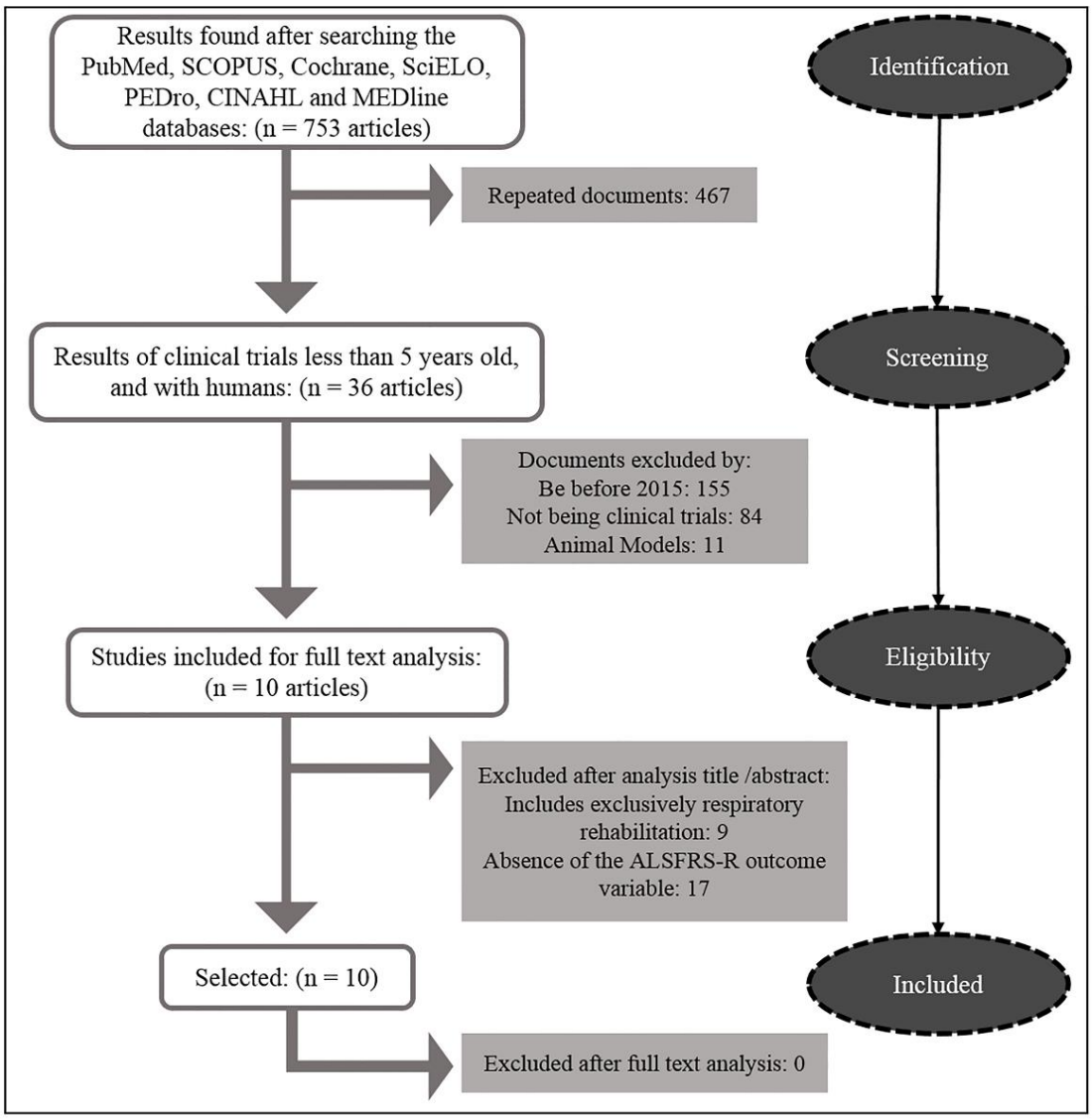

Figure 1. Search flow chart according to PRISMA model

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Table 1. PEDro Scale

Authors	Type of study	Randomization	Masked	Variable at startup	Blinded subjects	Blinded therapists	Evaluators blinded	Measures 85% of the sample	They consider total sample	Main variable results	Mean or standard deviation	PEDro Points
Marques Braga et al (2018) [9]	**ECA**	●	-	●	-	-	-	-	●	●	●	**5**
Kitano et al (2018) [14]	**EC**	-	-	●	-	-	-	●	●	●	●	**5**
Sivaramakrishnan et al (2019) [16]	**EC**	-	-	●	-	-	-	●	●	●	●	**5**
Clawson et al (2017) [13]	**ECA**	●	-	-	-	-	●	●	●	●	●	**6**
Kato et al (2018) [5]	**EC**	-	-	●	-	-	-	●	●	●	●	**5**
Van Groenestijn et al (2019) [17]	**ECA**	●	-	●	-	-	●	●	●	●	●	**7**
Ferri et al (2019) [12]	**ECA**	●	-	●	-	-	-	●	●	●	●	**6**
Merico et al (2018) [11]	**ECA**	●	-	●	-	-	●	-	●	●	●	**6**
Zucchi et al (2019) [10]	**ECA**	●	-	●	-	-	●	●	●	●	●	**7**
Lunetta et al (2015) [15]	**ECA**	●	-	●	-	-	●	-	●	●	●	**6**

