

The Role of Exercise in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor nervous system, involving the cortex, brainstem, and spinal cord. It causes progressive and cumulative physical disabilities in patients, and leads to eventual death due to respiratory muscle failure. The incidence of ALS is 1 to 2 cases per 100,000 population per year, and the prevalence is 4 to 7 cases per 100,000 population because of the short mean survival time [1]. It is estimated that 10,000 to 25,000 people are affected by ALS in the United States at any time. The disease is diverse in its presentation, course, and progression. We do not yet fully understand the cause or causes of the disease, nor the mechanisms for its progression; thus, we lack effective means for treating it. Currently, we rely on a multidisciplinary approach to manage and care for patients who have ALS symptomatically [2]. Rehabilitation plays an essential role in the care of patients who have ALS, along with pharmacologic interventions, respiratory support, nutritional supplements, communication devices, and social and psychologic support [3]. In

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the authors' experience, one of the most frequently asked questions by patients who have ALS is whether exercise is beneficial.

In this article, the authors review the literature on the role of exercise in patients who have ALS, and briefly compare what is known about exercise in other neuromuscular diseases. Specifically, they ask

1. What types of exercise (stretching, resistance/strengthening, and aerobic/endurance training) have been examined in patients who have ALS?
2. What kinds of exercise regimens (intensity, duration, and frequency) are beneficial for patients who have ALS?
3. What are the demonstrated benefits and how are they measured?

The authors also reviewed animal studies for comparison. They hope to determine whether clinicians may safely recommend a structured exercise regimen as a treatment intervention for patients who have ALS.

Importance of exercise for the general public

Exercise is widely promoted to the general population because of its great benefit to health and wellbeing. In 1996, the American Surgeon General published a health report [4] recommending (1) regular physical activity, consisting of moderate-intensity exercise for at least 30 minutes on most days of the week, for the general population of all ages; (2) more vigorous intensity of physical activity and of longer duration for greater health benefit; and (3) strength-developing exercises at least twice a week for most adults, to supplement the benefits of cardiorespiratory endurance exercise.

The health benefits of physical activity include enhancement of the cardiovascular, respiratory, musculoskeletal, and endocrine function, and psychologic wellbeing [5]. Moreover, exercise lowers the risks of developing chronic diseases that are associated with inflammation, such as coronary heart disease [6], hypertension [7], colon cancer [8], and diabetes mellitus [9]. The authors briefly discuss the potential mechanisms by which exercise improves health and reduces inflammation, based on data that are mostly derived from healthy people and animal studies.

Mechanisms by which exercise benefits health

Myofiber remodeling

During exercise, myofibers are activated, either by mechanochemical or mechanoelectric signals, which lead to an increased intracellular calcium concentration and subsequent signaling cascades. An intricate network of coordinated gene expressions, which are not yet fully understood, is then responsible for myofiber remodeling. Type I slow-twitch oxidative myofibers are induced after exercise training, as evidenced by the induction of myoglobin, troponin I slow, and myosin heavy chain type I molecules [10]. The

transition of myofibers from type II to type I may allow for enhanced muscle adaptability and a greater insulin-induced glucose uptake, thus presenting a lower risk for developing diabetes mellitus [11].

With exercise also comes an enhanced beta-oxidation of fatty acids, which is caused by the induction of the peroxisome proliferator activated receptor and its coactivator 1 (PGC-1 α) [12]. This results in an enhanced metabolism of fat and a reduction of adipose tissues, and, conceivably, contributing to the consequent reduction of inflammation associated with sedentary lifestyle. Resistance training also causes muscle hypertrophy, which is mediated by insulin-like growth factor (IGF-1) and the target of rapamycin (TOR) signaling pathway [13,14].

Antioxidative and anti-inflammatory adaptation

Besides modifying the muscle fiber types and mass, exercise also causes an initial increase in free radical production and oxidative stress, which is counteracted by the subsequent activation of the endogenous antioxidative defense mechanism [15,16]. A new homeostasis is achieved; thus, regular exercise of moderate intensity appears to result in a lower basal state of oxidative stress level [17–19]. Depending on the duration and intensity of the exercise and the age of the person, the myokine interleukin-6 is produced following exercise. It contributes to health by activating downstream anti-inflammatory pathways and enhancing the metabolic and immunologic response [20–22], which ultimately benefits the cardiovascular system in healthy and disease states [23].

