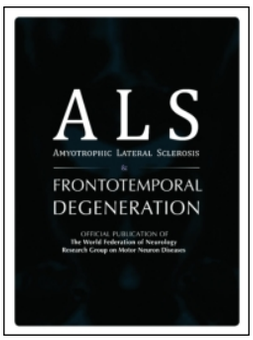

Amyotrophic Lateral Sclerosis

ISSN: 1748-2968 (Print) 1471-180X (Online) Journal homepage: https://www.tandfonline.com/loi/iafd19

A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS

Ali Jawaid, Santosh B. Murthy, Andrew M. Wilson, Salah U. Qureshi, Moath J. Amro, Michael Wheaton, Ericka Simpson, Yadollah Harati, Adriana M. Strutt, Michele K. York & Paul E. Schulz

To cite this article: Ali Jawaid, Santosh B. Murthy, Andrew M. Wilson, Salah U. Qureshi, Moath J. Amro, Michael Wheaton, Ericka Simpson, Yadollah Harati, Adriana M. Strutt, Michele K. York & Paul E. Schulz (2010) A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS, Amyotrophic Lateral Sclerosis, 11:6, 542-548, DOI: 10.3109/17482968.2010.482592

To link to this article: https://doi.org/10.3109/17482968.2010.482592

Amyotrophic Lateral Sclerosis, 2010; 11: 542–548

informa
healthcare

ORIGINAL ARTICLE

A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS

ALI JAWAID[1], SANTOSH B. MURTHY[1], ANDREW M. WILSON[1], SALAH U. QURESHI[1], MOATH J. AMRO[1], MICHAEL WHEATON[1], ERICKA SIMPSON[2], YADOLLAH HARATI[1], ADRIANA M. STRUTT[1], MICHELE K. YORK[1] & PAUL E. SCHULZ[1,3]

[1]*Department of Neurology, Baylor College of Medicine, Houston, Texas,* [2]*The Methodist Neurological Institute, Houston, Texas, and* [3]*Neurology Care Line, The Michael E. DeBakey VA Medical Center, Houston, Texas, USA*

Abstract

Our objective was to test the hypothesis that changes in body mass index (BMI) are associated with changes in the clinical course of ALS. We examined the relationships between BMI at first clinical visit and changes in BMI up to a two-year follow-up, and multiple clinical variables related to ALS: age of onset, rate of progression of motor symptoms, and survival. Baseline BMI was classified according to the World Health Organization (WHO) criteria. Changes in BMI were classified as a loss of >1 unit, no change, or a gain of >1 unit. Our results showed that baseline BMI was not associated with age of onset, rate of progression or survival. In contrast, a loss of BMI >1 over two years was associated with significantly shorter survival and a faster rate of progression. In a multiple regression model, these results were independent of gender, site of onset, history of diabetes mellitus and apolipoprotein (ApoE) genotype. In summary, a change in BMI after ALS diagnosis was significantly associated with rate of progression and survival. This raises the possibility that early changes in BMI may identify patients likely to have a more malignant course of the disease. However, further research is needed to clarify the relationship between BMI and ALS.

Key words: *Nutrition, survival, mitochondria*

Introduction

Several studies have explored the relationship between a slim body-type, athletic lifestyle and the risk of developing ALS, with conflicting results (1–7). Scarmeas et al. (2002) reported that the odds of having ALS were 2.21 times higher in chronically slim subjects and 1.70 times higher in former university athletes than their complements. Furthermore, there was a 2.48-fold increased risk of developing ALS for subjects whose premorbid BMI was in the normal or underweight range compared to those who were in the obese range, and a 6% increased risk for each unit decline of body mass index (BMI) was observed (5). Similar observations were made by Abel and Chio et al., who noted a higher incidence of ALS among professional athletes (3,4). Loss of BMI has also been associated with a shorter survival in ALS (8). In contrast, several studies have not shown an association between nutritional status, lifestyle and the risk of developing ALS (6,7).

Several other studies suggest that low BMI might be related to the pathophysiology of ALS, rather than being a risk factor. For example, Desport et al. (2005) demonstrated that two-thirds of ALS patients develop hypermetabolism during the course of the disease (9,10). Thus, weight loss could be a result of a change in metabolism associated with ALS, rather than being a risk factor.

