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To cite this article: Shyuan T Ngo, Jia D Mi, Robert D Henderson, Pamela A McCombe & Frederik J Steyn (2017) Exploring targets and therapies for amyotrophic lateral sclerosis: current insights into dietary interventions, Degenerative Neurological and Neuromuscular Disease, , 95-108, DOI: [10.2147/DNND.S120607](https://doi.org/10.2147/DNND.S120607)

To link to this article: <https://doi.org/10.2147/DNND.S120607>



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Published online: 25 Jul 2017.



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Exploring targets and therapies for amyotrophic lateral sclerosis: current insights into dietary interventions

Shyuan T Ngo¹⁻⁵

Jia D Mi¹

Robert D Henderson^{3,4}

Pamela A McCombe^{3,4}

Frederik J Steyn³⁻⁵

¹School of Biomedical Sciences,

²Queensland Brain Institute, ³Centre for Clinical Research, The University of Queensland, ⁴Department of Neurology, Royal Brisbane & Women's Hospital, ⁵Wesley Medical Research, The Wesley Hospital, Auchenflower, Brisbane, QLD, Australia

Abstract: A growing number of preclinical and human studies demonstrate a disease-modifying effect of nutritional state in amyotrophic lateral sclerosis (ALS). The management of optimal nutrition in ALS is complicated, as physiological, physical, and psychological effects of the disease need to be considered and addressed accordingly. In this regard, multidisciplinary care teams play an integral role in providing dietary guidance to ALS patients and their carers. However, with an increasing research focus on the use of dietary intervention strategies to manage disease symptoms and improve prognosis in ALS, many ALS patients are now seeking or are actively engaged in using complementary and alternative therapies that are dietary in nature. In this article, we review the aspects of appetite control, energy balance, and the physiological effects of ALS relative to their impact on overall nutrition. We then provide current insights into dietary interventions for ALS, considering the mechanisms of action of some of the common dietary interventions used in ALS, discussing their validity in the context of clinical trials.

Keywords: ALS, treatment, alternative off-label therapies, antioxidants, clinical trials, nutrition

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease caused by the loss of motor neurons in the cerebral cortex, brainstem, and spinal cord. Death of these neurons results in progressive paralysis and disability, culminating in respiratory failure and death within 2–5 years following diagnosis.^{1,2} In the absence of an effective treatment for ALS, there is increased emphasis on interventions to improve the quality and extend the duration of life.

Engagement in ALS multidisciplinary care increases the quality of life while extending survival.³ As part of this process, patients receive dietary guidance preferably by a dietician. While addressing dysphagia, nutritional management also seeks to address changes in appetite that can occur as part of the disease, possibly due to physiological and psychological effects of ALS. Worsening of nutritional state, as reflected by weight loss, is associated with worsening motor symptoms and survival.^{4,5} This highlights the critical need for patients to meet energy requirements. In this review, we summarize the merits and mechanisms of action of dietary interventions proposed for ALS. We discuss the variable impact of ALS on overall energy balance, noting the effects on appetite control and energy expenditure. We also discuss dietary interventions within the context of risk factors known to impact energy balance and dietary needs in ALS.

Correspondence: Frederik J Steyn
Centre for Clinical Research (CCR),
University of Queensland, Building
71/918, Royal Brisbane & Women's
Hospital, Herston, QLD 4029, Australia
Tel +61 7 3346 5530
Email f.steyn@uq.edu.au

Meeting energy needs and maintaining energy homeostasis in ALS

Undernutrition is observed in ALS;⁶ however, there is significant nutritional heterogeneity among individuals. This is of clinical importance as nutritional state may negatively impact survival,⁷ whereas maintenance of body weight is an effective strategy to extend survival.⁸ Moreover, recent discoveries of the compounding effects of coexisting neurodegenerative conditions (including behavioral variants of frontotemporal dementia [bvFTD]) on nutritional status and appetite control in ALS patients highlight additional complexities and heterogeneity of dietary control.⁹ This heterogeneity indicates a need for well-directed treatments to improve nutrition in ALS while calling for a greater understanding of all factors that might impair energy homeostasis in ALS.

In ALS, a number of studies provide evidence for impairments in control of energy homeostasis (the balance of energy supply and use), which may compromise the capacity to meet energy needs. In particular, patients can experience reduced appetite, leading to reduced intake of food, and thus a failure to meet their energy requirements.

