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Dietary Proteins and Amino Acids in the Treatment of Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Animal and Plant Protein, Amino Acid Therapy and Mechanisms

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a fatal neurodegenerative disease in which nutrition, weight loss and amino acid metabolism are closely involved. This review examines the evidence on dietary proteins from animal sources (meat, fish, dairy, eggs) and plant sources (legumes, soy, grains, vegetables), and on protein-derived supplements (branched-chain amino acids, threonine, L-serine and creatine). No randomised trial has tested a specific food protein as ALS treatment, so evidence for food proteins is observational. In an Italian case-control study, higher intake of total protein (OR 2.96), animal protein (OR 2.91) and glutamic acid (OR 3.63) was associated with higher risk [1], while in a cross-sectional cohort of 302 patients milk and lunch meats were associated with poorer function and vegetable-derived carotenes with better function [2]. Amino acid therapies have not succeeded: Branched-chain amino acids and threonine showed no benefit [3], creatine did not alter progression in a 175-patient trial [4], and L-serine was tolerated up to 30 g/day in a phase I study [5]. A high-caloric fatty diet did not improve overall survival but may benefit fast-progressing patients [6]. Mechanisms, tables and graphs are provided and research priorities are outlined herein.

Key words: Keywords: amyotrophic lateral sclerosis; motor neuron disease; dietary protein; animal protein; plant protein; amino acids; branched-chain amino acids; L-serine; creatine; nutrition.

1. Introduction and scope

ALS is characterised by progressive loss of upper and lower motor neurons, leading to paralysis and usually death from respiratory failure within a few years of onset [7,8]. Nutrition is a major clinical concern because weight loss is a negative prognostic factor [6], and because dietary habits have been explored as risk and modifying factors.

This review covers proteins in the nutritional sense: protein-rich foods of animal and plant origin, and amino acids and amino acid derivatives given as supplements. Therapeutic protein drugs (for example neurotrophic factors and antibodies) are outside its scope. An important limitation must be stated at the outset: there are no randomised trials comparing meat, fish, dairy, soy or other food proteins in ALS, so conclusions about food proteins rest on observational data that cannot establish causation. The overall relationship between protein sources, amino acid supply and ALS mechanisms is summarised in Figure 1.

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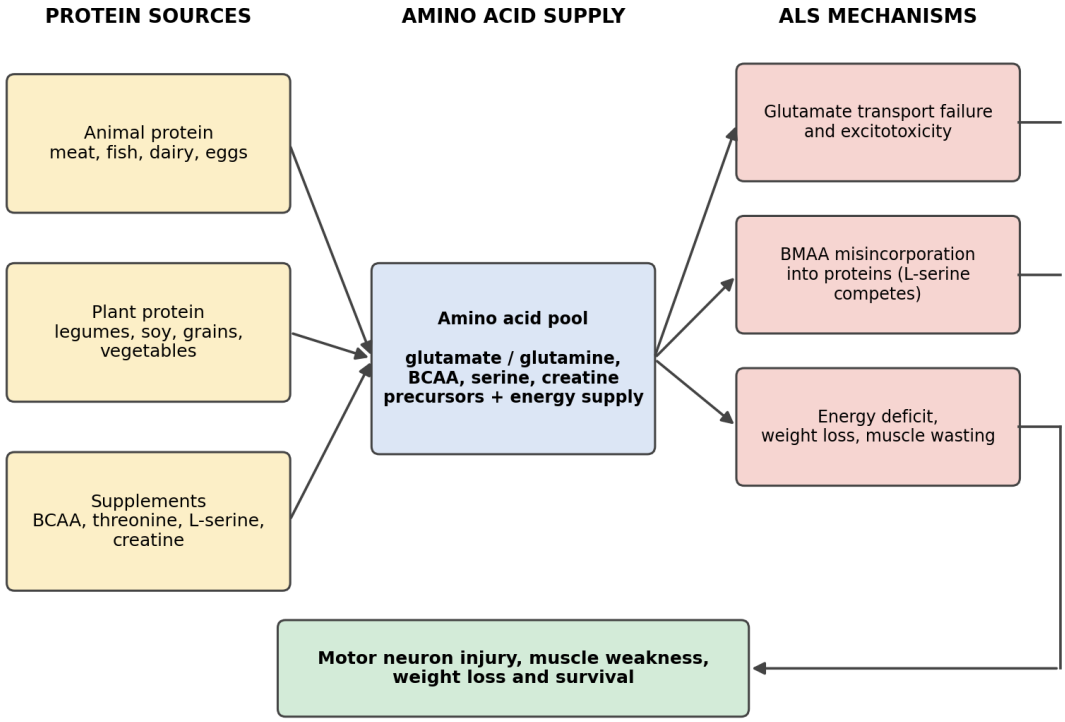


Figure 1. Dietary and supplemental protein routes and the ALS mechanisms they may influence.