In addition to hypermetabolism, other metabolic disturbances have also been observed in ALS, including an altered high density lipoprotein (HDL)/low density lipoprotein (LDL) ratio and glucose intolerance (11). Furthermore, two metabolic changes, hyperlipidemia (HLD) and diabetes mellitus (DM), have been suggested to have a 'protective' effect in

Correspondence: P. E. Schulz, Department of Neurology, NB-302 Baylor College of Medicine, 6501 Fannin Street, Houston, Texas 77030, USA. Fax: 713 798 8530. E-mail: pschulz100@gmail.com, cc. alijawaid84@gmail.com

(Received 9 November 2009; accepted 29 March 2010)

ISSN 1748-2968 print/ISSN 1471-180X online © 2010 Informa Healthcare
DOI: 10.3109/17482968.2010.482592

ALS (11,12). HLD and DM are often associated with heavier body weights; therefore it is unclear if the body weight, lifestyle, or the metabolic changes associated with these disorders are beneficial in ALS. Weight loss, in contrast, appears to have negative consequences for the progression of ALS. Malnourished ALS patients report a worse quality of life on validated scales, and the population has a 7.7-fold increased yearly mortality (13). Weight loss is an independent adverse prognostic factor for survival in ALS, after taking into account additional negative predictors including greater age, lower percent of predicted forced vital capacity (%FVC), and a shorter interval from symptom onset to diagnosis (8).

That body type, hypermetabolism, HLD, and DM have been associated with an altered clinical course for ALS suggests that BMI, a measure affected in all these disorders, could be important for predicting the progression of ALS. We hypothesized that baseline BMI would be an influential factor on age of onset for ALS, rate of motor disease progression and survival. In addition, we hypothesized that change in BMI after the diagnosis of the disease would be related to the rate of motor disease progression and survival in ALS.

Methods

Study design and participants

The patient sample comprised 285 consecutive patients with ALS recruited from the Baylor College of Medicine (BCM) Vicki M. Appel MDA/ALS clinic between 1999 and 2004. All patients were diagnosed with ALS using the El Escorial criteria for definite or probable ALS (14). Patients with ambiguous past medical history, uncertain diagnosis of motor neuron disease, familial ALS or diagnosis of a motor neuron disease other than ALS were not included in this study. The Institutional Review Board of Baylor College of Medicine approved this study.

Clinical assessment

Baseline assessment included collection of information about disease characteristics (site of onset, age of onset, family history, apolipoprotein genotype (ApoE) and premorbid medical history) as well as demographic details (gender, age and ethnicity). A clinical examination was also performed at baseline to determine the site severity of motor symptoms. The examination was performed by two board-certified neurologists unblinded to the study design. The severity of motor impairment was gauged using the Appel ALS score (AALSS). AALSS is a validated measure of severity of motor impairment in ALS, which consists of five subscores – bulbar, respiratory, muscle strength, lower extremity and upper extremity function. The total Appel ALS score is 30 for healthy subjects and 164 for those with maximal impairment (16). One study has suggested that the examination-based AALSS provides a better estimate of disease severity in ALS compared to the questionnaire-based ALS Functional Rating Scale (ALSFRS, (17)). Follow-up assessments were performed routinely at three-month intervals. The mean number of follow-up assessments for the cohort was 15.2 ± 4.1. These assessments lead to collection of information pertaining to patient survival and serial AALSS.

BMI assessment

All patients underwent a weight and height assessment at the time of first and at each clinical visit during the follow-up period. Standardized anthropometric measurements were used for weight and height assessment performed by two trained clinical nurses. The nurses were blinded to the fact that the information will be utilized in this study. The measured parameters were used to determine BMI for each patient using the formula: BMI = weight in kilograms/height in meters^2. The patient population was then divided into six categories based on the World Health Organization (WHO) BMI categories for North America (15). The categories were: Underweight (BMI <18.5), Normal (BMI 18.6–24.9), Overweight (BMI 25.0–29.9), Obese Class I (BMI 30.0–34.9), Obese Class II (BMI 35.0–39.9), and Obese Class III (BMI 40+). BMI values on each clinic visit were analyzed to determine change over the first two years of ALS diagnosis. Change in BMI over this time period was used to classify patients into one of three groups: patients with BMI gain >1 unit, patients with stable BMI (a gain or loss less than 1 unit), and patients with BMI loss >1 unit.