Central nervous system stimulation and plasticity

Exercise has an effect on the central nervous system; reorganization and an increase in motor neuron excitability have been demonstrated in the motor cortex and the spinal cord following resistance training [24,25]. The central nervous system thus has a role in contributing to increased strength following exercise training.

Neuroendocrine effect

Exercise also activates the hypothalamic-pituitary-adrenal (HPA) axis, increases the production of cortisol and catecholamines, and enhances cellular metabolism [26]. However, the interplay of exercise on the neuroendocrine system, including the HPA axis, the thyroid function, and the reproductive hormones, is complex. The response of the neuroendocrine system depends on the intensity, type, and duration of exercise, as well as the age, gender, and fitness level of the person. Although exercise in general benefits health, in some cases such as chronic intense training, it may affect the neuroendocrine system negatively [27]. This possibility should be borne in mind whenever exercise regimens are being recommended.

Exercise and neuromuscular diseases

In a recent meta-analysis by the Cochrane review group of 35 exercise trials in muscle diseases from 1966 to 2002, only two studies met rigorously defined criteria for inclusion [28]. To be included, studies have to be randomized, use a nonintervention group as a comparison, and have a standardized training protocol of at least 10 weeks' duration. One study involved patients who had fascioesca pulohumeral muscular dystrophy and the other, myotonic dystrophy. The investigators concluded that in patients who had either of these two diseases, moderate intensity strength training showed no significant benefit or harm.

A more inclusive review of exercise studies in patients who had neuromuscular diseases found 58 studies to be of sufficient methodological quality for analysis [29]. The investigators examined the effects of strengthening exercise, aerobic exercise, or a combination of the two, in diseases of the anterior horn cells, nerves, and muscles. Nearly all the studies included an individualized, progressive strengthening protocol as defined by established guidelines for healthy adults [30] and the protocols were of moderate intensity. Despite variations in the types of exercises and muscle used, the interventions in nearly all disease groups caused no adverse effects. The investigators concluded that the combination of strengthening and aerobic exercises is likely to be effective (level II evidence) in patients who have muscle diseases, and that aerobic exercises may be effective (level III evidence) for patients who have muscle diseases. In addition, breathing exercises may be effective (level III evidence) for patients who have myasthenia gravis and neuromuscular diseases. Evidence was insufficient of a beneficial effect of strengthening alone in all neuromuscular diseases included in the review.

Rehabilitation for patients who have stroke and multiple sclerosis deserves some mentioning here, because these patients often exhibit spasticity, which is also commonly seen in patients who have ALS. A systematic review of progressive resistance strength training in poststroke patients showed that such training can increase muscle strength without increasing spasticity or reducing range of movement [31]. A review of the literature on physical training and multiple sclerosis also showed that exercise is beneficial for these patients, without adverse effects [32,33]. These findings are encouraging and suggest that exercise may be safely applied to ALS patients who have spasticity.

Exercise and amyotrophic lateral sclerosis (human studies)

Below, the authors review studies of exercise, grouped by the types of exercise regimen, in patients who have ALS.

Stretching exercise

Stretching, or exercises that improve flexibility, can maintain muscle and soft tissue extensibility and joint mobility, and can prevent contractures [34].

Muscle weakness in ALS can cause an imbalance between agonist and antagonist muscle groups, predisposing patients who have ALS to muscle shortening, joint contractures, and poor posture. Claw hand deformity is a good example of this disparity and occurs in ALS patients. Stretching weakened and unaffected muscle groups prevents contractures, maintains good postural alignment, reduces pain from hypomobility, and helps lessen the potential complexities of functional mobility and performing activities of daily living. Because stretching does not impact muscle strength, it is often used as a placebo or a control in studies examining the benefits of other types of exercise in ALS (Table 1). It, itself, has not been randomized against nonstretching in the study of exercise in ALS.

