Effect of nutritional supplementation with milk whey proteins in amyotrophic lateral sclerosis patients

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ABSTRACT

Objective: We evaluated the efficacy of oral supplementation with milk whey proteins and modified starch (70%WPI:30%MS), on nutritional and functional parameters of patients with ALS. **Method:** A prospective randomized double-blind study was performed with 16 ALS patients, divided in two groups, the treatment group received (70%WPI:30%MS) and the control group received (maltodextrin). They underwent prospective nutritional and functional assessment for 4 months. **Results:** Patients in the treatment group presented weight gain, increased body mass index (BMI), increased arm muscle area and circumference, higher albumin, white blood cell and total lymphocyte counts, and reduced creatine-kinase, aspartate aminotransferase and alanine aminotransferase. In the control group, biochemical parameters did not change, but weight and BMI declined. **Conclusion:** Our results indicate that the agglomerate 70%WPI:30%MS may be useful in the nutritional therapy of patients with ALS.

Key words: amyotrophic lateral sclerosis, nutrition status, anthropometry.

Efeito da suplementação nutricional com proteínas do soro de leite em pacientes com esclerose lateral amiotrófica

RESUMO

Objetivo: Avaliar a eficácia da suplementação nutricional oral com proteínas do soro do leite e amido modificado (70%WPI:30%MS), nos parâmetros nutricionais e funcionais de pacientes com esclerose lateral amiotrófica (ELA). **Método:** Foi realizado estudo randomizado duplo-cego, com 16 pacientes com ELA, divididos em dois grupos, um que recebeu 70%WPI:30%MS e um controle que recebeu maltodextrina. Os pacientes foram submetidos a avaliação nutricional e funcional durante quatro meses. **Resultados:** Nos pacientes que receberam o suplemento 70%WPI:30%MS, foi observado ganho de peso, aumento na contagem de linfócitos e redução de creatina kinase, aspartato aminotransferase and alanina aminotransferase. No grupo controle, os parâmetros bioquímicos não sofreram modificações; no entanto, peso e índice de massa corporal diminuíram. **Conclusão:** Nossos resultados indicam que o aglomerado 70%WPI:30%MS pode ser útil na terapia de pacientes com ALS.

Palavras-chave: esclerose lateral amiotrófica, estado nutricional, antropometria.

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of motor neurons in the cerebral cortex, brainstem, and spinal cord[1]. ALS patients show multiple clinical features, since the disease affects bulbar and/or spinal systems according to the site of motor neuron involvement. As the disease progresses, both upper and lower motor neurons may be affected, and various symptoms may overlap[2]. During the course of ALS, there is often a decline in nutritional status that is not properly managed in clinical practice, even though it is a significant and independent prognostic survival factor[3].

Nutritional status should be routinely monitored to identify poor food intake and malnutrition[4]. Patients may experience rapid weight loss associated with reduced nutritional intake, prolonged meal times, fatigue, dehydration and depression. Unfortified texture-modified diets for dysphagic patients may hasten weight loss due to their low protein and energy content[5,6]. When these nutrition-depleting co-factors are present the insidious onset of malnutrition is inevitable.

Ingredients such as milk whey proteins, when chemically or physically modified, can alter the viscosity of food systems. However, on their own, they are unable to reach the viscosity standardised by the ADA[7] for fluids, but agglomerated with carbohydrate sources such as modified starch, they could increase the viscosity of food systems to values close to those cited by the ADA.

Based on the high malnutrition index and difficulty in nutritional handling, the main objective of this study was to evaluate the effect of supplementation with the agglomerate with 70% milk whey protein isolate and 30% modified starch (70%WPI:30%MS), on anthropometrics, body composition and biochemists parameters in ALS patients.

METHOD
Study design and population
We performed a prospective randomized double-blind controlled clinical trial to evaluate oral supplementation of milk whey protein in patients with ALS. We recruited 16 patients (14 males) with clinically definite ALS from the Neuromuscular outpatient clinic of Campinas University (UNICAMP). Patients were divided in two groups of 8 patients each, and randomized to receive either milk whey protein or maltodextrin (control), for 16 weeks, and submitted to bimonthly evaluation.

The study was conducted between July 2006 and July 2007. The study was approved by the ethics committee of the School of Medical Sciences - UNICAMP and all patients accepted a written consent.