Complications of appetite control and ALS

Hunger represents our need to eat, a sensation that is generally guided by intrinsic mechanisms that promote behaviors that seek food. Appetite, by contrast, is a far more complex behavior, defined as our desire and capacity to consume

energy. Many intrinsic and external factors may contribute to appetite, including emotions and/or our physical capacity to access food.¹⁰ Considerable changes in appetite and eating behavior are observed in ALS.¹¹ Impaired appetite control in ALS could directly contribute to calorie deficit or excess, compounding weight loss, or weight gain. In ALS, appetite can be affected by physical difficulties, including difficulties in swallowing (dysphagia) or progressive disability that restricts access to food (including paralysis resulting in loss of use of hands), or dysfunction of endogenous processes that regulate hunger, satiety, and mood. Mechanisms of impaired appetite control discussed in this review are summarized in Figure 1.

Progressive loss of cranial nerves contributes to difficulties in regulating the complex swallowing process.¹² This results in poor control of the food bolus during swallowing. When observed alongside declining respiratory status, weakening oral control can lead to fear of choking, a reduction in calorie and fluid consumption, and possibly malnutrition.¹³ In ALS, 25%–35% of patients experience bulbar onset of weakness with dysphagia, and 70%–80% of patients develop dysphagia throughout the course of the disease.^{14,15} Initial management of dysphagia involves modification of food and fluid consistency (blending food, adding thickeners to liquids) and education of patients and carers in swallowing techniques.¹⁶ Swallowing difficulties can be managed through enteral feeding.

Disabilities other than dysphagia can increase the risk of calorie deficit in ALS; upper extremity weakness can impair the capacity to prepare or manipulate food. This can be circumvented through assistance from a caregiver; however, prolonged mealtimes and fatigue increase the risk

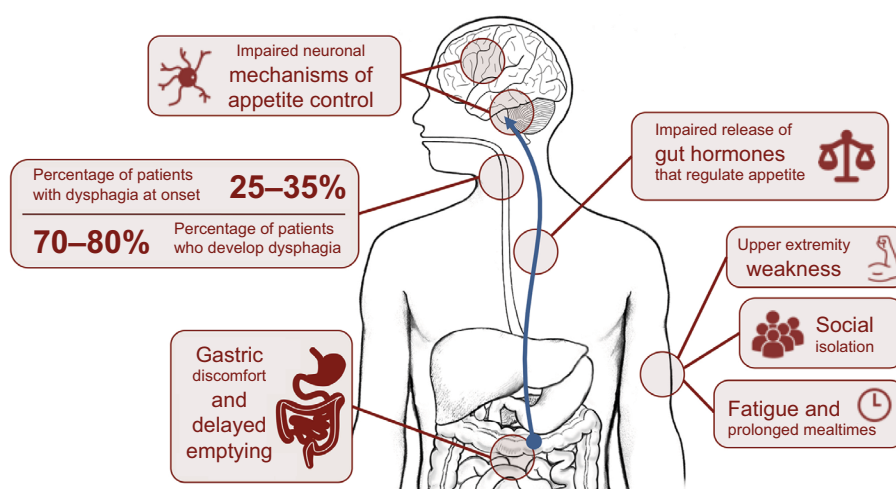


Figure 1 Mechanisms of impaired appetite control in amyotrophic lateral sclerosis (ALS).

Notes: Appetite control in ALS may be compromised by progressive worsening of disability or dysfunction of mechanisms that control hunger and satiety. Disability may result in dysphagia, upper extremity weakness resulting in a reduced capacity to access food or self-feed, social isolation during mealtimes, and/or fatigue and prolonged mealtimes resulting in reduced calorie or liquid consumption. Evidence suggests dysfunction of endogenous processes that control appetite regulation in ALS, including gastric discomfort and delayed gastric emptying, reduced release of gastric hormones that control appetite, or dysfunction of neuronal processes that control appetite.

of developing dehydration and suboptimal nutrition.¹⁷ Disability can also result in social isolation and embarrassment, further compromising a patient's nutritional status. Social aspects of eating can be affected by dysphagia or time-consuming and exhausting practices associated with eating. Introduction of adapted eating utensils can help a patient to maintain autonomy.¹⁸ Sialorrhoea (drooling or excessive salivation) can further burden patients during mealtimes, especially within social settings,^{16,19} lessening the desire to eat, and the enjoyment of meals. Treatment options range from anticholinergic drugs and botulinum toxin injections to reduce saliva production, through to radiological and surgical interventions.¹⁹ Gastric emptying and colonic transit times can also be delayed in ALS.²⁰ While contributing to discomfort associated with eating, impairments in gut function or delayed gastric emptying can also impact the release of gut hormones²¹ associated with appetite control,²² resulting in altered perception of hunger and satiety.