Resistance/strengthening exercise

Strengthening exercise, or exercises that are used to maintain or improve a muscle's ability to generate force, helps maintain function, avoid injury, and prevent disability [34]. Skeletal muscle weakness is the cardinal sign and symptom of motor neuron degeneration in ALS. Strengthening exercises can be tailored for weak and strong muscle groups and can be performed with or without resistance [34].

One of the first published reports of the beneficial effects of strengthening in ALS was a case study using upper extremity resistive exercise for 75 days [35]. Isometric strength, assessed with a strain gauge, demonstrated improvements in 14 upper extremity muscle groups and diminished strength in 4 muscle groups, resulting in a subjective report of functional improvement.

The first prospective, randomized study examining the effect of strengthening exercise in patients who have ALS was done in 2001 [36]. The investigators randomized 25 patients to either an exercise or a nonexercise group. A moderate-intensity exercise program was developed for the individual and performed by patients at home for 15 minutes twice a day. At 3 months, differences in functional improvements were noted between the exercise and control groups, as measured by the ALS Functional Rating Scale (ALSFRS) and the Ashworth Spasticity Scale, but not in manual muscle testing scores or reports of fatigue and quality of life. At 6 months, no significant difference was noted between the groups on any measures. Unfortunately, the investigators did not define the training regimen or the length of the training regimen more specifically, making it difficult to duplicate or use for comparison.

A multicenter, prospective, randomized study published in 2007 using 27 subjects who had ALS was the first to use a scientifically defined training protocol recognized by the American College of Sports Medicine [37]. Subjects were assigned to one of two groups: a treatment group consisting of an individually tailored, home resistance exercise program three times weekly along with a daily stretching program, or a control group consisting of a daily stretching program only, for 6 months. The exercise group had

Table 1
Exercise studies in amyotrophic lateral sclerosis

Types of exercise	Studies	Outcomes
Stretching	No RCT	
Enhances connective tissue		
Strengthening	Bohannon et al, [35] case study	Improved isometric strength in 14 U/E muscles Decreased isometric strength in 4 muscles Subjective improvement of functions
Myofiber remodeling		
Reduces inflammation		
Enhances metabolism	Drory et al, [36] randomized	Improved function (ALSFRS) at 3 months Improved spasticity (ASS) at 3 months No changes in MMT, fatigue, and QOL
CNS adaptation	Bello-Haas et al, [37] randomized	Improved function (total and subtotal ALSFRS-R) at 6 months Improved QOL (SF36) at 6 months
Aerobic	Sanjak et al, [40] case control	Examined biophysical and metabolic responses: Increased oxygen cost of work Decreased lipid metabolism
Myofiber remodeling		
Reduces inflammation		
Enhances metabolism	Pinto et al, [42] case control	Improved the rate of functional decline (Spinal Norris)
CNS adaptation	Siciliano et al, [43,44] case control	Improved QOL on FIM scale, but not Bartels Increased lactate and lipid peroxides Precocious anaerobic threshold achieved

Abbreviations: ALSFRS, ALS Functional Rating Scale; ALSFRS-R, ALS Functional Rating Scale-Revised; ASS, Ashworth Spasticity Scale; CNS, central nervous system; FIM, Functional Independence Measure; MMT, manual muscle testing; QOL, quality of life; RCT, randomized controlled trial; U/E, upper extremity.

significantly higher functions (as measured by the total ALSFRS and combined upper and lower extremity subtotal ALSFRS scores) and an improved quality of life, (as measured by the 36-Item Short Form Health Survey Physical Function Subscale) at 6 months. This exercise study in ALS is the best to date, providing class II evidence of the positive effect of exercise for these patients, as defined by the American Academy of Neurology [38]. The number of subjects who were recruited and who completed the study was small; this problem is commonly encountered in ALS research, and it should be addressed in future studies.