2. Why amino acids matter in ALS: Mechanisms

2.1 Glutamate handling and excitotoxicity

Glutamate, a protein-derived amino acid, is the main excitatory neurotransmitter, and abnormal glutamate metabolism was described in ALS patients decades ago [9]. High-affinity glutamate uptake in ALS tissue is markedly reduced: the maximal transport velocity was 59% lower in spinal cord, 70% lower in motor cortex and 39% lower in somatosensory cortex than in controls, with no such defect in visual cortex, striatum or hippocampus [10] (Figure 4a). The resulting excess of extracellular glutamate is thought to contribute to motor neuron injury. This is the rationale for investigating amino acid metabolism as a therapeutic target, although the transport defect is a property of the diseased nervous system and not evidence that dietary glutamate causes ALS.

2.2 Competition with a protein-misincorporated toxin

The non-protein amino acid β-methylamino-L-alanine (BMAA) has been proposed as a neurotoxin that can be misincorporated into proteins; exogenous L-serine was shown in cultured neurons to prevent this, and L-serine was proposed as a therapy on that basis [5]. Whether BMAA contributes to sporadic ALS remains unresolved.

2.3 Energy supply and muscle

Weight loss is an independent prognostic factor in ALS [6], which makes protein and energy adequacy relevant to muscle mass and survival. Creatine, an amino acid derivative, was studied as a mitochondrial and energy buffer [4]. The proposed mechanisms and the status of each strategy are shown in Figure 2.