Inclusion criteria
ALS patients meeting El Escorial criteria (1998)[8] for defined disease, either with bulbar or appendicular onset, regularly assisted in the Clinic, were included in the study.

Exclusion criteria
Patients with nasogastric tube or gastrostomy, on assisted mechanical ventilation and without intervening neurological illnesses.

Nutritional intervention phase
Patients were randomized to receive either maltodextrin (control group) or oral supplementation with whey protein (treatment group). This is a nutritional supplement developed at UNICAMP containing 70% of milk serum protein and 30% modified starch (70% WPI:30% MS). Patients received maltodextrin or whey protein for 16 weeks. Nutritional assessment, including anthropometric and biochemical measures, was performed at the onset, two months and four months after supplementation. We performed functional assessment at the onset and four months after supplementation.

Nutritional supplementation
Individual daily needs of protein are 1.2 g/kg of body weight. We offered whey protein to the patients, approximately 30% of the daily protein requirements.

Nutritional supplementation was administered twice a day (morning and afternoon) for 16 consecutive weeks. Patients did not receive the supplement concurrently with Riluzole. They were instructed to keep the product in a refrigerator and to solubilize it before administration; on an individual basis, assays to the adequate viscosity were performed with orange juice (pH=4.0 and 1.5% of solid components).

Dietary evaluation
After nutritional anamnesis and socio-economic data collection, we applied the 24h record method[9] in 6 different days for every patient. We inquired about the usual diet of the patient, including amount, commercial brand and the cooking procedure. We estimated energy requirement (ER); proportion of carbohydrates, proteins and lipids; proportion of saturated, polyunsaturated and monounsaturated fat relative to ER; and the intake of fibers, calcium, iron, retinol and ascorbic acid. Estimates were accomplished by the *software* DIET PRO 4.0[10]. The amount of fibers, cholesterol, saturated, polyunsaturated and monounsaturated fat was analyzed by DIET PRO 4.0 in accordance with the Brazilian food composition table[11] and the table of the United States Department of Agriculture (USDA – Release 16)[12].

We evaluated macronutrient and protein nutritional adequacy in accordance with the Recommended Di-

etary Allowances (RDA)[13] and the recommendations of the Brazilian Society of Food and Nutrition[14], respectively. We used the guidelines of the Institute of Medicine to analyze intake of micronutrients. The Harris and Benedict equation, modified by Long et al.[15] was employed to analyze resting energy requirements.

Nutritional evaluation

Body weight (kg)[16] and height (m) were assessed, owing to the fact that four patients older than 60 were limited to wheelchairs, the Chumlea et al. method was used[17.] Body mass index (BMI - kg/m^2) and midarm circumference (MAC - cm)[18,19] were determined; the tricipital (TSF), bicipital (BSF), supra-iliac (SISF) and subscapular (SESF) skinfolds (SF) were measured using the scientific Lange branded 0.1mm-accuracy adipometer, in order to classify ALS patients according to the estimates of relative body fat[18]; midarm muscle circumference (MAMC), arm muscle area (AMA) and arm fat area (AFA) were obtained from MAC and TSF according to Heymsfield et al. and Frisancho[19,20]. The percentage of weight loss (%WL) was determined based upon the usual and the actually measured weight of the patient[21]. The protein-caloric malnutrition score (PCMS)[18] was used to classify nutritional status of patients.

Clinical and biochemical parameters

We determined the serum levels of C-reactive protein, albumin, pre-albumin, creatine-kinase (CK), creatine, urea, glucose, aspartate transferase (AST), alanine transferase (ALT), total lymphocyte count, platelets, sodium and potassium for each patient.

Table 1. Influence of the nutritional supplementation with the 70%WPI:30%MS agglomerate on body weight (kg), body mass index (BMI-kg/m^2), fat mass (%) and fat free mass (%), tricipital skinfold (TSF), bicipital skinfold (BSF), supra-iliac skinfold (SISF), subscapular skinfold (SESF) and sum of the four skinfolds (mm), midarm circumference (MAC), wrist circumference, midarm muscle circumference (MAMC), arm muscle area (AMA) and arm fat area (AFA) (cm^2).