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Table 2. Characteristics of the included studies

Author	Sample size	Age (years)	ALS time	Intervention	Session frequency	Outcome variables
Marques Braga et al (2018) [9]	**50** [48] G1 = SC: **25** [24] G2 = AECI: **25** [24]	G1: **63** (±13.0) G2: **62** (±12.0)	G1 = SC: **9.5** months G2 = AECI: **9** months	G1 AECI: Aerobic exercise of controlled and moderate intensity + SC G2 SC: Standard care (ROM + Gear)	G1: AECI(2 sessions / week) + daily SC - 6 months G2: daily SC - 6 months	ALSFRS-R CPET FVC, FSS
Kitano et al (2018) [14]	**105** G1 = Home-ex: 21 [15] G2 = Control: 84	G1: **62.8** (±10.2) G2: **62.7** (±12.1)	G1**: 2.2** (±2.4) years G2**: 1.5** (±1.7) years	Strength, functional and stretching exercises for upper limbs and trunk muscles	Daily / individualized frequency for 6 months. G1 = unsupervised	ALSFRS-R MMT
Sivaramakrishnan et al (2019) [16]	**9** G1 = Aerobic G: 9	G1: **59.22** (±12.3)	G1: **2.37** (±1.9) years	Reclining stepped aerobic exercise of moderate intensity. 70 steps / minute.	40 minutes. 3 sessions a week. For 4 weeks.	ALSFRS-R 6MWD, TUG FSS, SF-12, BDI
Clawson et al (2017) [13]	**59** G1= ROM: 21 G2=RESISTANCE: 18 G3= ENDURANCE: 20	G1**: 57.68** (±9.72) G2: **63.65** (±10.55) G3**: 57.82** (±11.88)	G1: **11.08** (±13.21) G2: **7.25** (±7.21) G3**: 7.30** (±6.80) months	G1: Held stretches (30 sec) G2: strength exercises (70% RM) G3: moderate / high intensity resistance exercises.	3 sessions a week. For 6 months.	ALSFRS-R FVC, FSS ASS, VAS VO2 MÁX
Kato et al (2018) [5]	**2** G1 = Strengt G: 2	G1**: 56** (±8)	G1: **1.1** (±0.5) años	Moderate / high intensity strength and endurance exercises.	30 minutes. 7 sessions a week, For 2 weeks.	ALSFRS-R KEMS, FVC FAC
Van Groenestijn et al (2019) [17]	**57** [32] G1= AET: 27 [10] G2= UC: 30 [22]	G1: **60.9** (±10) G2: **59.9** (±10.7)	G1: **15.5** (±10.9) G2: **18** (±14.0) months	G1 AET: Aerobic exercise therapy in cycle ergometer + UC G2 UC: usual care	50 minutes. 3 sessions a week. For 16 weeks.	ALSFRS-R ALSAQ-40+FS-36 MCS, PCS, FVC
Ferri et al (2019) [12]	**16** G1= TRAIN: 8 G2= UC: 8	G1: **50.7** (±3.3) G2**: 55.5** (±5.95)	G1: **20.5** (±20.3) G2: **13.4** (±6.6) months	G1 TRAIN: Moderate / high intensity aerobic and strength exercise. G2 UC: usual care	50 minutes. 3 sessions a week. For 12 weeks.	ALSFRS-R 6MWD, TUG VO2 MAX, Mc GILL
Merico et al (2018) [11]	**38** G1= EP: 23 G2= SNT: 15	G1: **61.6** (±10.6) G2**: 59.8** (±14.7)	G1: **30.2** (±11.8) G2: **30.3** (±6.7) meses	G1 EP: Submaximal aerobic exercise 65% HR and 80% strength RM G2 SNT: neuromotor standard exercise	50 minutes. 7 sessions a week. For 5 weeks.	ALSFRS-R 6MWT, FIM, CK FSS, VO2 MAX
Zucchi et al (2019) [10]	**65** G1= IER: 32 G2= UER: 33	G1: **65,14** (±9,90) G2: **64,74** (±10,10)	G1: **15,67** (±9,74) G2: **16,64** (±8,98) months	G1: High frequency aerobic and resistance training. G2: Aerobic exercise, low frequency.	45 minutes. G1: 5 / week and G2: 2 / week For 10 weeks.	ALSFRS-R FVC FSS ALSAQ-40 + Mc GILL
Lunetta et al (2015) [15]	**60** [47] G1= SMEP: 30 [22] G2= UCP: 30 [25]	G1: **61.1** (±10.1) G2: **60.3** (±9.9)	G1: **15.2** (±7.2) G2: **13.7** (±6.1) months	G1 SMEP: passive, active and cycle ergometer exercises, strictly supervised. G2 UCP: passive habitual care.	G1: and G2: 2 / week For 6 months.	ALSFRS-R FVC

