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High-Fat and Ketogenic Diets in Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis is a fatal neurodegenerative disease. Epidemiologic data suggest that malnutrition is a common feature in amyotrophic lateral sclerosis and being overweight or obese confers a survival advantage in this patient population. In amyotrophic lateral sclerosis mouse models, a high-fat diet has been shown to lead to weight gain and prolonged survival. However, little research has been conducted to test whether nutritional interventions might ameliorate the disease course in humans. Here we review the currently available evidence supporting the potential role of dietary interventions as a therapeutic tool for amyotrophic lateral sclerosis. Ultimately, determining whether a high-fat or ketogenic diet could be beneficial in amyotrophic lateral sclerosis will require large randomized, placebo-controlled clinical trials.

Keywords

ketogenic; fat; diet; amyotrophic lateral sclerosis; ALS

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder of motor neurons leading to paralysis and death. Death usually occurs 2 to 5 years from symptom onset, usually from respiratory paralysis.[1] The only United States Food and Drug Administration (FDA)–approved therapy for amyotrophic lateral sclerosis, riluzole, increases survival by a modest 2–3 months.[2–4] Thus there is a strong need for more effective therapies in amyotrophic lateral sclerosis.

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Author Contributions

Dr Paganoni participated in executing the project and reviewing and critiquing the manuscript. Dr Wills participated in the conception, organizing and executing the project and writing the first draft of the manuscript.

Declaration of Conflicting Interests

Dr Wills receives consultant payments from Asubio Pharmaceuticals.

Ethical Approval

Partners Healthcare Institutional Review Board approval was obtained for the High Fat/High Calorie versus Optimal Nutrition in ALS clinical trial mentioned in this article.

Dietary interventions to treat amyotrophic lateral sclerosis are attractive for several reasons. First, there is evidence that malnutrition contributes to the weight loss that occurs as the disease progresses.[5] Malnutrition can be due to dysphagia from bulbar weakness, or it can be due to an imbalance between calories consumed and an increase in metabolic demand reported in some studies.[6–9] Kasarskis et al showed that amyotrophic lateral sclerosis subjects consumed only 84% of the recommended daily allowance of calories.[5] For this reason, amyotrophic lateral sclerosis patients are encouraged to consume more calories than their calculated needs, although there are no specific dietary recommendations for amyotrophic lateral sclerosis.[5,10–14] Second, multiple groups have reported an association between nutritional status (as measured by body mass index) and survival, with malnourishment being associated with shorter disease survival.[5–8,15–17] Interestingly, a recent prospective study has also found a reduction in amyotrophic lateral sclerosis risk in patients who are overweight and obese.[18]

A dietary intervention that is high in calories from fat could be interesting for several reasons. There is epidemiologic evidence that increased dietary fat intake may reduce the risk of developing amyotrophic lateral sclerosis. A recent prospective epidemiologic study of 891920 US subjects found a trend toward reduced amyotrophic lateral sclerosis risk with increased intake of fatty meat and fried food.[19] A Japanese case-control retrospective study found that the odds ratios for the highest tertile of intake compared to the lowest were 0.41 (95% confidence interval 0.21–0.80) for total fat, 0.30 (95% confidence interval 0.16–0.5) for saturated fatty acids, 0.35 (95% confidence interval 0.18–0.69) for monounsaturated fatty acids, and 0.58 (95% confidence interval 0.40–0.96) for polyunsaturated fatty acids.[20] A Dutch case-control retrospective study found an odds ratio of 0.4 (95% confidence interval 0.2–0.7) for developing amyotrophic lateral sclerosis in the highest tertile of polyunsaturated fatty acid intake, but not total fat intake.[21] Contrary to these findings, a US case-control retrospective study reported a nonsignificant trend toward increased risk of amyotrophic lateral sclerosis in subjects who reported a diet high in fat calories, however this study was not adjusted for tobacco use.[22]