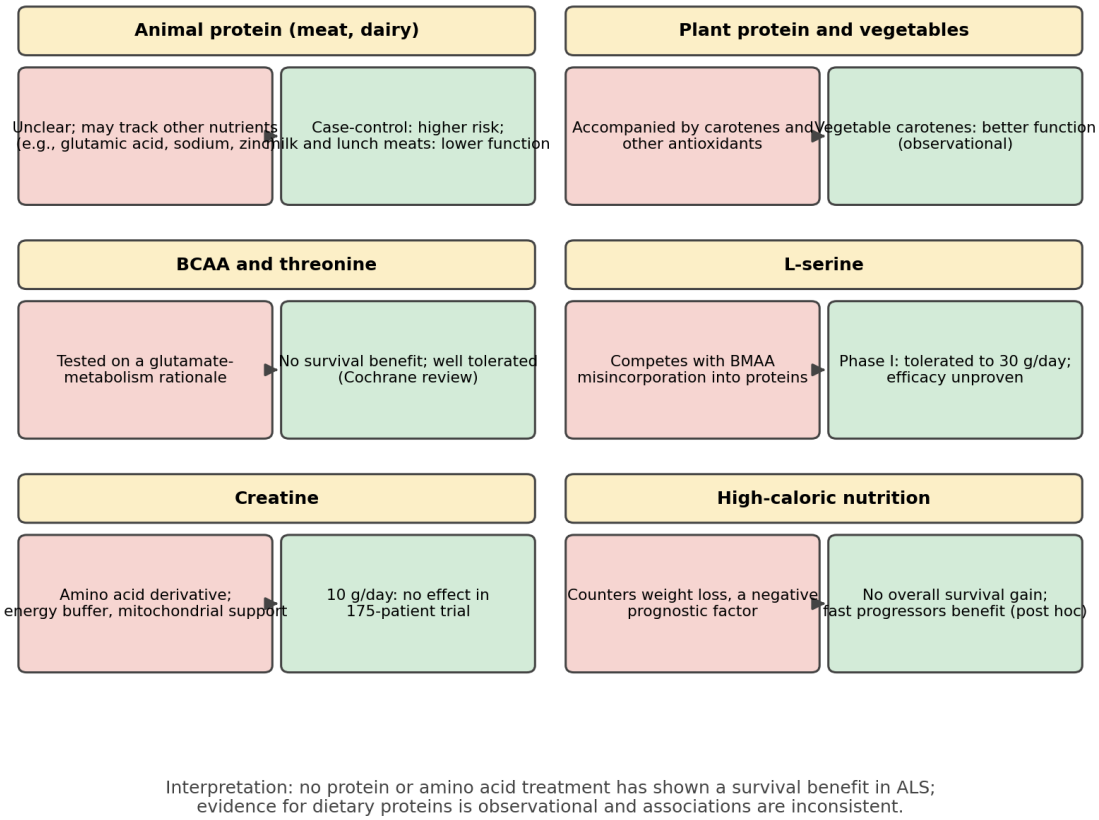


Figure 2. Proposed mechanisms of action (left) and clinical status (right) of proteins, amino acids and related nutrition.

3. Dietary protein and ALS: Observational evidence

3.1 Animal protein

In a case-control study of newly diagnosed ALS patients from three Italian regions, intake was estimated with a food-frequency questionnaire covering habitual diet before symptoms. Higher risk was found for total protein (OR 2.96, 95% CI 1.08–8.10), animal protein (OR 2.91, 95% CI 1.33–6.38), glutamic acid (OR 3.63, 95% CI 1.08–12.2), sodium (OR 3.96) and zinc (OR 2.78), although without a linear trend for some nutrients [1] (Figure 3). In a cross-sectional analysis of 302 patients, higher consumption of milk and lunch meats was associated with lower functional scores [2]. These associations may reflect correlated nutrients, reverse causation (changes in diet after onset) or confounding, and they do not show that animal protein causes ALS.

3.2 Plant protein and vegetables

In the same cross-sectional cohort, higher intakes of antioxidants and carotenes from vegetables were associated with better ALSFRS-R scores or forced vital capacity [2]. Pooled prospective cohorts likewise linked higher dietary carotenoid intake to lower ALS risk (RR 0.75, 95% CI 0.61–0.91 for the highest versus lowest quintile) [11]. These findings concern vegetable-derived antioxidants rather than plant protein itself; no study identified here isolated soy, legume or grain protein as a protective factor.

Table 1. Observational studies of dietary protein and related nutrients in ALS.

Study	Design	Main finding (as reported)
Pupillo et al. [1]	Case-control; Italy; food-frequency questionnaire	Higher risk with total protein (OR 2.96), animal protein (OR 2.91), glutamic acid (OR 3.63), sodium and zinc.
Nieves et al. [2]	Cross-sectional; 302 patients	Vegetable antioxidants and carotenes: better function; milk and lunch meats: lower function.
Fitzgerald et al. [11]	Pooled analysis of 5 prospective cohorts	Higher dietary carotenoids: lower risk (RR 0.75); vitamin C not associated.

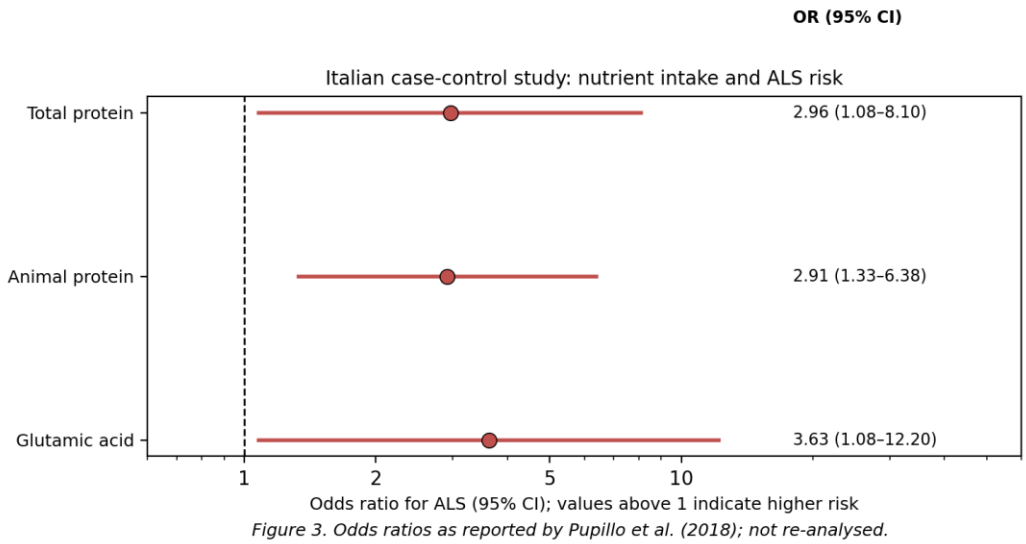


Figure 3. Odds ratios as reported by Pupillo et al. (2018); not re-analysed.