ALSFRS-R: revised functional scale for amyotrophic lateral sclerosis, ALSAQ-40: Assessment of subjective health status in amyotrophic lateral sclerosis, ASS: Ashworth Spasticity Scale, BDI: Beck's depression inventory, CPET: cardiopulmonary exercise test, FAC: functional walking test, FIM: functional measure of independence, FSS: fatigue severity scale, FVC: forced vital capacity, KC: creatine kinase, KEMS: strength knee extensor muscles, MCS: mental component summary, MMT: manual muscle test, PCS: physical component summary, TUG: get up and walk test, VAS: visual analog scale, VO2Máx: maximum oxygen consumption, 6MWD: 6 minute walk test,

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Tabla 3. Summary of the ALSFRS-R result variable

Variable	Author		Baseline (SD)	Short-Term (1 month)	Medium-Term (3 months)	Long-Term (6 months)
ALSFRS-R (0-48)	**Marques Braga et al (2018)** [9]	**Cases**	**40.25** (±5.00)	-	-	**34.1** (±7.1)
		Control	**37.25** (±4.9)	-	-	**29.5** (±7.7)
	Kitano et al (2018) [14]	**Cases**	**41.1** (±4.5)	-	-	**38.1** (±5.9)
		Control	**40.3** (±4.4)	-	-	**33.1** (±9.2)
	Sivaramakrishnan et al (2019) [16]	**Cases**	**32.75** (±7)	**33.25** (±7.55)	**32.62** (±7.4)	-
		Control	**32.75** (±7)	-	-	-
	Clawson et al (2017) [13]	**Cases**	**39.36** (±4.92)	-	-	**33.54** (±1.38)
		Control	**39.67** (±3.71)	-	-	**35.41** (±1.26)
	Kato et al (2018) [5]	**Cases**	**43** (±2)	-	-	**33.5** (±1)
		Control	**43** (±2)	-	-	-
	Van Groenestijn et al (2019) [17]	**Cases**	**42.4** (±4.3)	-	**40.52** (±3.48)	-
		Control	**42.2** (±3)	-	**38.28** (±5.52)	-
	Ferri et al (2019) [12]	**Cases**	**40.4** (±1.5)	-	**35.7** (±2.6)	-
		Control	**35** (±3.4)	-	**23** (±5.6)	-
	Merico et al (2018) [11]	**Cases**	**36.1** (±4.71)	**36.1** (±4.71)	-	-
		Control	**34.5** (±3.6)	**34.5** (±3.6)	-	-
	Zucchi et al (2019) [10]	**Cases**	**39.84** (±5.7)	-	**34.87** (±8.49)	**33.08** (±9.76)
		Control	**40.15** (±5.17)	-	**36.39** (±8.01)	**33.0** (±9.42)
	Lunetta et al (2015) [15]	**Cases**	**39.1** (±4.7)	**37.0** (±5.1)	**35.1** (±6.2)	**32.8** (±6.5)
		Control	**38.3** (±5.1)	**38.1** (±4.3)	**34.3** (±6.4)	**28.7** (±7.5)

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Table 4. Summary of secondary outcome variables FVC, FSS, 6MWD

Variable	Study		Baseline	End of Study		
				1 month	4 months	6 months
FVC (%)	**Clawson LL et al (2017)** [13]	Control	**101.19** (±17.9)	**-**	**-**	**88.59**
		Cases	**88.14** (±17.03)	**-**	**-**	**74.34**
	Lunetta et al (2015) [15]	Control	**93.9** (±14.7)	**-**	**-**	**66.5** (±26.9)
		Cases	**92.5** (±23.3)	**-**	**-**	**75.8** (±23.6)
	Kato et al (2018) [5]	Cases	**69.05**	**-**	**-**	**72.2**
	Van Groenestijn et al (2019) [17]	Control	**95.4** (±15.4)	**-**	**81.88**	-
		Cases	**86.9** (±20.2)	**-**	**79.22**	-
	Zucchi et al (2019) [10]	Control	**90.70** (±17.68)	**-**	-	**77.91** (±31.82)
		Cases	**91.88** (±18.98)	**-**	-	**66.24** (±44.96)
FSS (1-7)	**Sivaramakrishnan et al (2019)** [16]	Cases	**32.87** (±10.45)÷9	**28.62** (±11.9)÷9	-	-
	Merico et al (2018) [11]	Control	**5.4** (±0.2)	**5.19** (±0,16)	-	-
		Cases	**5.4** (±0.27)	**6.69** (±0.21)	-	
	Zucchi et al (2019) [10]	Control	**36.50** (±16.53)÷9	-	-	**37.38** (±18.73)÷9
		Cases	**35.63** (±15.31)÷9	-	-	**41.42** (±18.49)÷9
6MWD (metros)	**Sivaramakrishnan et al (2019)** [16]	Cases	**232.5** (±192.32)	**235.16** (±195.49)	-	-
	Merico et al (2018) [11]	Control	**236.26** (±76.26)	**239,16** (±5.48)	-	-
		Cases	**265.17** (±81.37)	**336,73** (±50.72)	-	-

%FVC: percentage of forced vital capacity, FSS: fatigue severity scale, 6MWD: 6 minute walk test.