Outcome variables

The primary outcome variables of the study were age at onset, rate of disease progression and survival. 'Age of onset' was defined as the chronological age of the patient at the time of ALS onset. These data was gathered at the time of first clinical visit. 'Rate of disease progression' was calculated using serial AALSS scores. The motor findings for all patients with ALS were recorded at the time of diagnosis and at each follow-up visit, and the severity of their symptoms was gauged using the AALSS. The difference between the AALSS scores at the first and last clinical visit (prior to recorded death) of each individual patient was divided by the number of months that separated the two evaluations to determine the rate of motor progression. 'Survival' was defined as the number of years a patient with ALS survived after onset. This information was entered into the database as the patients died. By the end of fiscal year 2008, survival data for most patients ($n = 251$) had become available.

Our hypothesis was that baseline BMI or change in BMI over a two-year period would be associated with these outcome variables. Three factors are known to modify the clinical disease course of ALS: age at onset (before vs. after 45 years), gender, and site of onset. A disease modifying role has been suggested for ApoE genotype and a history of DM (12,18–21). We wished to control for these known/postulated disease modifiers as we examined the relationship between BMI and ALS. To do this, we used multiple regression analysis to adjust for several of these major disease modifying factors – gender, site of onset, DM and ApoE. No adjustment was made for age at onset (before vs. after 45 years) because only four patients had an onset before 45 years of age and hence it was unlikely to be a contributory factor to our findings.

Statistical methods

The data were entered into SPSS version 16 (SPSS Inc, Chicago, IL, USA) and validated through dual entry prior to being analyzed. For the outcome variables of 'age of onset' and 'survival', a fraction of the data was unavailable. Pair-wise deletion method was used to treat missing data for these variables. Associations between categorical variables were established through χ^2 and Fisher's exact calculations. Age at onset, rate of motor disease progression and survival were compared between ALS patients belonging to different baseline BMI groups through a Kruskal-Wallis test.

Survival and rate of disease progression were also compared among patients with varying degrees of BMI change over the two-year period using a one-way ANOVA. Multiple linear regression models were then built for survival and rate of disease progression to adjust for possible confounding effects of gender, site of onset, ApoE genotype and history of DM. Finally, Spearman's correlations were calculated between the BMI change over the two-year period post ALS diagnosis and survival and rate of disease progression in ALS.

Results

Demographics and neurological assessment

We examined the clinical data of 285 patients with sporadic ALS. Eleven patients were excluded from the analysis because of insufficient clinical data as they were lost to follow-up. Thus, 274 patients were included in the final analyses.

The gender distribution in our cohort was 66% males and 34% females. There was bulbar onset in 24% of patients and limb onset in 76% and the majority (86.3%) was Caucasian. Other ethnicities included African-Americans (8.8%), Hispanics (2.5%), Asians (1.4%) and others (1.0%). Mean age at ALS onset was 52.38±13.54 years. Mean AALSS at diagnosis was 55.4 (range 36–90). Mean survival was 4.59±2.75 years and the mean rate of progression was 2.64±2.17 AALSS/month.

In accordance with the previous studies, age of onset was earlier in males (50.9±13.8 years vs. 55.6±12.3 years in females, $p=0.01$) and later in diabetics (60.8±10.0 vs. 52.0±13.5 in non-diabetics, $p=0.01$). A trend toward a shorter survival was observed for bulbar-onset patients (4.08±1.70 vs. 4.89±3.04, $p=0.09$).

BMI at the time of diagnosis

At baseline, patients were divided according to BMI using the WHO classification. Table I presents some of the demographic and disease characteristic variables at time of diagnosis classified by BMI. BMI groups did not differ with regard to ethnicity ($p=0.75$), gender ($p=0.11$), site of onset ($p=0.91$), or the distribution of ApoE genotype ($p=0.11$). A history of DM was significantly more common among overweight and obese patients ($p=0.01$). Patients belonging to different BMI groups also did not differ with regard to age of onset ($p=0.41$), rate of progression ($p=0.13$) or survival ($p=0.23$) (Table I).

