

Diets for Patients with Amyotrophic Lateral Sclerosis: Pay Attention to Nutritional Intervention

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive degeneration of upper and lower motor neurons. Typical clinical features of ALS are limb paralysis, muscle atrophy, dysphagia, dysarthria, shortness of breath, and respiratory failure. Approximately 90% of ALS cases are classified as sporadic ALS, the remaining 10% are classified as familial.^[1,2] Researchers have found that the survival of ALS patients is related to several factors, including clinical phenotype, age at onset, sex, early presence of respiratory failure, and treatment with riluzole. We recently found that there is a potential linear relationship in ALS between serum lactate and motor deterioration, and that slower lactate elimination rate might be associated with faster disease progression.^[3] In addition, several studies have reported that nutritional status is closely related to the survival time of ALS patients, and there exists a U-shaped association between patients' body mass index (BMI) and mortality.^[1,4] The main cause of malnutrition (BMI ≤ 18.5 kg/m²) in ALS patients is an imbalance between intake and consumption, and some symptoms, such as dysphagia, can lead to insufficient energy intake. More importantly, recent studies have shown that ALS patients are in states of hypermetabolism.^[5,6]

HYPERMETABOLISM IN AMYOTROPHIC LATERAL SCLEROSIS

It is difficult to explain the association between hypermetabolism and ALS, but it has been found in mutant Cu Zn-superoxide dismutase (SOD1) transgenic mice as well as in ALS patients. Resting energy expenditure (REE) is one reason for increased consumption for ALS.^[6] Dupuis *et al.*^[7] found that SOD1^{G86R} and SOD1^{G93A} mice have increased REE

compared to control mice. Desport *et al.*^[8] found that REE significantly increased by an average of 14% in 168 ALS patients compared to the calculated value, and 62.3% of ALS patients were considered hypermetabolic. Bouteloup *et al.*^[5] confirmed that hypermetabolism existed in 48% of all ALS patients, but there was no significant improvement in survival time between the hypermetabolism and normal metabolism groups ($P = 0.08$). In contrast to these studies, Vaisman *et al.*^[9] found that the measured REE as a percentage of the predicted REE was not different between the groups and was within the normal range, i.e., $\pm 10\%$ of the predicted rate; however, the measured and predicted REEs were significantly lower in ALS patients, and when normalizing REE by lean body mass (LBM), REE/LBM was significantly higher in ALS patients than that in the healthy controls.

KETOGENIC DIET IN AMYOTROPHIC LATERAL SCLEROSIS

Ketone bodies are three small water-soluble molecules of acetoacetate, 3-hydroxybutyrate, and acetone. They are produced from acetyl-CoA by enzymatic synthesis in the mitochondria of hepatocytes and can pass the blood-brain barrier and intramuscular capillary walls. When the body is under extended periods of fasting or glucose deficiency, instead of glucose, ketone bodies serve as the primary energy resource of the brain.^[10]

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A ketogenic diet consists of one that is high in fats and low in carbohydrates, simulating of a fasting state. Initially, a ketogenic diet proved to be an effective therapy in pharmaco-resistant epilepsy. It has also been found effective in some neurodegenerative diseases and mitochondrialopathies, which might involve mitochondrial impairment.^[11] As previously mentioned, ALS could be caused by an energy imbalance, which is a common phenomenon in SOD1 transgenic mice as well as ALS patients. A ketogenic diet could also be a potential therapy for ALS. Some studies showed that mitochondrial complex I activity is decreased in ALS, and that ketone bodies can restore the function of this complex.^[12]

Adenosine monophosphate-activated protein kinase (AMPK) is a type of intracellular pressure sensor that maintains energy homeostasis. AMPK is activated during energy stress by various upstream kinases that require phosphorylation of threonine 172 within the catalytic subunit.^[13] As a consequence of AMPK activation, glucose intake and fatty acid oxidation are increased, while cholesterol, lipid, and protein synthesis are inhibited.^[14] We recently found that increased activity levels of AMPK caused decreased levels of heat shock proteins 70 (HSP70) in SOD1^{G93A} mutant mice.^[15] HSP70 are molecular chaperones that help newly synthesized protein to fold correctly and they play an important role in stress-induced protein denaturation.^[16] It was found that calorie-restricted (CR) SOD1^{G93A} mice had higher AMPK activity, lower HSP70 expression, and shorter survival time compared to standard *ad libitum* (AL) SOD1^{G93A} mice; in contrast, SOD1^{G93A} mice that fed a high-fat diet had inhibited AMPK activity, increased HSP70 expression, and longer survival time compared to that of standard AL SOD1^{G93A} mice;^[15] therefore, we might conclude that a high-fat diet could improve ALS survival time by inhibiting AMPK activity.