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4. Discussion

This study has focused on analysing the functional changes that a therapeutic physical exercise programme is capable of causing in patients suffering from ALS as measured by the ALSFRS-R scale. After a search and exclusion of clinical trials in different databases (Figure 1), 10 of these studies were analysed in full-text, which were evaluated using the PEDro scale (Table 1). In them, 421 patients were the subject of a study between groups of cases (treated with therapeutic exercise) and groups of controls (with habitual passive treatments), of which results were obtained on different scales, mainly the ALSFRS-R (a scale of functionality that is currently accepted to quantify the capacity of these patients to carry out their routine activities [4]), and as secondary measures, attention was set according to its frequency of appearance and correlation with the study, the FSS, FVC and 6MWT. Furthermore, due to the different duration of each clinical trial, it was possible to obtain a visualization of the effect of neurorehabilitation at different stages of the disease. Thanks to this, it can be compared in the short, medium and long terms and behavioural trends can be observed between the scores of the different patients treated. Likewise, the following results have been obtained from them (Table 3).

In most of the clinical trials in which the behaviour of a treatment based on physical exercise is studied in the progression of ALS, an improvement in the strength of the patients is usually observed in those muscles that are trained. However, there is still a discrepancy when it comes to functionality. In fact, there are claims about possible ineffectiveness in improving function in patients with ALS through moderate-high intensity strengthening exercise therapy according to the Borg Scale [18]. That is, it was found that, by training the lower limbs of the patients who participated, they managed to increase strength in actions such as knee extension but did not progress in activities such as climbing stairs or walking. Faced with this question, the results of the studies analysed are broken down according to the moment.

Short-term effects

In the first month of rehabilitation, even improvements in the ALSFRS-R score can be found [16]. This is a relevant fact, since, when dealing with the rehabilitation of a degenerative disease, it is to be expected that the function will be lost with the passage of time [3]. In fact, in the rest of the trials in which measurements were taken after 1 month, it was found that the scores of cases and controls decreased around 2 points [15] or they

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stayed the same [11]. A fact that is considered positive in the progress, and considering these qualifications, it seems that therapeutic physical exercise manages to slightly improve, maintain or slow down the natural degenerative progress of the patients, as observed when comparing the control groups of the respective selected trials.

Comparing the results of one of the groups with the other studies that carried out a follow-up at 1 month, a significantly greater reduction in the score can be observed [15]. This could be due to the frequency of intervention, since their groups performed physical exercise only twice a week, a more reduced continuity than in the rest of the studies. In addition, this trial included patients with a disease duration of < 2 years and a very high ALSFRS-R score (39.1 points). A fact that did not occur in the rest of the patients and which may be indicative that a decrease such as the one that occurred at 1 month could return to normal, since it is difficult to maintain such high score levels in a disease that is characterized by early degeneration of nervous tissue [19].

It seems that, after a month of rehabilitation, the effects of physical exercise are still not clear and that the hypertrophy caused by physical rehabilitation appears after the month [18]. Prior to this, there is the so-called recruitment by collateral outbreak, which is caused by muscle cells without neurological damage [20]. This could explain why there are some cases in which function is improved early in this type of rehabilitation. However, in other pathologies, such as multiple sclerosis, there are studies in which improvements in physical condition linked to quality of life have been observed in just 3 weeks of rehabilitation training, with characteristics similar to the exercise plans proposed in the patients studied with ALS—moderate intensity, twice a week and aerobic skills combined with strengthening [21].

Medium-term effects

It seems that, within 3 months, significant differences begin to be seen between the groups treated with therapeutic exercise and those treated with passive conventional treatment [12, 15, 17]. In all of them, the ALSFRS-R scores decreased between 2 [17] and 7 points [12] in the training group compared to those in the control and passive therapy groups, which had a decrease in the greater functionality score. However, a different perspective was also reflected in which a group trained less frequently (two sessions/week) obtained better results than the group that performed the exercises five times/week [10]. This fact supports the theory that training must balance between overworking and underworking

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muscles [22]. It is also correlated with the involutional factor of ALS, in which valid neurons decrease as time passes, and it is recommended not to tire the patient [18], thus implementing a treatment with a moderate and not an intense tendency. In addition, other studies defend that light and moderate exercises (such as a swimming regimen) help to preserve motor neurons, but more intense levels obtained the opposite effect, even decreasing survival [23].