Appetite is controlled by peripheral and central mechanisms that sense and respond to changing energy balance. Energy homeostasis is achieved when circulating signals inform the brain of available fat stores and the brain then responds by stimulating corrective adjustments to food intake to maintain these stores. Various brain centers receive information on energy availability, calorie provision, and energy needs while also responding to behaviors and rewards (pleasure) associated with eating.²³ Dysfunction of any component within this network or changes in the way our brain responds to food could result in impairments in appetite control, leading to impairments in maintenance of body weight.

There is evidence of impairment of appetite-regulating pathways in ALS.²⁴ Hypothalamic neurons that promote satiety are less responsive in mouse models of ALS and in ALS patients than in controls.²⁵ Dysfunction of appetite control is further highlighted by TDP43 pathology in the lateral hypothalamus of some ALS patients,²⁶ with the accumulation of TDP43 thought to impair the function of, or contribute to the death of neurons that control appetite. TDP43 proteinopathy is also observed in areas of the brain associated with appetite motivation,²⁶ and thus impairments in appetite control in ALS may extend beyond hypothalamic control of energy homeostasis.

Clinical implications of altered appetite regulation in ALS, particularly with respect to weight management and prognosis, are still under investigation. Understanding of these pathways could lead to suggestions for therapy, and so it is important that we understand the changing energy needs of ALS patients.

Challenges to metabolic balance and ALS

Hypermetabolism in ALS^{5,27,28} has been suggested to contribute energy deficit, weight loss,²⁹ and reduced survival.²⁷ However, weight loss in ALS occurs regardless of the metabolic status.³⁰ Therefore, hypermetabolism in ALS may only contribute to energy deficit and weight loss, should appetite be impaired. Given that hypermetabolism is linked to shorter survival,²⁷ attempts to define the cause of hypermetabolism and to manage hypermetabolism in ALS remains of interest.

Dietary interventions in ALS

There is evidence that ALS patients are adopting self-prescribed dietary strategies. Over 600 dietary strategies and/or supplements are reported to be used by ~9500 ALS patients currently registered with Patients Like Me, a web-based community where members share details about their treatments.³¹ This is in line with findings that ~80% of ALS patients use high-dose vitamins, minerals, and other nutraceuticals.³² Common dietary strategies include avoidance of certain dietary components, adoption of very specific dietary regimes, or use of dietary supplements. Of these strategies, the majority have not been tested in clinical trials, or have produced no positive effects when tested. Below, we discuss dietary interventions for which there is some evidence of benefit. Outcomes are summarized in Table 1.

Dietary interventions that address dysphagia in ALS

Customizing dietary strategies to suit ALS

Management of dysphagia needs to be progressively adjusted to accommodate the changing degree of impairment throughout the course of ALS. While dysphagia may not be observed early in disease course, early education regarding nutrition should be considered. At the onset of upper extremity and/or bulbar dysfunction, greater care should be taken to maintain stable body weight, and it is recommended that assessments of dietary efficiency occur at 3-month intervals. Weight and respiratory capacity should be assessed, and patients are encouraged to consult with speech pathologists for advice on improving swallowing techniques.¹⁷ Patients may consider more effective dietary strategies to reduce the risk of choking or aspiration including altering the texture and consistency of food,^{15,16,33} consuming smaller portions more frequently, consuming calorie-rich foods, and increasing mastication time.¹⁷ With progressive bulbar dysfunction, the introduction

Table I Dietary interventions proposed to improve capacity to meet energy needs or treat complications associated with ALS