4. Amino acid and protein-derived therapies

4.1 Branched-chain amino acids and threonine

Branched-chain amino acids (L-leucine, L-valine and L-isoleucine) and L-threonine were used as experimental therapy for ALS. The Cochrane review of randomised and quasi-randomised trials found no benefit of either branched-chain amino acids or L-threonine on survival; both were well tolerated, with adverse events comparable to control [3]. The reviewers concluded that there was no evidence to support their use [3].

4.2 L-serine

L-serine was tested for safety in ALS on the BMAA rationale described above. In a six-month phase I trial in which patients received oral L-serine at increasing doses up to 30 g/day, treatment was well tolerated, and a reduced rate of functional loss was noted at the highest dose compared with control patients [5]. Because this was a small safety study, the functional observation cannot be taken as evidence of efficacy, and larger controlled trials are needed.

4.3 Creatine

Creatine was studied in a randomised, double-blind, placebo-controlled sequential trial of 175 patients, who received 5 g twice daily or placebo; the trial found no effect on survival or on functional measures between one and 16 months, and no safety concern [4]. The authors considered that the trial effectively ruled out value at that dose, although a smaller benefit could not be excluded.

4.4 High-caloric nutrition

Although this is a calorie and fat intervention rather than a protein one, it addresses the same problem of weight loss and is relevant to protein-energy planning. In the LIPCAL-ALS randomised trial of 201 patients, a high-caloric fatty diet did not prolong survival in the whole population (survival probability 0.37 versus 0.39 with placebo at 28 months; hazard ratio 0.97), but post hoc analysis showed a significant survival benefit in fast-progressing patients [6] (Figure 4b). This subgroup finding needs prospective confirmation.

Table 2. Interventional studies of amino acids and nutrition in ALS/MND.

Study	Intervention	Design	Outcome (as reported)
Parton et al. [3]	Branched-chain amino acids; L-threonine	Cochrane review of randomised trials	No survival benefit; well tolerated.
Levine et al. [5]	L-serine up to 30 g/day	Phase I; 6 months	Tolerated; reduced functional loss at highest dose (safety study).
Groeneveld et al. [4]	Creatine 5 g twice daily	Randomised, sequential; 175 patients	No effect on survival or function.
Ludolph et al. [6]	High-caloric fatty diet	Randomised; 201 patients	No overall survival gain (HR 0.97); post hoc benefit in fast progressors.

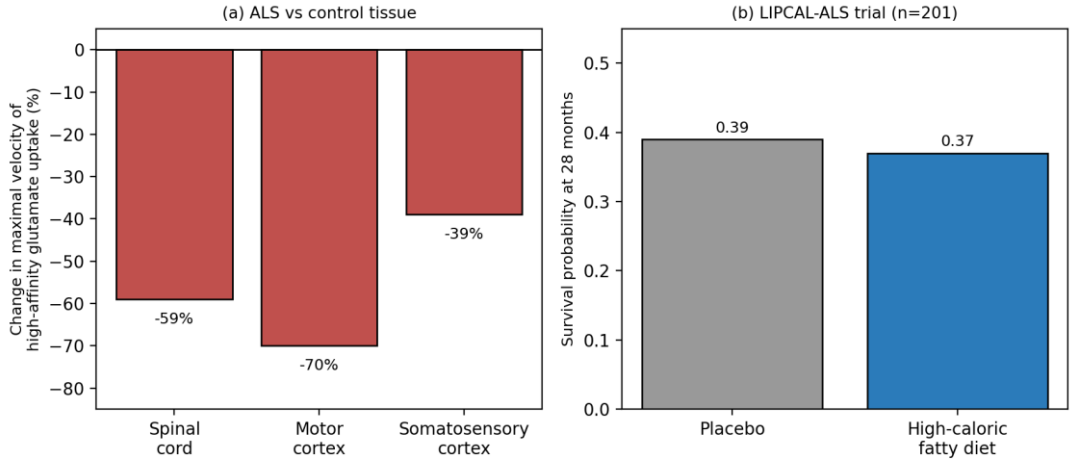


Figure 4. Reported values from Rothstein et al. 1992 (a) and Ludolph et al. 2020 (b); plotted from values given in the text of each paper.