Furthermore, other studies have shown that there may not be significant differences in physical health status in people with chronic musculoskeletal disorders who did a workout twice a week compared to that in the group who did it three times a week. This can be understood, as once a point of maximum tolerated load has been reached, the benefits of training no longer show significant improvements. Therefore, the costs of resources and treatments could be saved without apparently affecting these results [24].

Regardless of the intensity and frequency of the sessions throughout the week, it can be seen that in none of the trials analysed did the duration of therapy exceed 60 minutes per session. Although taking into account that the effort tolerance of a patient with ALS could be lower than that of a healthy subject, this could lead to a regression in therapy and in their own disease. Therefore, it is a matter of study and should focus on finding a balance between the accumulated load and the frequency of sessions and their duration.

It was also observed that there were scores on the functionality scale that decreased more than in the rest of the studies that carried out the measurement at 3 months and that their cases and controls obtained very different results, since the points in the usual care control patients dropped from 35 to 23 and dropped from 40 to 35 in the motor rehabilitation patients. However, this can be justified with the fact that they started with 40 points, significantly more than the controls [12]. Regarding the large drop in this study in just 3 months in the score on the ALSFRS-R scale, it could be reflected on whether the age of the patients in this trial had an influence compared to the rest, since the mean age in this study was 53 and 61 in the other studies (Table 2). This finding is related to the fact that, as a general rule, the musculoskeletal system of an adult 10 years older will be more impaired or have more signs of muscle immobilization than an adult 10 years younger [25]. Therefore, in turn, this condition of weakness will make changes and advances more noticeable in patients who entered the studies with worse physical condition or in this case older. In fact, elderly people with Parkinson's underwent strength training for 4 months and were compared with a control group (passive) in terms of respiratory muscle

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strength and quality of life. The result was that the older people who underwent active neurorehabilitation looked significantly better [26]. For this reason, the development of this type of protocol could be of interest, since previous studies with different degenerative pathologies and, in turn with effective results, have been shown.

Long-term effects

A significant difference can be observed in most of the studies analysed [9, 14, 15], as patients treated with therapeutic exercise benefited most at a functional level compared to those who continued with a more sedentary lifestyle. There were functional results of groups (physical exercise or stretching) that were similar; however, an analysis of the falls of patients was subsequently carried out, and they observed that the group that worked with strength and resistance had fewer falls compared to the group that worked with joint range of motion and stretch [13]. Both the number and frequency of falls has been reduced in other neurodegenerative pathologies (such as Parkinson's) thanks to a programme of therapeutic physical exercise [27].

However, functional improvements were seen in some patients only at the beginning of treatment when their score was higher than 40 points. Then, they underwent rehospitalization and physical exercise after those months proved to be of little efficacy in more advanced stages, thus giving the feeling that some patients may not respond to this type of therapy when their score on the ALSFRS-R scale falls below 40 points and distances themselves from the initial stages of the disease [5].

Analysing and comparing the scores obtained in the studies that measured the ALSFRS-R scale at 6 months, the similarity of behaviour between the different groups of cases, but not of controls, can be observed. That is, the observed trend is for a drop of approximately 6 points on the functionality scale in this period of time, having performed moderate intensity physical exercise regardless of whether it focused more on aerobic or strengthening exercise. However, in the case of controls, there were groups that, with the usual therapy, fell to 10 points from the start [9, 15] or just between 4 and 7 points [10, 13, 14]. Therefore, it could be inferred that, in a rehabilitation that did not include therapeutic physical exercise, the possibilities of slowing down the disease would be exposed to heterogeneous conditions and the patient's own circumstances; however, with extra physiotherapy rehabilitation, a non-evolutionary evolution could be expected. This is completely unfavourable for the patient, and a controlled decrease in the ALSFRS-R

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score is usually associated with managing activities of daily living, probably for a longer period of time than other patients whose therapy is mostly passive.

Although most of the studies cited above and analysed in this review obtained satisfactory results with therapies based on therapeutic physical exercise, there remain divergences in some other trials in which the progression of the disease was not stopped as much as expected. This could be due to some of these treated patients exceeding the intensity of the exercise, since there seems to be a correlation between patients who perform moderate exercise and a higher density of motor neurons in the ventral horn of the spinal cord, which leads to initially slower muscle deterioration and the opposite occurs if the musculature is overloaded. You can even find sedentary patients with better progress than those who fatigue excessively [28].

In the longer term, if the training therapy is continued around 10 months, it seems that an improvement is not observed in part [5], and routine activities become heavier so that the ALSFRS-R score in the follow-up could plummet, as seen in the case where it is below 30 points [10]. When this happens, most cells are usually poorly innervated, and it is the job of the "healthy" to counteract this weakness. For this reason, it is important to boost healthy muscle cells in time, and physical therapy in ALS could be used preventively before the onset of weakness in gait [18]. In this way, therapeutic exercise would be recommended to be implemented before and during the onset of the disease [5].