Symptom/intervention	Approach/rationale	Outcomes
Dysphagia		
Customized dietary strategies	Progressive adjustment to diet to degree of physical impairment; nutritional education	Improved weight management extends survival ⁸
Enteral nutrition	PEG, RIG, and PIG to supplement or provide nutrition	Hypercaloric feeding improved survival; ^{43,46} Early introduction, use to prevent weight loss extended survival ^{34,35}
Weight loss		
High-calorie diets	Calorie-rich diet to prevent or reverse weight loss	Slowed functional decline, ⁴³ extended survival; ⁴⁶ clinical trials in progress (NCT02306590)
Reduced appetite		
Cannabis	Activation of CBI to stimulate appetite	Patients report improved appetite and sialorrhoea; ⁵¹ adverse health effect concerns; ⁵⁹ no clinical trials specific to appetite regulation
Dietary fiber	Aid laxation ⁶⁷ to reduce gut discomfort and promote appetite	No change in ALS risk relative to fiber intake; ⁶⁸ diet rich in fiber associated with improved function in ALS ⁶⁹
Cramps and fasciculations		
Quinine	Reduce nocturnal leg cramps, ⁷⁸ life-threatening complications, ⁷⁹ prohibition of use for cramps	Patient reports of reduced muscle cramps following consumption as tonic water; no validated clinical trials in ALS
Vitamin E	Plant-based antioxidants; ⁸⁰ suggested improvements in leg cramps with vitamin E deficiency ⁸¹	Reduction in the risk for ALS with higher vitamin E levels ⁸² and with supplementation when vitamin E levels are low; ^{85–87} no impact on survival and quality of life; ^{88–91} clinical trial completed, data not available
Magnesium	Deficiency may lead to neuronal excitability, enhancing neuromuscular transmission ⁹² to cause cramps	No protective effects, no association between magnesium intake and ALS risk; ⁹⁴ no validated studies assessing the use of magnesium to treat cramps in ALS
Spasticity and stiffness		
L-Threonine	Essential α -amino acid, acting as precursor to increase glycine to treat spasticity ¹⁰⁰	Modest antispasmodic effect in spinal spasticity; ¹⁰¹ no effect in ALS; ¹⁰² evidence for the use in the treatment of ALS of low quality; ¹⁰³ use for spasticity not supported
Cannabis	THC transiently improved spasticity in MS; ¹⁰⁴ use of cannabinoid agonists to ameliorate spasticity in MS is established ^{106,107}	Benefits for spasticity limited to patient self-reports; ⁵¹ did not improve cramp intensity; ¹¹¹ use to treat spasticity in ALS is not clinically supported and studies are needed to explore other treatment effects ¹¹²
Low energy, fatigue, and weakness		
Caffeine	Stimulant, promotes alertness, memory, performance, and coordination ¹¹³	Reduced ALS risk with increased coffee intake ¹¹⁵
Ketogenic diet	High fat, restricted protein, and carbohydrate intake ¹²¹ to promote ketone use as alternative fuel; ¹²⁵ proposed to aid mitochondrial function ^{126–130} and glucose metabolism in muscle ^{131,132}	No human data to support the use of ketogenic diet in ALS; clinical trial (NCT01016522) initiated in 2009, study terminated, data not available; promotes weight loss by reducing appetite and increasing breakdown of fat stores ¹³⁴ and thus could exacerbate malnutrition
Deanna protocol	Treat disease processes including glutamate excitotoxicity/oxidative stress, ¹³⁵ and increase protein ¹³⁶ and alpha-ketoglutarate synthesis ^{135,137}	Benefits limited to anecdotal patient reports; ¹³⁵ further research in ALS is needed
Creatine	Proposed to increase phosphocreatine availability, ¹³⁹ stimulating mitochondrial respiration, ¹⁴⁰ antioxidant ¹⁴¹	Patient reports suggest improved muscle function, ¹⁴⁵ no improvement in strength, ^{146,147} function or survival ¹⁴⁸
Protein	Thought to aid muscle recovery and slow muscle loss	Supplementation prevented weight loss in ALS, stabilizing functional decline over 4 months; ⁴⁵ may improve nutritional status

Table I (Continued)