	Control group*			Treatment group*		
	Months			Months		
Parameters	**0**	**2**	**4**	**0**	**2**	**4**
Body weight (kg)	65.8±1.2ª [49.8-81.0]	64.7±1.3ᵇ [48.0-80.0]	64.3±1.3ᵇ [48.0-80.0]	62.3±1.5 [45.4-81.5]	63.3±1.5 [46.1-81.6]	63.4±1.5 [45.9-81.7]
BMI (kg/m^2)	22.9±0.4ª [17.2-26.9]	22.5±0.4ᵇ [17.0-27.7]	22.2±0.4ᵇ [17.0-27.7]	21.7±0.4ᴮ [18.12-27.03]	22.1±0.4ᴬ [18.20-27.17]	22.3±0.5ᴬ [18.43- 27.51]
Fat mass (%)	26.1±0.7 [15.6-40.4]	28.1±0.3 [15.6-39.9]	27.3±0.3 [15.6-40.0]	20.8±0.6 [10.38-26.5]	20.5±0.6 [10.2-25.5]	20.4±0.6 [10.01-25.9]
Fat free mass (%)	73.8±0.3 [59.6-84.4]	71.9±1.2 [60.1-84.4]	72.7±1.2 [60.0-84.4]	79.1±0.6 [73.5-89.62]	79.5±0.6 [74.5-89.8]	79.6±0.6 [74.1 89.99]
TSF (mm)	14.9±0.5 [7-23]	14.4±0.5 [7-23]	15.8±0.5 [6.5-24]	9.6±0.2ᴮ [6-12]	10.7±0.2ᴬ [7-13]	11.1±1.2ᴬ [8-13]
BSF (mm)	7.4±0.3ᵇ [3-12]	7.4±0.2ᵃᵇ [4-12]	8.6±0.2ª [3.5-12.6]	6.2±0.1ᴬ [4-8]	5.6±0.1ᴮ [4-7]	5.5±0.1ᴮ [4-7.1]
SISF (mm)	15.5±0.7 [5-25]	16.1±0.7 [5-25]	16.2±0.7 [5-26]	12.4±0.3 [6-18]	11.8±0.3 [6-17]	11.7±0.3 [6-17]
SESF (mm)	12.9±0.4ᵇ [8-22]	13.5±0.5ª [8-22.3]	13.6±0.5ª [8-22.4]	11.5±0.2ᴬ [8-14]	10.8±1.2ᴮ [8-13.8]	10.2±0.2C [8-13.5]
Σ SF (mm)	50.6±1.5 [24-71]	51.4±1.5 [25-71]	66.6±1.6 [23.1-3 .8]	39.8±0.4 [35-46]	39.1±0.3 [34.8-44]	38.5±0.3 [34.5-43]
MAC (cm)	27.2±0.3 [20.5-31]	27.3±0.1 [20-31]	27.2±0.1 [20-31]	25.3±0.5 [19.5-30.8]	25.5±0.5 [19.5-30]	25.8±0.4 [21-30]
wrist circ (cm)	16.7±0.1 [14.4-18]	17.1±0.1 [15-18]	16.7±0.1 [14.5-18.2]	17.1±0.2 [14.8-19]	17.1±1.3 [14.8-19]	17.1±1.3 [14.8-19]
MAMC (cm)	23.3ª±0.3 [18.3-26.5]	22.8±0.3 [17.8-26.9]	22.6±0.3ᵇ [17.9-27.1]	22. 5±0.5 [15.4-27.3]	22.8±0.5 [15.7-28.3]	23.9±0.5 [16.9-28.4]
AMA (cm^2)	42.1±2.1ª [15.9-67.8]	42.1±2.1ª [15.9-67.2]	39.9±2.1ᵇ [14.4-67]	47.8±2.5 [23.1-69.9]	48.6±2.3 [30.1-71.9]	48.4±2.2 [31.0-71.6]
AFA (cm^2)	61.3±1.4ª [33.4 75.4]	61.4±1.4ª [33.9-76.4]	64.2±1.4ᵇ [34-78. 2]	20.9±0.6ᴬ [10.3-26.5]	20.1±0.6ᴮ [10.2-25.5]	19.8±0.6ᴮ 10.1-25.2]

*Values correspond to means±standard error of three determinations and minimum and maximum values. Values not sharing similar letter in the same line referent to control group (a) and treatment group (A) are different (p<0.05) in Tukey test.

Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R)

ALSFRS-R is a questionnaire-based scale for activities of daily living. This scale contains 12 items grouped into three domains that encompass appendicular function (gross motor tasks), bulbar and respiratory function. Each item has a 5-point scale (0 for unable. 4 for normal) and scores ranging from 0 to 48. Low scores denote a serious disease status[22].

The patients were evaluated by an interdisciplinary group. The nutritional assessment was done by a nutritionist and the ALSFRS-R assessment by physiotherapists.

Statistical analysis

We used the Kolmogorov-Smirnov test to evaluate whether the studied variables had normal distribution. Independent variables with normal distribution were expressed as mean±standard deviation, and compared with a two-sided t test. Prospective data were analyzed with a paired t-test. We used the Mann-Whitney test to compare independent groups without normal distribution. The value was set at 5%.

RESULTS

The average age of the patients was 53 (ranging between 32 and 69 years old) and the illness time, 2 years±1. In 10 patients, the impairment was predominantly appendicular, whereas in the remaining 6 it was bulbar (GB).

We found increased food intake in both control and supplemented groups after nutritional intervention. In both groups, patients followed nutritional advice as shown by the relevant improvement in macro and micronutrient intake.

At the time of enrollment, patients in the control group exhibited 77% nutritional adequacy, but after 4 months, the percentage rose to 90.27 (p=0.032). Carbohydrate intake (70.8% vs 82%, p=0.022) significantly increased in 4 months, as did the lipid intake (93% vs

Table 2. Influence of nutritional supplementation with the 70%WPI:30%MS agglomerate on clinical and biochemical parameters.

Parameters	Control group*			Treatment group*		
	Months			Months		
	0	2	4	0	2	4
C-reative protein (mg/dL)	0.21±0.03 [0.04-0.7]	0.21±0.03 [0.05-0.74]	0.18±0.02 [0.05-0.5]	0.10±001[B] [0.02-0.23]	0.13±0.01[A] [0.02-0.28]	0.12±0.03 [0.02-0.27]
Albumin (g/dL)	4.51± 0.03 [4.15-4.9]	4.47±0.04 [4.0-5.1]	4.48±0.05 [3.9-5.3]	4.30±0.05[C] [3.6-4.8]	4.51±0.03[B] [4.2-4.9]	4.76±0.01[A] [4.4-4.9]
Pre-Albumin (mg/dL)	28.2±0.7 [19.5-39.1]	29±0.8 [17.2-34.3]	29.2±0.9 [19.5-36.7]	26.3±0.6 [17.7-32.3]	30.6±0.5 [35.4-23.6]	30.6±0.7 [24.5-39.2]
CK (U/L)	338.7±31.1 [100-774]	310±27 [87-645]	335.5±29.4 [84-626]	449.6±30.3[A] [117-795]	375±31.6[AB] [87-888]	307±12.2[B] [143-403]
Urea (mg/dL)	29.5±0.8 [22-43]	29.25±0.9 [20-45]	29.5±1.2 [17-40]	27.5±1.1[A] [19.9-46]	26.1±0.7[B] [22-43]	26.7±0.8 [19-42]
Creatine (mg/dL)	0.56±0.02 [0.39-1.02]	0.63±0.03 [0.4-1.06]	0.57±0.03 [0.35-1.13]	0.74±0.02 [0.35-1.02]	0.63±0.03 [0.25-1.0]	0.61±0.03 [0.25-1.1]
Glucose (mg/dL)	85±1.7 [55-99]	86±1.5 [72-103]	89±1.4 [76-111]	81.6±0.7 [74-90]	80±0.7 [73-88]	80±0.8 [69-87]
AST (U/L)	27.1±1.1 [13-41]	25.6±0.8 [14-34]	25.2±0.9 [14-37]	28.6±1.2[A] [19-45]	27.1±1.1[B] [15-40]	26.2±1.3[C] [16-42]
ALT (U/L)	28.1±1.3 [10-41]	26.6±1.4 [10-41]	27.1±1.6 [9-47]	32.9±1.9[A] [8-55]	31.5±1.8[B] [8-53]	27.2±1.8[C] [8-47]
Lymphocytes (cels × 10³/mm³)	2.36±0.08 [1.61-3.46]	2.4±0.1 [1.44-4.13]	2.4±0.1 [1.64-4.02]	2.1±0.8 [0.9-3.1]	2.3±0.1[B] [1.29-2.67]	2.5±0.1[A] [1.58-3.12]
Leukocytes (cells × 10³/mm³)	7.67±0.25 [4.13-9.72]	7.80±0.22 [5.06-10.8]	7.64±0.22 [4.47-9.87]	6.75±0.18[C] [4.07-9.3]	7.37±0.19[B] [4.37-9.8]	8.77±0.24[A] [5.8-12.55]
Platelets (cells × 10³/mm³)	243.7±9.8 [132-376]	237.9±8.3 [131-359]	238.7±8.1 [121-335]	233.6±4.6 [186-291]	235.4±4.9 [192-297]	237.6±4.8 [181-275]
Potassium (mEq/L)	4.35±0.02 [4.1-4.6]	4.32±0.02 [3.9-4.5]	4.37±0.03 [4.0-4.7]	4.1±0.02 [3.8-4.3]	4.1±0.02 [3.8-4.4]	4.1±0.1 [3.8-4.3]
Sodium (mEq/L)	139.9±0.4 [137-146]	140.1±0.4 [136-145]	140.2±0.3 [137-144]	139.9±0.2 [136-142]	140.7±0.2 [138-143]	141.6±0.4 [138-149]