Neurorehabilitation with physical exercise seems to help strengthen the musculature in the "disuse factor" of this; therefore, patients with ALS who started with physical exercise and who were previously sedentary or were hospitalized would have greater results than patients who started rehabilitation in good shape [10]. This could be one of the reasons why the analysed studies varied in terms of results, and a common improvement trend was not obtained in all the exercised groups.

Although some groups of cases achieved greater progress than their control group in terms of functionality, the same did not occur with survival, which was not related to the ALSFRS-R score [9]. It seems that the measures of this scale are not linked to the probability of surviving a longer time [10].

However, there are some aspects that do correlate with this scale. For example, a braking of muscular atrophy that is normally caused by progressive inactivity that gives the involutional character of this disease [11]. In addition, aerobic fitness and respiratory

function are benefited [12, 14]. It is even inferred that it could influence factors such as appetite, sleep or mood [29]. For this reason, other secondary outcome variables that appeared in the reviewed studies were analysed, which will make it possible to relate the functionality of the ALSFRS-R scale with other aspects such as fatigue (measured with the FSS scale), the distance covered in the 6MWT and the spirometric test of FVC (Table 4).

In the case of the FSS, different results can be observed depending on the treatment. There are cases in which patients who performed resistance and strength training at 80% of their MR worsened, thus increasing their score on the FFS after 1 month of rehabilitation, obtaining even worse scores than those of the controls of the same study, which were maintained [11]. However, when reviewing the scores obtained after 1 month of treatment, other studies were favourable and reduced their FFS score [16]. This could be related to the fact that, in this last study, the rehabilitation consisted of aerobic exercise and did not include strengthening exercises, in addition to the fact that it was performed only three sessions per week, while in the trial that obtained the worst results, the frequency of training was daily, seven sessions per week. This can lead to us infer about the importance of cardiovascular training in these patients, since the respiratory muscles in more advanced stages of the disease are severely affected [30]. It would be the object of study if moderate aerobic exercise would act as an adjunct against this critical factor of ALS, in order to reduce the anguish and fatigue that this generates in patients. Although, as has been seen in the case of multiple sclerosis, the mechanisms related to fatigue and corticospinal function are altered by the abnormalities in the CNS causing these neurological diseases, the response to exercise and fatigue seems to be different from that in healthy subjects [31].

Even so, in both aforementioned studies, the distance in the 6MWT was improved after 1 month [11, 16]. Regardless of the fatigue that it caused, it seems that the patients who underwent strength training and perceived greater fatigue were able to walk a greater distance compared to that obtained as soon as they started treatment. Specifically, the difference was 71 m, while it was maintained in the controls with usual treatment. That is, it seems that, with passive patient care, fatigue can be controlled more safely than with strength exercises, which can lead to a feeling of exhaustion [32]. However, they seem to be more able to carry out activities of daily living and their muscles could be more prepared to carry out fundamental activities (such as walking) for a longer period of time

than patients with a more sedentary lifestyle, according to the results of the tests that have been compared.

This raises questions about the relevance of a balance between perceived fatigue and the improvements obtained with physical exercise therapy. Since what is observed in this review is that the appearance of fatigue is not always an indication of regression in the disease, but a stage that sometimes extends to a few days, and rest would be recommended in them, with continued improvement [11]. For this reason, recovery from this post-training weakness is of vital importance. In fact, there are studies that focus precisely on the recovery cycles of muscle speed in relation to the number of motor units and the changes that occur in sickness [33].

In the longer term, specifically 6 months after beginning rehabilitation, the FSS was performed on patients, and a score increase on this scale (which is not positive) was observed in the group that performed the tests. Exercises with the highest frequency (5 days/week) compared to the group that had workout sessions 2 days/week [10]. A fact that agrees with the results analysed after only 1 month of treatment. Consequently, it is possible to meditate on whether establishing more than 3 days of weekly training could increase the exhaustion of the patients, according to the scores obtained from the FSS. If this fact is related to the measurement of FVC that this trial took in its patients (also at 6 months), it can be seen how the group that worked with a lower volume of sessions exceeded by more than 10% the group of cases in spirometry. Therefore, it is suggested that perhaps submaximal aerobic activity in patients with neuromuscular diseases, allowing for adequate rest, avoids overexertion [34] and that this is not effective to achieve a greater lung capacity, but all treatment or physical exercise must be adapted to the capacities of the patient with ALS [35].

Regarding the rest of the FVC percentages extracted from the long-term studies reviewed (6 months), it was observed that the patients in the control group had a decrease of around 15-25% in their spirometric values, while patients in the case groups had a decrease of around 7-15% in their spirometric values [5, 13, 15, 17]. Therefore, it could be said that physical exercise therapy has a positive impact on slowing down the deterioration of the patient's respiratory muscles.