	Approach/rationale	Outcomes
Vitamin D	Improves musculoskeletal function in elderly ¹⁴⁹ suggesting possible benefits for treatment in ALS	Low vitamin D status correlates with a faster functional decline, reduced life expectancy in vitamin D-deficient patients; ¹⁵² modest slowing of functional decline with supplementation may have some benefits ¹⁵³
Pathological mechanisms of ALS		
Vitamin B12	Supports health of the nervous system ¹⁵⁸	Phase III clinical trial (NCT00444613) found lesser decline in ALSFRS-R and prolonged survival if active vitamin B12 was administered within 12 months of symptom onset; ¹⁶¹ replication of findings and further validation of use needed ¹⁶²
Carnitine	Proposed to protect against oxidative stress and damage ¹⁶³	Slower functional decline and increased median survival when used in combination with riluzole ¹⁶⁴
Coenzyme Q10 (CoQ10)	Proposed to boost mitochondrial function and act as free radical scavenger	Doses of up to 3000 mg/day were found safe and tolerable in ALS; ¹⁶⁶ no significant treatment benefit in ALS was observed ¹⁶⁷
Mitoquinone (MitoQ)	A synthetic derivative of CoQ10, strong antioxidant ¹⁶⁸	Trial in Parkinson's Disease demonstrated no positive effects; ¹⁷⁰ no clinical trials in ALS
Edaravone	Potent antioxidant and ROS scavenger ¹⁷¹	Clinical trial (NCT01492686) showed lesser decline in ALSFRS-R and less deterioration in quality of life at 6 months; ¹⁷⁵ oral formulation returned positive results in a Phase I trial, and Phase II/III trial in progress

Abbreviations: PEG, endoscopic gastrostomy; RIG, radiologically inserted gastrostomy; PIG, per-oral image-guided gastrostomy; CBI, cannabinoid receptors; MS, multiple sclerosis; ROS, reactive oxygen species; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised.

of enteral nutrition should be offered. While not an attractive option to all patients,¹⁷ this does improve survival.^{34,35}

It is important that caregivers are actively engaged. Those who take on a caregiver role need to adapt to cater for the specific issue of ALS. Due to physical disabilities in ALS, carers may be responsible for the majority of meal preparation³⁶ and, thus, should be aware of dietary needs specific to ALS. Recently, the Motor Neurone Disease Association released information, recipes, and advice to assist patients and caregivers in sustaining optimal dietary intake while also providing advice on how to maintain enjoyment for food in social settings.³⁷

Enteral nutrition

As bulbar symptoms progress, or when patients lose >10% of their baseline body weight, enteral feeding is often indicated.³⁸ A recent prospective study assessing the use of gastrostomy in ALS suggests that enteral feeding should be considered when patients lose 5% of their baseline body weight, and when their nutritional intake does not match their energy requirements.^{39,40}

Enteral feeding in ALS can be delivered via nasogastric tubing (NGT) or gastrostomy. Although feeding through NGT is a minor and noninvasive procedure, migration of the NGT, oropharyngeal secretion, nasopharyngeal discomfort, pain,

and ulceration limits its long-term use in ALS.^{16,17} Gastrostomy is commonly used for patients who require long-term enteral nutrition,⁴¹ and methods used in ALS include percutaneous endoscopic gastrostomy (PEG), radiologically inserted gastrostomy (RIG), and per-oral image-guided gastrostomy (PIG).⁴² For more information on the use of gastrostomy in ALS, we encourage the reader to consult recent reviews.^{41,42}

Recently, a double-blind, Phase II randomized clinical trial reported benefits of hypercaloric feeding via enteral nutrition. High-calorie supplementation improved survival outcome compared to an isocaloric intervention.⁴³ Importantly, it has also been found that placement of PEG in patients with dysphagia³⁴ and early introduction and efficient use of PEG to prevent weight loss is able to extend survival in ALS.³⁵ Hence, refinements in the use of PEG might further improve disease outcome for those with ALS.

Dietary interventions that address weight loss in ALS

High-calorie diets

Use of high-calorie supplementation in ALS has stemmed from the finding that calorie-rich diets prevent or reverse weight loss in ALS^{5,44} by offsetting malnutrition and increasing energy requirements. In ALS, a limited number of studies have assessed caloric supplementation by modifying

protein,⁴⁵ carbohydrate, or fat^{43,46} content in dietary regimens. While such studies report improvements or stabilization of body weight⁴⁵ or ALS Functional Rating Scale-Revised (ALSFRS-R),⁴³ only the prospective interventional study by Wills et al was able to demonstrate improvements in survival following high-calorie/high-carbohydrate, or high-calorie/high-fat supplementation.⁴³ Congruent with this, Dorst et al recently reported that high-calorie intake via PEG was associated with longer survival in ALS.⁴⁶ While these data are promising, small study sample size and limited experimental design necessitate that larger, double-blinded randomized clinical trials are conducted to clarify dietary strategies that improve prognosis in ALS. In this regard, a double-blinded randomized clinical trial to assess the efficacy, safety, and tolerability of high-lipid and -calorie supplementation in 200 ALS participants (NCT02306590) is currently underway. With the primary endpoint of the trial being survival time from randomization until death or date of study completion, data from this trial will shed some light on the utility of high-calorie supplementation as a treatment approach for ALS.