*Values correspond to means ± standard error of three determinations and minimum and maximum value. Values not sharing similar letter in the same line referent to control group (a) and treatment group (A) are different (p<0.05) in Tukey test.

101.4%, p=0.038). Protein and fiber intake also improved at the end of this period (82.04% vs 93.53%, p=0.043, and 50.44% vs 63.6%, p=0.034, respectively). Ingestion of calcium (p=0.002), ascorbic acid (p=0.035), vitamin E (p=0.012) and retinol (p=0.041) increased.

We found similar changes in the supplemented group. Energy adequacy rose from 78.55 to 92.20% (p=0.034) in two months. Intake of carbohydrates (72.61% vs 91.1%, p=0.021), lipids (94.66% vs 107.2%, p=0.001), proteins (79.24% vs 105.6%, p=0.001) and fibers (49.96% vs 74.48%, p=0.002) improved in this group after two months. Calcium and vitamin E ingestion also increased (p=0.002 and 0.014, respectively).

Table 1 shows body weight, BMI, fat and lean body mass in the control and supplemented groups. There was a significant reduction of body weight and BMI in the control group (p=0.029 and 0.003, respectively), whereas in the supplemented group we found increased BMI (p=0.041). Differences between groups did not reach statistical significance. Table 1 also shows TSF, BSF, SISF and SESF skinfolds in both groups.

In the control group only, we found decreased MAMC and AMA in the follow-up (p=0.003 e p=0.019), whereas AFA increased (p=0.042). MAC and wrist circumference did not change in the supplemented patients (p=0.062 e p=0.090, respectively) (Table 1).

There was significant improvement in serum albumin levels (p=0.001), total lymphocyte count (p=0.004) and white blood cell count (0.002) among supplemented patients. In this group, CK, AST and ALT levels significantly decreased (p=0.028, 0.004 and 0.003, respectively), as depicted on Table 2.

ALSFRS-R scores in both groups are on Table 3.

DISCUSSION

Patients with ALS included in this study share the characteristic epidemiologic features of the disease[23]. We did not find relevant differences between patients with bulbar and appendicular predominance.

Most patients had low income (88% received <$1,000.00) and education level (80% studied up to the 4th grade). Ten patients (62%) had 5 or 6 daily meals, four (25%) had 4, and two (13%) had 3 daily meals.

Rio and Cawadias[24] reviewed nutritional guidelines for patients with ALS in the United Kingdom and found that calorie and protein supplementation was the cornerstone of nutritional therapy. Heffernan et al.[25] also emphasized the relevance of education and nutritional intervention in these individuals. In a previous study with 20 patients, authors were able to modify the nutritional status classification in 70% of individuals after oral supplementation. They have shown that oral supplementation avoided worsening the nutritional status, but could not normalize the overall nutritional adequacy[26]. In accordance with Karsarskis et al.[27] and Desport et al.[1], we have found progressive decline of body weight and BMI in non-supplemented patients. However, BMI improved in patients that received oral supplementation. In this group, fatty and lean body mass did not decline in the follow-up, leading to higher PCMS.