BMI change over two years after ALS diagnosis

The pattern of changes in BMI did not vary between patients according to gender ($p=0.13$), ethnicity ($p=0.39$), ApoE genotype ($p=0.95$) or DM status ($p=0.06$). There was an association between bulbar site of onset and BMI loss >1 ($p=0.01$). Survival and rate of disease progression were compared between ALS patients with varying degrees of BMI change over the two-year period post diagnosis. Patients with BMI loss >1 had a significantly shorter survival ($p=0.02$) and a faster rate of progression ($p=0.001$; Tables II, III).

Table I. Disease characteristics between different BMI groups at baseline.

WHO BMI classification	Underweight ($n=3$)	Normal ($n=92$)	Overweight ($n=114$)	Obese classI ($n=45$)	Obese class II ($n=14$)	Obese class III ($n=6$)
Age at onset (years)*	61.6±11.1	53.6±14.3	52.2±14.3	49.9±12.0	52.9±14.2	56.7± 14.6
Rate of progression (AALSS/month)*	1.66±1.23	2.64±2.50	2.66± 2.36	2.69±1.87	2.05±1.74	2.98±1.70
Survival (years)*	3.59±1.44	4.47± 2.75	4.82±3.09	4.32±2.59	4.28±1.19	4.32±1.40

*No significant between group difference on Kruskal-Wallis test.

Table II. Comparison (ANOVA) of survival and the rate of motor disease progression between different BMI change groups.

	BMI loss >1 (n=131)	BMI stable (n=88)	BMI gain >1 (n=57)	F	p-value
Survival (years)	4.04±1.90	5.41±3.53	4.89±3.21	4.24	0.02
Rate of motor disease progression (AALSS/month)	3.27±2.36	2.16±2.11	1.88±2.00	10.6	0.001

Multiple linear regression models were developed to adjust for possible confounding effects of gender, site of onset, ApoE genotype and history of DM on the relationship between changes in BMI and survival or the rate of disease progression (Table IV). Significant relationships were identified between BMI and survival (p=0.001) and BMI and rate of disease progression (p=0.001) (Table IV).

The relationship between survival and change in BMI was further reinforced through finding a significant direct correlation between the two factors (r=0.21, p=0.01). Similarly, a significant inverse correlation was found between change in BMI and rate of motor disease progression (r=–0.36, p=0.001).

Discussion

This investigation found that changes in BMI over the first two years after ALS diagnosis correlated significantly with survival and the rate of progression of motor symptoms. However, the baseline BMI was not associated with age at onset, rate of motor disease progression or survival.

On initial inspection, the association between BMI change and rate of disease progression seems to be stronger than the association between BMI change and survival. The results in Table II indicate that there is a significant difference in mean survival of the different BMI groups. On post-hoc analysis (Table III), a significant difference was observed between BMI loss >1 and stable BMI (p=0.02). However, the difference between BMI loss >1 and BMI gain >1 was not significant (p=0.43). On the other hand, the associations observed for 'rate of disease progression' remained significant after post-hoc analysis (Table III). The reason for this is unclear; however, one can speculate that while preventing weight loss leads to an overall favorable outcome in ALS, patients with a significant gain in BMI may have a shorter survival because they are at greater risk of other fatal conditions, e.g. stroke or coronary artery disease.

Weight loss has been previously suggested to predict poor prognosis in ALS (8). Our study reinforces this suggestion. The relationship between changes in BMI and progression of ALS has largely remained unclear. We explore several possible hypotheses that associate BMI to risk or pathophysiology of ALS.