Aerobic/endurance exercise

Aerobic exercise has been shown to maintain cardiorespiratory fitness and to benefit mood, appetite, and sleep in healthy people [39]. Few studies have been done that address whether aerobic exercise affects the functional outcomes in patients who have ALS. Instead, most of these studies were performed to examine the immediate physiologic and metabolic responses of ALS patients to exercise. The first such study was done in 1987, when investigators studied 35 ALS patients and compared their physiologic response to bicycle ergometer aerobic exercise with healthy controls [40]. They found that the autonomic response (heart rate and ventilatory response) to exercise was similar in patients and controls. However, the use of oxygen and metabolism of lipid in response to exercise is altered in patients who have ALS. It is therefore logical to ensure adequate oxygenation, aeration, and carbohydrate loads when recommending exercise for patients who have ALS. The last is especially important because studies have shown that carbohydrate supplementation in healthy subjects reduces oxidative stress load [41].

In 1999, one study was published whereby ALS patients were asked to perform a ramp treadmill exercise up to an anaerobic threshold, either with the assistance of a noninvasive ventilation (bilevel positive airway pressure) or without [42]. The investigators then measured the respiratory function, Barthel score, Functional Independence Measure Scale, and Spinal and Bulbar Norris scores. The purpose of this study was to determine if the compensation of alveolar hypoventilation with noninvasive ventilation support in ALS patients during exercise can achieve a greater conditioning effect. Their results demonstrated significant differences between the exercise group and a nonexercise control group in the rate of decline and absolute values on the Spinal Norris scale, a functional rating scale not widely used. Quality of life was different as measured by Functional Independence Measure, but not by Barthel scores. Their results suggest that exercise may be beneficial in ALS and may be performed even when respiratory insufficiency is present, with the support of noninvasive ventilation.

In subsequent years, two other studies were done to examine the oxidative stress responses in ALS patients versus controls after an incremental bicycling test, by measuring the lactate and lipoperoxide levels [43,44]. Both

studies were small, with 11 and 10 patients, respectively. The investigators found that baseline lactate and lipoperoxide levels were higher in ALS patients than in controls, and that the anaerobic threshold was precociously activated in ALS patients, suggesting that mitochondrial dysfunction occurs in the exercising skeletal muscle of ALS patients.

Based on the authors' analysis, only two class II studies of exercise as a therapeutic intervention in ALS have been done [36,37]. Although both studies were small, and only single blinded, they allowed the authors to conclude that individualized strengthening exercise during the early stage of the disease is probably effective in improving the function of patients who have ALS, and such a recommendation should be considered. Although cardiovascular exercise appears safe in the early and late stages of ALS, the data are insufficient at this time to make further recommendations regarding endurance training for ALS patients (see Table 1).

Exercise and amyotrophic lateral sclerosis (animal studies)

Because only a few studies in humans on exercise and ALS have been published, one must turn to animal studies to further our understanding of the effects of exercise on ALS. Transgenic mice overexpressing the human superoxide dismutase gene, G93A-SOD1, are used as an animal model of ALS, because these mice exhibit hindlimb weakness, spasticity, and atrophy at 3 months of age, and progress to paralysis within 4 to 5 months of age [45]. All four animal studies used treadmill running (aerobic/endurance training) as the mode of exercise, in contrast to the human studies, in which resistance training was used.

Veldink's group [46] randomized 65 low-copy SOD1 transgenic mice and 16 wild-type controls to either treadmill exercise or a sedentary group. The animals were trained from 8 weeks of age, when they were presymptomatic, to a median age of 26 weeks throughout the disease course, running on a treadmill at 16 m/min, for 45 minutes daily, 5 days per week. The outcome measurements were onset of disease (measured by hindpaw extension reflex), progression of disease (measured by beam balance test and the loaded grid test), and survival. In this study, it was found that moderate exercise starting at a presymptomatic stage delayed the disease onset in the low-copy SOD1 female mice by 48 days. When the investigators repeated the study using 20 high-copy SOD1 female mice, they found that the survival was prolonged by 4 days compared with the sedentary female mice. The outcome measurements for the male SOD1 mice showed no statistically significant differences.