Strengths and weaknesses

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As a strength, this is the first scientific document that studies the relationship between therapeutic physical exercise in patients with ALS and the effect it produces in these subjects, both at a functional level on subjective scales (ALSFRS-R and FSS) and on objective physiological aspects (FVC and 6MWT).

In this study, the lack of revision of those articles that were not written in one of the following languages can be considered as a weak point: English, French, German, Spanish or Portuguese. Likewise, it is possible that certain nuances of the original version of the articles analysed may not have been accurately interpreted in their translation.

In addition, those documents that were outside the analysed databases (PubMed, SCOPUS, Cochrane, SciELO, PEDro, CINAHL and MEDLINE) remained outside the scope of this study.

5. Conclusion

Therapeutic physical exercise could help to slow down the deterioration of the musculature of people with ALS, thus facilitating the performance of their daily activities and therefore maintaining the levels of their scores on the ALSFRS-R functionality scale, especially in the medium and long terms, compared to those in patients with ALS with mostly passive treatments.

The survival of patients was not benefited in relation to a therapeutic physical exercise programme, but their respiratory muscles did improve the levels measured in the FVC, which leads to an improvement in their quality of life until the end of their disease.

Carrying out a treatment that includes physical activity in patients with ALS helps to counteract the muscle weakness caused by the degeneration of poorly innervated cells, as it strengthens healthy cells, and these patients obtained better results in the 6MWT after several months of rehabilitation.

Regarding the type of exercise, it could be inferred that a moderate intensity and not very high frequencies (two sessions/week) combining strengthening and aerobic resistance could be the best option to observe improvements in patients with ALS and avoid the onset of fatigue in these patients, since it is possible that their FSS values increase with more intense therapies.

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Author Contributions

Laura Prados-Hombrados, Guadalupe Torres-Molina, Manuel Gonzalez-Sánchez and María Ruiz-Muñoz, conceived the study, and all authors participated in the study design.

Laura Prados-Hombrados, Guadalupe Torres-Molina, Alejandro Galán-Mercant, and María Ruiz-Muñoz collected the data.

Laura Prados-Hombrados, Guadalupe Torres-Molina, Alejandro Galán-Mercant and Manuel González-Sánchez analyzed the data and

Laura Prados-Hombrados, Guadalupe Torres-Molina, Alejandro Galán-Mercant, Manuel González-Sánchez and María Ruiz-Muñoz drafted the manuscript.

All authors gave comments on the earlier versions of the manuscript. All authors edited the manuscript and approved the final version.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Brown DG, Shorter J, Wobst HJ. Emerging small-molecule therapeutic approaches for amyotrophic lateral sclerosis and frontotemporal dementia. *Bioorganic Med Chem Lett* **2020**; 30: 126942.

[2] Orient-López F, Terré-Boliart R, Guevara-Espinosa D, et al. Tratamiento neurorrehabilitador de la esclerosis lateral amiotrófica. *Rev Neurol* **2006**; 43: 549–555.

[3] Abril Carreres M, Ticó Falguera N, Garreta Figuera R. Enfermedades neurodegenerativas. *Rehabilitación* **2004**; 38: 318–324.

[4] Salas Campos T, Rodríguez-Santos F, Esteban J, et al. Spanish adaptation of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). *Amyotroph Lateral Scler* **2010**; 11: 475–477.

[5] Kato N, Hashida G, Konaka K. Effect of muscle strengthening exercise and time since onset in patients with amyotrophic lateral sclerosis: A 2-patient case series

study. *Medicine (Baltimore)* **2018**; 97: 1–4.

[6] Khan F, Turner-Stokes L, Ng L, et al. Multidisciplinary rehabilitation for adults with multiple sclerosis (Review). *Cochrane Libr* **2007**; 1–61.

[7] Arpa Gutiérrez J, Enseñat Cantallops A, García Martínez A, et al. *Guía para la Atención de la Esclerosis Lateral Amiotrófica (ELA) en España*, http://www.elaandalucia.es/WP/wp-content/uploads/guia-para-la-atencion-de-la-ela-en-espana.pdf (2009).

[8] Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* **2003**; 83: 713–721.

[9] Marques Braga AC, Pinto A, Pinto S, et al. The role of moderate aerobic exercise as determined by cardiopulmonary exercise testing in ALS. *Neurol Res Int* **2018**; 1–10.

[10] Zucchi E, Vinceti M, Malagoli C, et al. High-frequency motor rehabilitation in amyotrophic lateral sclerosis: a randomized clinical trial. *Ann Clin Transl Neurol* **2019**; 6: 893–901.

[11] Merico A, Cavinato M, Gregorio C, et al. Effects of combined endurance and resistance training in Amyotrophic Lateral Sclerosis: A pilot, randomized, controlled study. *Eur J Transl Myol* **2018**; 28: 132–140.

[12] Ferri A, Lanfranconi F, Corna G, et al. Tailored Exercise Training Counteracts Muscle Disuse and Attenuates Reductions in Physical Function in Individuals With Amyotrophic Lateral Sclerosis. *Front Physiol* **2019**; 10: 1–13.