Weight loss may indicate a more rapid neurodegenerative course in ALS

A plausible explanation for the observed association between faster progression of ALS and decreases in BMI is that more rapid neurodegeneration accelerates motor weakness, which leads to more severe weight loss. There are at least two scenarios by which this could occur. One possibility would be that increasing dysphagia may lead to decrease in oral intake and hence weight loss. In this scenario, more rapid bulbar neurodegeneration would lead to an early dysphagia and a greater weight loss. Therefore, a decrease in BMI would be an indicator of bulbar progression. In the current study we did observe a significant association between bulbar onset and a decrease in BMI over the two-year follow-up period. However, the association between change in BMI and the rate of disease progression was independent of bulbar onset (Table IV); thus, bulbar onset does not fully explain the decline in BMI. Another possibility is that loss of muscle mass in ALS could produce a decrease in BMI. In this scenario, more rapid neurodegeneration would produce greater muscle loss and hence greater decrease in BMI. However, some evidence suggests that the loss of muscle mass in ALS may be partially balanced by a compensatory gain of fat body mass (22). Both scenarios predict that weight maintenance in ALS patients would not affect disease outcome since weight loss is a marker of disease progression rather than a causal factor.

Table III. Multiple pair-wise comparison between change in BMI during the first two years post ALS diagnosis and survival and rate of motor disease progression*.

	BMI change group	BMI change group	Mean difference	p-value	95% CI
Survival (years)	BMI loss >1	BMI stable	−1.36	0.02	−2.52, −0.20
		BMI gain >1	−0.85	0.43	−2.23, 0.54
Rate of progression (AALSS/month)	BMI loss >1	BMI stable	1.10	0.001	0.37, 1.84
		BMI gain >1	1.38	0.001	0.53, 2.22

*Post-hoc analysis with Bonferroni correction.

Table IV. Multivariate association between candidate factors and rate of motor disease progression and post-diagnosis survival in ALS.

	Rate of motor disease progression (AALS/month)			Survival (years)		
	Regression coefficient	95% CI	*p*-value	Regression coefficient	95% CI	*p*-value
Gender	0.02	−0.53, 0.73	0.76	0.16	−0.01, 1.91	0.05
DM	−0.07	−2.40, 0.74	0.30	0.10	−0.93, 3.49	0.25
ApoE genotype	0.09	−0.19, 1.03	0.18	−0.04	−1.14, 0.70	0.64
Site of onset	0.01	−0.63, 0.75	0.86	−0.01	−1.08, 0.94	0.89
BMI change	0.25	0.03, 1.00	0.001	−0.26	−1.31, −0.03	0.001

Multiple Linear Regression Model.
Reference Category: Female for gender, +ive history of DM for DM.
ApoE4 for ApoE genotype, limb onset for site of onset, BMI loss >1 for BMI change.
CI=confidence interval.

Hypermetabolism may lead to faster neurodegeneration in ALS

A growing body of evidence suggests that patients with ALS are 'hypermetabolic' (9,10). Desport et al. (2005) reported that 62% of ALS patients develop a steady state of hypermetabolism early in the course of the disease characterized by an increase in REE (9). Multiple explanations have been proposed for this state of hypermetabolism. First, there is evidence suggesting mitochondrial changes in ALS. Consequently, reduced efficiency of mitochondrial production of ATPs may result in a compensatory hypermetabolism. Secondly, mitochondrial dysfunction could also lead to an altered homeostasis of reactive oxygen species, which would result in an altered cellular pH (23). Alternatively, another theory suggests that hypermetabolism in ALS is a late and unsteady phenomenon (22).

Regardless of when or how hypermetabolism occurs in ALS, it could result in motor neurons acquiring insufficient calories or lead to greater production of toxic metabolic by-products. Motor neurons are known to have greater metabolic requirements and hence are highly vulnerable to caloric restriction (24). In this scenario, the development of hypermetabolism (especially when not compensated by caloric supplementation or greater fat stores) may lead to swifter motor neuron loss. This possibility has an important therapeutic implication predicting that increasing caloric intake and preventing weight loss would reduce motor neuron loss.