5. Comparative assessment of protein sources

Table 3 compares the protein sources considered. For animal proteins, the only evidence is observational and suggests possible harm at high intake, with a mechanism that is unclear [1,2]. For plant foods, the signal relates to antioxidant-rich vegetables rather than to plant protein [2,11]. For supplements, randomised trials have been negative for creatine and branched-chain amino acids [3,4], and L-serine awaits efficacy trials [5]. Figure 5 shows that the interventional studies are small, with the L-serine safety study the smallest.

Table 3. Protein sources and amino acids considered for ALS/MND: evidence and assessment.

Source	Evidence	Design quality	Assessment
Animal protein (meat, dairy)	Higher risk with total and animal protein; lower function with milk and lunch meats [1,2]	Observational; confounding likely	Hypothesis only
Plant protein, vegetables	Vegetable carotenes: better function; carotenoids: lower risk [2,11]	Observational	Supports vegetable-rich diet; not plant protein per se
BCAA, threonine	No benefit [3]	Randomised trials	Not supported
L-serine	Tolerated to 30 g/day [5]	Phase I	Needs efficacy trial
Creatine	No effect [4]	Randomised, 175 patients	Not supported
High-caloric diet	No overall survival gain; fast progressors may benefit [6]	Randomised, 201 patients	Needs confirmation in subgroup

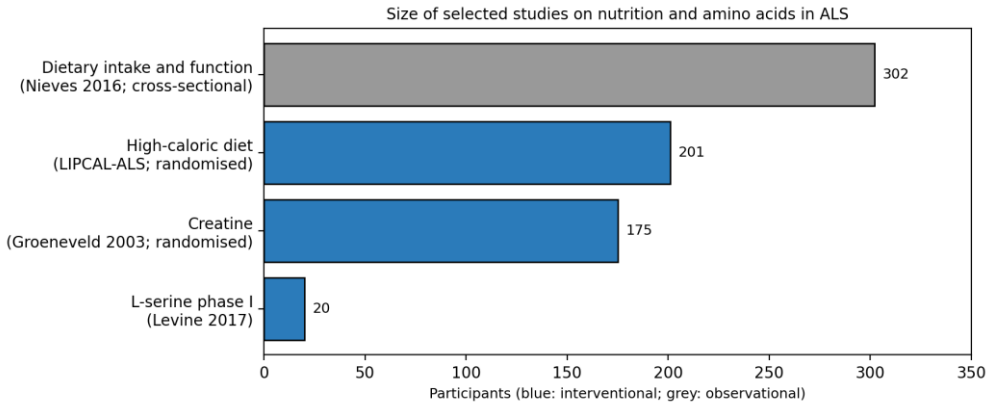


Figure 5. Sample sizes reported in the cited studies.

6. Limitations and future directions

The main limitations are the absence of trials of food proteins, reliance on retrospective questionnaires subject to recall bias, and small interventional studies [1,5]. Dietary change after symptom onset, reduced appetite and swallowing difficulty make cross-sectional associations hard to interpret [2]. Priorities include (i). prospective cohort studies that measure protein source and amount before diagnosis; (ii). randomised trials of protein dose and source for muscle mass and function; (iii). efficacy trials of L-serine, building on the phase I safety data [5]; (iv). prospective confirmation of the benefit of high-caloric nutrition in fast-progressing patients [6]; and (v). studies that link nutritional intake to glutamate-related biomarkers [10]. Patients should receive individual nutritional assessment, and supplements should be used only under medical supervision.

7. Conclusions

There is no evidence that any dietary protein, animal or plant, or any amino acid supplement, slows ALS. Observational data suggest caution about high intake of animal protein and favour a vegetable-rich diet, but they are hypothesis-generating [1,2,11]. Branched-chain amino acids, threonine and creatine have failed in trials [3,4], L-serine is being developed [5], and high-caloric nutrition may help selected patients [6]. Nutrition in ALS should aim to maintain weight and muscle under professional supervision rather than to use protein as a disease-modifying drug.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological sciences.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. Mineral supplementation or chelation should be undertaken only for a clinically justified indication and with appropriate medical monitoring.

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