[13] Clawson LL, Cudkowicz M, Krivickas L, et al. A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Front Degener* **2017**; 19: 1–9.

[14] Kitano K, Asakawa T, Kamide N, et al. Effectiveness of Home-Based Exercises Without Supervision by Physical Therapists for Patients With Early-Stage Amyotrophic Lateral Sclerosis: A Pilot Study. *Arch Phys Med Rehabil* **2018**; 99: 2114–2117.

[15] Lunetta C, Lizio A, Sansone VA, et al. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled

trial. *J Neurol* **2016**; 263: 52–60.

[16] Sivaramakrishnan A, Madhavan S. Recumbent stepping aerobic exercise in amyotrophic lateral sclerosis: a pilot study. *Neurol Sci* **2019**; 40: 971–978.

[17] van Groenestijn AC, Schröder CD, van Eijk RP, et al. Aerobic Exercise Therapy in Ambulatory Patients With ALS: A Randomized Controlled Trial. *Neurorehabil Neural Repair* **2019**; 33: 153–164.

[18] Kato N, Hashida G, Kobayashi M, et al. Physical therapy improves lower limb muscle strength but not function in individuals with amyotrophic lateral sclerosis: A case series study. *Ann Phys Rehabil Med* **2018**; 61: 108–110.

[19] Rodríguez de Rivera F, Oreja Guevara C, Sanz Gallego I, et al. Evolución de pacientes con esclerosis lateral amiotrófica atendidos en una unidad multidisciplinar. *Neurología* **2011**; 26: 455–460.

[20] Mancuso R, Martínez-Muriana A, Leiva T, et al. Neuregulin-1 promotes functional improvement by enhancing collateral sprouting in SOD1G93A ALS mice and after partial muscle denervation. *Neurobiol Dis* **2016**; 95: 168–178.

[21] Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: A systematic review to inform guideline development. *Arch Phys Med Rehabil* **2013**; 94: 1800–1828.

[22] Dal Bello-Haas V. Physical therapy for individuals with amyotrophic lateral sclerosis: current insights. *Degener Neurol Neuromuscul Dis* **2018**; 8: 45–54.

[23] Shefner JM. Effects of Strength Training in Amyotrophic Lateral Sclerosis: How Much Do We Know? *Muscle and Nerve* **2019**; 59: 6–7.

[24] Cuesta-Vargas AI, White M, González-Sánchez M, et al. The optimal frequency of aquatic physiotherapy for individuals with chronic musculoskeletal pain: A randomised controlled trial. *Disabil Rehabil* **2015**; 37: 311–318.

[25] Zaragoza Casterad J, Serrano Ostariz E, Generelo Lanaspa E, et al. Dimensiones de la condición física saludable: evolución según edad y género. *Rev Int Med y Ciencias la Act Física y del Deport* **2005**; 5: 50–67.

 doi:10.20944/preprints202011.0555.v1

[26] Alves WM, Alves TG, Ferreira RM, et al. Strength training improves the respiratory muscle strength and quality of life of elderly with Parkinson disease. *J Sports Med Phys Fitness* **2019**; 59: 1756–1762.

[27] Lai CH, Chen HC, Liou TH, et al. Exercise Interventions for Individuals with Neurological Disorders: A Systematic Review of Systematic Reviews. *Am J Phys Med Rehabil* **2019**; 98: 921–930.

[28] Lisle S, Tennison M. Amyotrophic lateral sclerosis: the role of exercise. *Curr Sports Med Rep* **2015**; 14: 45–46.

[29] Lopes de Almeida JP, Silvestre R, Pinto AC, et al. Exercise and amyotrophic lateral sclerosis. *Neurol Sci* **2012**; 33: 9–15.

[30] Ferreira GD, Costa ACC, Plentz RD, et al. Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. *Physiotherapy* **2016**; 102: 221–228.

[31] Stroud NM, Minahan CL. The impact of regular physical activity on fatigue, depression and quality of life in persons with multiple sclerosis. *Health Qual Life Outcomes* **2009**; 7: 1–10.

[32] Orsini M, Hasue RH, Leite MAA, et al. Neuromuscular diseases: revisiting the 'overtraining'. *Fisioter e Pesqui* **2014**; 21: 101–102.

[33] Kristensen R, Bostock H, Tan S, et al. MScanFit motor unit number estimation (MScan)and muscle velocity recovery cycle recordings in amyotrophic lateral sclerosis patients. *Clin Neurophysiol* **2019**; 130: 1280–1288.

[34] Barros G, Moreira I, Ríos R. Tratamiento – rehabilitación y manejo global de las enfermedades neuromusculares. *Rev Médica Clínica Las Condes* **2018**; 29: 560–569.

[35] Hernández-Vázquez FJ. El deporte para atender la diversidad: deporte adaptado y deporte inclusivo. *Apunt Educ física y Deport* **2000**; 2: 46–53.