DIETS OF DIFFERENT CALORIE CONSTITUTIONS FOR AMYOTROPHIC LATERAL SCLEROSIS

Previous studies found that caloric restriction was beneficial to age-related diseases and prolonged lifespan in healthy insects, rodents, and nonhuman primates.^[17] Some researchers have subsequently focused on the CR diet and its effect on ALS patients. Contrary to the hypothesis, Pedersen and Mattson^[18] found that the age of disease onset in CR mice was not significantly different from that in AL mice, and the duration of the disease was significantly less in the CR mice than in the AL mice ($P < 0.01$). Similarly, Hamadeh *et al.*^[19] showed that the age of mice at clinical onset was even younger in CR mice than in AL mice, and CR mice tended to reach end point sooner, although there was no significant difference between the two groups. In addition, they found that CR increased mitochondrial biogenesis, lipid peroxidation, and inflammation. This decreased the mitochondrial oxidative capacity and cellular stress response, and led to heightened apoptosis, which finally resulted in a faster clinical onset and shorter lifespan in the mutant SOD1

transgenic mouse models.^[20] In our recent study, the negative effect of a CR diet on ALS was again confirmed when clinical onset was shortened by 10 days ($P = 0.003$) and survival time was shorter ($P < 0.001$) in SOD1^{G93A}-CR mice compared to that in SOD1^{G93A}-AL mice;^[15] therefore, it appears that the CR diet is not an appropriate therapy for ALS.

In contrast to the CR diet, the ketogenic and high-fat diets seem to be beneficial to ALS patients. The results of three studies based on mutant SOD1 transgenic mouse models indicated that the ketogenic diet-fed SOD1^{G93A} mice maintained motor function longer and had a significantly longer survival time than standard diet-fed mice.^[21] Ari *et al.*^[21] demonstrated that the ketogenic diet and Deanna Protocol (a diet consisting of 10% arginine alpha-ketoglutarate, 1.0% gamma aminobutyric acid, 0.1% ubiquinol, 10% medium-chain triglyceride)-fed mice had a significantly longer survival time than the standard diet-fed mice. In studies on high-fat diet and its effect on ALS, it was shown that the clinical onset was significantly slower and the survival time was significantly longer compared to that in the standard diet-fed mice.^[7,15] Dupuis *et al.*^[7] considered the improvement of nutritional status as an explanation to longer survival in the high-fat diet-fed mice because of their significantly higher body weight.

In clinical practice, some researchers investigated the different effects of a high-carbohydrate diet and a high-fat diet on patients with ALS.^[22-24] After 12 weeks of nutritional intervention, BMI of the patients increased in both groups, while no significant change in median serum lipid levels was observed. The researchers did not analyze the survival of the two diet groups because no controls were enrolled in the study.^[22] In another randomized, double-blind, placebo-controlled trial, ALS patients were divided, respectively, into three groups as follows: an isocaloric diet group, a high-carbohydrate/hypercaloric diet (HC/HC) group, and a high-fat/hypercaloric diet (HF/HC) group. Diet intervention was maintained for 4.0 months and follow-up continued for 5.0 months. The estimated median survival in the HC/HC group appeared to be longer compared to that in the other groups but there was no statistically significant difference ($P = 0.07$); however, the survival in the HF/HC group was unexpectedly shorter. The researchers believed that the results were unreliable because the participants no longer maintained the study diet after the end of follow-up.^[23]

ANTIOXIDANT INTAKE IN AMYOTROPHIC LATERAL SCLEROSIS

In addition to these energy intake studies, Nieves *et al.*^[25] recently adopted a condensed version of the Food Frequency Questionnaire for 302 ALS patients to assess their daily dietary intake. The effects of different foods on ALS Functional Rating Scale-Revised score and forced vital capacity were analyzed. Food that reduces the risk of ALS or that is rich in antioxidants is classified as “good”, whereas

food that causes oxidative stress or increases the risk of ALS is classified as “bad”. The study found that intake of vegetables and foods high in antioxidants and carotenoids was associated with higher ALS function when diagnosed.

SUMMARY

In mutant SOD1 transgenic mouse models, a high-caloric, high-fat diet or ketogenic diet generally had protective effects on ALS; however, in the mouse models, the pathogenesis is mainly associated with oxidative stress. The effect of energy intake and diets on other ALS mechanisms should be further investigated. On the other hand, studies have provided certain evidences to support hypercaloric nutrition as a potential intervention for ALS patients, but large sample-size, placebo-controlled, double-blinded trials are needed to provide further powerful evidences.

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