Skinfolds are a useful clinical method to evaluate body composition, namely the proportion of fat mass[28,29]. We found in the control group that BSF and SESF increased in the follow-up, thus suggesting higher proportions of body fat mass. Increased TSF in supplemented patients may have been caused by higher food intake during the study. Slowie[4] identified a relationship between reduced food intake and smaller TSF. Modifications in TSF may have contributed to improved PCMS scores in this group.

MAMC and AMA are markers of striated muscle protein mass[28]. MAC and wrist circumference did not change in the follow-up in either group (Table 1). MAMC and AMA declined in the control group, whereas AFA increased; this may indicate a fatty change in the skeletal muscle due to chronic denervation. MAMC and AMA remained stable in the supplemented group, but AFA declined, suggesting preserved lean body mass and reduced fat body mass. Similar findings were reported by Stanich et al.[26] among patients with ALS receiving hypercaloric supplementation. Karsarsis et al.[27] identified progressive AMA decline over disease course.

Patients in both groups were classified as eutrophic according to the BMI. However, PCMS takes into account body composition measures and is therefore a more reliable tool to evaluate nutritional status. In the control group, PCMS were 80.13, 77.67 and 79.93 at the onset and after 2 months and 4 months of follow-up, respectively. Meanwhile, PCMS progressively increased among the supplemented patients (75.26, 77.13 and 78.89). Despite the different courses, patients in both groups were classified as having moderate malnutrition (70-80%).

Table 3. ALSFRS-R: Level of significance among the first and second time of control and supplemented groups.

	Control group*			Treatment group*		
	0	4	p-value	0	4	p-value
ALSFRS-R	27.0±3.8[a]	23.6±4.4[b]	0.03	29.1±2.4	27.0±3.5	0.17

ALSFRS-R: score of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised at first (0) and second times (4 months), respectively. Values correspond to means±standard error of three determinations. Values not sharing similar letters in the same line are different (p<0.05) by the Tukey test.

Clinical and biochemical parameters showed normal values for albumin, pre-albumin and C-reactive protein (CRP) in patients with ALS. Kasarskis et al.[27] previously found that pre-albumin and retinol-binding protein serum levels did not change over disease course. These results are much similar to the ones observed in our supplemented group. Desport et al.[1] also found normal values for CRP, white blood cell and total lymphocyte counts in ALS. We found increased serum albumin, white blood cell and total lymphocyte counts in supplemented patients; this may be related to immunomodulatory properties of milk proteins[28]. Muscle turnover, expressed by CK, AST and ALT levels, also decreased in this group.

The bioactive properties of milk whey protein were observed in studies made in order to analyze the different effects of food proteins in the immune system of animals. It was noticed that the whey protein isolate contains high levels of glutathione, and its precursors cystine and glutamylcystine, and that the combination of these factors plays an important role in maintaining the necessary cellular glutathione levels to guarantee an efficient immune response[29]. Considering these bioactive properties, benefic effects may be implied in the analyzed parameters. Different from proteins, modified starch used in the treatment group was only composed by carbohydrates, calculated as part of the recommended daily energetic ingestion of the individuals' diet.

ALSFRS-R is a reliable tool useful to predict survival in ALS[30,31], survival after mechanical non-invasive ventilation, and to estimate overall functioning of patients with ALS[32]. ALSFRS-R scores did not change among supplemented patients (p=0.173), but significantly declined in the control group (p=0.003).

In Conclusion, during the follow-up study, intake of carbohydrates, lipids, proteins, fibers, calcium and vitamin E significantly increased in both control and supplemented groups. BMI, MAMC and AMA declined over time in the control group, which received maltodextrin. In the supplemented group, however, serum albumin, white blood cell and total lymphocyte counts increased. Lean body mass seems to be preserved in this group, and skeletal muscle turnover markers (CK, AST and ALT) declined. The ALSFRS-R scores did not change in the supplemented group, while patients in the control group presented a progressive decline. Our results indicate that 70%WPI:30%MS improved the nutritional status of patients with ALS, and may be useful in the clinical management of the disease.

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