Several studies have shown that a high-fat diet can slow disease progression in the mutant superoxide dismutase 1 mouse model, the most frequently used preclinical model of amyotrophic lateral sclerosis. These mice harbor a genetic mutation in the superoxide dismutase 1 gene which is one of the most common genetic causes of amyotrophic lateral sclerosis. In these animals, a diet consisting of 38% carbohydrates, 47% fats, and 15% protein (by calorie content) increased the median survival time of G93A superoxide dismutase 1 mice by approximately 90%.[23] In a second study, a high-fat diet consisting of 21% butter fat and 0.15% cholesterol (by weight) increased the mean survival of G86R superoxide dismutase 1 mice by 20 days.[24] Conversely, calorie restriction in the mutant superoxide dismutase 1 mouse model significantly reduced survival.[25,26]

Zhao et al tested a ketogenic diet (consisting of 60% fat, 20% carbohydrate, and 20% protein) in the same mutant superoxide dismutase 1 mouse model. While they did not show a significant increase in survival, they did demonstrate an improvement in rotarod performance. In addition, they were able to demonstrate an increase in ATP production from mitochondria purified from amyotrophic lateral sclerosis mouse spinal cord when treated

with β-hydroxybutyrate.[27] The same group has also reported that treatment with caprylic acid (a medium chain triglyceride that is metabolized into ketone bodies) appeared to improve mitochondrial function and motor neuron numbers in the amyotrophic lateral sclerosis mouse model, although it did not lead to overall increased survival.[28]

The mechanism by which increased dietary fat prolongs survival in the mutant superoxide dismutase 1 mouse is unknown. Fergani et al found that a diet consisting of 21% butter fat normalized serum cholesterol levels, which were reduced in the mutant superoxide dismutase 1 mice fed a regular diet.[24,29] Phospholipids and cholesterol are essential for axonal membrane assembly, and cholesterol biosynthesis is reduced in peripheral nerves during degeneration and regeneration (reviewed in Vance et al[30]). In experimental models of peripheral nerve injury, there is a dramatic increase in the expression of low-density lipoprotein receptors which allow the regenerating nerve to import cholesterol into the cell, possibly bound to Apolipoprotein E, for the purpose of axonal repair.[31–33] Exogenous low-density lipoproteins, but not high-density lipoproteins, can rescue axonal growth after it has been suppressed by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin drugs) in cultured sympathetic neurons.[34] Thus, elevated dietary fats may result in elevated circulating low-density lipoprotein levels which, in turn, could lead to improved survival of peripheral motor neurons. There is also epidemiologic data from humans that elevated cholesterol levels may be associated with improved amyotrophic lateral sclerosis survival,[35] although this association was not observed when overall nutritional status, as measured by body mass index, was included in the analysis.[17,36]

While there is great interest in pursuing dietary interventions for amyotrophic lateral sclerosis, there has been little clinical research into the topic to date. Stanich et al performed a small trial of a protein supplement (18 grams of protein and 275 Kcal) in 20 subjects with amyotrophic lateral sclerosis for 6 months and found no effect on disease progression or loss of muscle mass, although this was a small, non-placebo-controlled study without careful analysis of calorie intake.[37] Silva et al tested oral supplementation with milk whey proteins and modified starch in a small study of 16 subjects treated for 4 months and demonstrated modest weight gain in the supplement arm while the controls continued to lose weight.[38] Intriguingly, the supplement arm appeared to have a slower rate of decline in the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised.[38] We are currently conducting a small phase II double-blind placebo-controlled randomized trial comparing the safety and tolerability of 3 different enteral feeding regimens: (a) hyperalimentation using an enteral tube feed formula which contains 55% calories from fat, (b) hyperalimentation using a standard tube feed regimen, (c) replacement calories using a standard tube feed regimen (Clinicaltrials.gov ID NCT00983983).

In summary, there are strong epidemiologic data showing that malnutrition is a common symptom of amyotrophic lateral sclerosis both in humans and in mice and may contribute to disease progression. There is also epidemiologic evidence that increased dietary fat and cholesterol intake might reduce the risk of amyotrophic lateral sclerosis and the rate disease progression. Finally, data from animal studies strongly suggest that increasing dietary intake of fat ameliorates disease progression. However, determining whether amyotrophic lateral

sclerosis patients should be treated with a high-fat or ketogenic diet can be based only on randomized double-blind placebo-controlled interventional trials.

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