There is some indirect evidence supporting this hypothesis. Diabetes mellitus and hyperlipidemia appear to have a 'protective' effect in ALS (11,12). These findings suggest that patients with higher serum lipids or glucose or who consume a higher caloric diet may be able to counter the effects of hypermetabolism. Hence, their motor neurons may be damaged to a lesser degree by the hypermetabolism of ALS. This hypothesis would appear to account for the later age at diagnosis for ALS in DM, the longer survival for patients with HLD or BMI gains >1, and the slower rate of motor disease progression when BMI gains are >1. Therapeutically, it would be very important to confirm whether hypermetabolism leads to a faster disease progression in ALS. Future studies should also employ indirect calorimetric measurements for estimation of REE in ALS as weight loss may not be a constant predictor of hypermetabolism.

Decreases in BMI may compromise ALS patients through a compromise of immunity

Another possibility is that weight loss leads to a shorter survival in ALS through mechanisms that are unrelated to the pathophysiology underlying the disorder. For example, weight loss may compromise the immune system, thereby leading to a greater frequency of infections, such as pneumonia, that may lead to death (25). While infections might account for shorter survival, however, it is not apparent how they would account for increases in the rate of motor progression.

Therapeutic implications

Our results reveal that survival in ALS patients with stable BMI is 16 months longer than that of patients with BMI loss >1 (Table II). This survival benefit is greater than the survival benefit observed for riluzole (26). A similar observation was made by Dupuis et al. (2008) regarding the protective effect of hyperlipidemia (11). Survival benefit of a high-calorie diet and ketogenic diet has also been observed in animal models of ALS (27,28). If the association between prevention of weight loss and better clinical outcomes in ALS is reinforced by further studies, it will have massive implications on the management of this disease.

There are several caveats to this study, however, that need to be critically considered before drawing conclusions regarding weight maintenance. First, this study was performed in a tertiary care clinical setting, and hence our observations regarding ALS and BMI may not be applicable to the general ALS population. Certain features of our cohort are slightly different from other reported registries. For example, the mean survival in our cohort (4.5 years) is slightly longer. Also, the male: female ratio is 2:1. These factors are critical to consider when generalizing the

results of this study. Secondly, we lacked quantitative data regarding serum lipid values and specific lipid agents. We do know, however, that apart from a few cases ($n=32$) where it was contraindicated, refused or not tolerated, almost all the patients were on riluzole. Another important limitation is that the disease duration prior to first clinical visit is not included as an independent variable in the study. Some studies suggest diagnostic delay or time from onset to diagnosis as important prognostic factors in ALS (29,30). It was challenging to determine the time from onset to diagnoses in all the patients, as some of them had already been diagnosed elsewhere. We tried to address this issue by measuring Appel ALS score (AALSS) in all patients at the time of first clinical visit. The mean AALSS was 55 (range 36–90), which suggests 'early disease' in most of these patients. However, not including 'disease duration prior to first clinical visit' is an important limitation of this study.

In the future, it will be important to investigate the effects of changes in BMI on the clinical course of ALS through a prospective clinical trial addressing the factors noted above. An association between BMI and respiratory function should also be investigated as it is a very important prognostic factor in ALS. However, even though this association requires further exploration, it seems prudent to suggest to patients with ALS that they maintain their weight until any cause-and-effect relationship between weight loss and worse clinical outcome is clarified.

Acknowledgement

The authors wish to thank the ALS patients and physicians of the MDA and ALS Association Clinics at The Methodist Hospital and Baylor College of Medicine. The authors also thank the Lou DeGeorge Family for its continued generous support.

Declaration of interest: The authors report no conflict of interests. The authors are also responsible for the content and writing of the paper.