Another study performed by Kirkinetzos' group [47] showed that 10 weeks of treadmill training (from age 7 weeks to 17 weeks) in SOD1 mice, with 13 m/min of treadmill running for 30 minutes, 5 days per week, expanded the average lifespan for the male mice from 129 days to 139 days, and for the female mice from 139 days to 144 days. In this study, the

beneficial effect in expanding life expectancy was statistically significant for the male mice but not for the female mice. The investigators proposed that this finding may be caused by the effect of testosterone on muscle build-up. However, it is unclear as to why the effect of sex on exercise and survival outcome is different for these two animal studies. Parenthetically, no data in humans suggest that men and women with ALS respond differently to exercise regimens.

In another study, performed by Mahoney and colleagues [48], SOD1 mice were trained from 6 weeks of age onward with a high-intensity endurance treadmill exercise, running to a peak of 22 m/min, 45 minutes per day, 5 times per week, until the mice were symptomatic and unable to maintain running at 9 m/min for 45 minutes. The investigators found that such high-intensity endurance training does not affect the age or probability of disease onset in either male or female SOD1 mice but it hastened death by 11 days in SOD1 male mice.

Finally, Liebetanz and colleagues [49] studied lifetime vigorous exercise, consisting of 400 minutes of daily treadmill running (40 × 10 minutes running at 3.4 m/min interspersed with 5-minute rest intervals) in SOD1 mice, starting at 5 weeks of age. The investigators did not find a deleterious effect on the onset or progression of motor degeneration. Instead, a nonsignificant positive survival trend was found for the exercise group.

The authors conclude from these animal studies that (1) SOD1 mice may have an inverse response of survival to the exercise intensity, with a lower treadmill running speed (3.4 to 16 m/min) prolonging survival [46,47,49] and an intense treadmill running speed (22 m/min) decreasing survival [48] and (2) prolonged exercise is not necessarily harmful to the survival of SOD1 mice, as long as the exercise periods are regularly interspersed with rest periods, allowing for proper physiologic adaptations [49].

Whether one may extrapolate the above findings to humans remains to be demonstrated, because the SOD1 gene mutation explains only 2% of all human ALS cases. The treadmill running protocols were also initiated early in mice, equivalent to the teenage years in humans. The positive effect of “prehabilitation” with moderate endurance training in prolonging survival will be practically impossible to replicate in humans, except for a few identified familial ALS cases.

The debate surrounding strenuous physical activity and amyotrophic lateral sclerosis

The issue of whether highly intense and strenuous physical activity leads to an increased risk for ALS is still debated. Case reports and retrospective studies have shown a link between intense physical activity and ALS, as in professional soccer players and war veterans [50,51]. However, it is difficult to ascertain the relative risk ratio from retrospective analyses [52–54]. People have proposed that other common factors, such as a genetic

predisposition, may exist between high levels of athleticism and the pathogenesis of ALS, rather than the act of intense physical exertion itself as a causative factor for the development of ALS. Although investigators have shown that the resting energy expenditures in ALS patients are higher than in controls [55,56], it is not clear if the hypermetabolic state is a causative or correlated feature of the disease. Further studies are needed to clarify the questions raised here.

Summary

Based on the authors' review of the few human and animal studies of exercise and motor neuron degeneration, they conclude that exercise is likely to be more beneficial than deleterious for patients who have ALS. In particular, they recommend individualized and carefully monitored, progressive resistance exercise in patients who have early ALS, for functional improvement. This recommendation is based on the positive results of two class II studies [36,37].

Studies are needed to examine stretching and endurance training, and a combination of endurance and strengthening exercises as therapeutic means for patients who have ALS. Lessons learned from SOD1 mice suggest that it is important for future studies of endurance training in humans to define the training protocol clearly, including the intensity, duration, and frequency of training, and the pretraining functional status of the patients. It is to be hoped that such measures will help standardize the investigative effort and further our understanding about how each type of exercise may affect patients who have ALS. Finally, it remains unknown whether oral and breathing exercises would help the bulbar and respiratory function in patients who have ALS. Studies are clearly needed in this respect. The authors hope this article stimulates further discussions and investigations among neurologists, physiatrists, physical therapists, researchers, and scientists in addressing the important question as to whether and how exercise may be used to alter the course of the disease and to improve the strength, function, and quality of life for people who have ALS.

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