References

1. Brooks BR. Natural history of ALS: symptoms, strength, pulmonary function, and disability. Neurology. 1996:47: S71–81.
2. Okamoto K, Kihira T, Kondo T, Kobashi G, Washio M, Sasaki S, et al. Nutritional status and risk of amyotrophic lateral sclerosis in Japan. Amyotroph Lateral Scler. 2007;8:300–4.
3. Abel EL. Football increases the risk for Lou Gehrig's disease, amyotrophic lateral sclerosis. Percept Mot Skills. 2007;104:1251–4.
4. Chiò A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain. 2005; 128:472–6.
5. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and university athletics in ALS. Neurology. 2002;59:773–5.
6. Longstreth WT, McGuire V, Koepsell TD, Wang Y, van Belle G. Risk of amyotrophic lateral sclerosis and history of physical activity: a population based case-control study. Arch Neurol. 1998;55:201–6.
7. Veldink JH, Kalmijn S, Groeneveld GJ, Titulaer MJ, Wokke JH, van den Berg LH. Physical activity and the association with sporadic ALS. Neurology. 2005;64:241–5.
8. Desport JC, Preux PM, Truong CT, Courat L, Vallat JM, Couratier P. Nutritional assessment and survival in ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:91–6.
9. Desport JC, Torny F, Lacoste M, Preux PM, Couratier P. Hypermetabolism in ALS: correlations with clinical and paraclinical parameters. Neurodegener Dis. 2005;2:202–7.
10. Bouteloup C, Desport JC, Clavelou P, Guy N, Derumeaux-Burel H, Ferrier A, et al. Hypermetabolism in ALS patients: an early and persistent phenomenon. J Neurol. 2009;256:1236–42.
11. Dupuis L, Corcia P, Fergani A, Gonzalez de Aguilar JL, Bonnefont-Rousselot D, Bittar R, et al. Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. Neurology. 2008;70:1004–9.
12. Jawaid A, Salamone AR, Strutt AM, Murthy SB, Wheaton M, Simpson E, et al. ALS disease onset may occur later in patients with premorbid diabetes mellitus. Eur J Neur. 2010;17:733–39
13. Pessolano FA, Súarez AA, Monteiro SG, Mesa L, Dubrovsky A, Roncoroni AJ, et al. Nutritional assessment of patients with neuromuscular diseases. Am J Phys Med Rehabil. 2003;82:182–5.
14. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial 'Clinical limits of amyotrophic lateral sclerosis' workshop contributors. J Neurol Sci. 1994;124:96–107.
15. World Health Organization Global Database on Body Mass Index. Available online: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed online: July 8, 2009.
16. Appel V, Stewart S, Smith G, Appel S. A rating scale for amyotrophic lateral sclerosis: description and preliminary experience. Ann Neurol. 1987;22:328–33.
17. Voustianiouk A, Seidel G, Panchal J, Sivak M, Czaplinski A, Yen A, et al. ALSFRS and Appel ALS scores: discordance with disease progression. Muscle Nerve. 2008;37:668–72.
18. Qureshi MM, Hayden D, Urbinelli L, Ferrante K, Newhall K, Myers D, et al. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler. 2006;7:173–82.
19. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population based study. Neurology. 2003;60:813–9.
20. Zetterberg H, Jacobsson J, Rosengren L, Blennow K, Andersen PM. Association of APOE with age at onset of sporadic amyotrophic lateral sclerosis. J Neurol Sci. 2008;273:67–9.
21. Li YJ, Pericak-Vance MA, Haines JL, Siddique N, McKenna-Yasek D, Hung WY, et al. Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. Neurogenetics. 2004;5:209–13.
22. Kasarskis EJ, Berryman S, van der Leest JG, Schneider AR, McClain CJ. Nutritional status of patients with amyotrophic lateral sclerosis: relation to the proximity of death. Am J Clin Nutr. 1996;63:130–7.
23. Menzies FM, Ince PG, Shaw PJ. Mitochondrial involvement in amyotrophic lateral sclerosis. Neurochem Int. 2002;40: 543–51.
24. Mattson MP, Cutler RG, Camandola S. Energy intake and amyotrophic lateral sclerosis. Neuromolecular Med. 2007;9:17–20.
25. Katona P, Katona-Apte J. The interaction between nutrition and infection. Clin Infect Dis. 2008;46:1582–8.
26. Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Samarelli V, et al. Riluzole and amyotrophic lateral sclerosis

survival: a population based study in southern Italy. Eur J Neurol. 2007;14:262–8.
27. Dupuis L, Oudart H, René F, Gonzalez de Aguilar JL, Loeffler JP. Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. Proc Natl Acad Sci U S A. 2004;101:11159–64.
28. Zhao Z, Lange DJ, Voustianiouk A, MacGrogan D, Ho L, Suh J, et al. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci. 2006;7:29.
29. Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. J Neurol. 2006; 253:1428–36.
30. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population based study. Neurology. 2003;60:813–9.