Dietary interventions that address reduced appetite and digestive health in ALS

Cannabis

Cannabis plants contain over 500 distinct chemical functional molecules, of which delta-9-tetrahydrocannabinol (THC) is considered the most biologically active.⁴⁷ Cannabinoids (CBs) such as THC modulate their effects via CB receptors expressed throughout the brain (predominantly CB1 receptors) and immune system (predominantly CB2 receptors).⁴⁸ The reader is encouraged to consult recent reviews on the use of cannabis and pharmacological targeting of the endocannabinoid system in treating disease.^{49,50} We limit the discussion to advances in the use of cannabis and cannabis-derived factors in treating symptoms associated with ALS, including appetite and spasticity.

ALS patients report improvements in appetite and sialorrhea following the use of cannabis,⁵¹ suggesting that CBs may negate some effects of ALS on appetite control.⁵² Studies in mice show that CBs act via the CB1 receptor to promote food intake. Specifically, CBs promote the activity of hypothalamic pro-opiomelanocortin (POMC)-expressing neurons (a neuronal population better known to promote satiety⁵³), stimulating β -endorphin release.⁵⁴ In turn, β -endorphins promote food intake, acting on additional brain circuitry.⁵⁵ These actions of CBs on POMC-expressing neurons are thought to occur via selective modification of mitochondrial

activity.⁵⁴ Since mitochondrial dysfunction^{56–58} and aberrant hypothalamic control of appetite regulation occurs in ALS,^{25,26} use of CBs may not improve appetite control across all ALS patients. There are potential adverse health effects of cannabis,⁵⁹ so there is a need for alternative compounds to promote hunger in ALS. Ghrelin is a potent endogenous orexigenic factor that stimulates appetite to increase calorie consumption.⁶⁰ Given the reduced circulating levels of ghrelin in ALS,^{21,61} treatment with ghrelin may improve appetite. Moreover, as ghrelin has been shown to protect spinal cord motoneurons from chronic glutamate excitotoxicity while inhibiting microglial activation,^{62,63} benefits of ghrelin treatment may extend beyond improvements in appetite control.⁶⁴ To our knowledge, no clinical trials have assessed the use of cannabis, CBs, or orexigenic factors such as ghrelin in promoting appetite in ALS. Of interest, a patent for the use of an analog that targets the ghrelin receptor as treatment in ALS has been filed (Patent Cooperation Treaty number JP2013/078743).

Dietary fiber

Fiber lowers the concentrations of inflammatory markers and can reduce the risk of mortality in some inflammatory diseases.^{65,66} Moreover, dietary fiber is known to promote gut health, thereby improving laxation.⁶⁷ Improvements in gut function following increased ingestion of fiber may also aid the production and release of key gut hormones (including ghrelin), thereby enhancing appetite control.⁶⁷ Comparing outcomes from five large cohort studies, no change in ALS risk relative to dietary fiber intake was observed.⁶⁸ Of interest, a diet rich in antioxidant nutrients, carotenoids and fiber, and vegetables is associated with improved function in ALS patients.⁶⁹ Whether improved function was due to increased fiber intake was not specifically addressed. It remains unclear whether dietary fiber led to improved gut health, reduced colonic transit times to improve laxation, or improved appetite control in ALS.

Dietary interventions directed toward physical disability in ALS

Dietary modification for cramps and fasciculations

Muscle cramping and fasciculations are widely reported in ALS,⁷⁰ with symptoms presenting prior to the onset of weakness and/or muscle wasting.^{71,72} Fasciculations occur as a consequence of abnormal excitation of the terminal branches of motor axons,⁷³ whereas cramps may occur as a consequence of mechanical excitation of the motor nerve

terminal,⁷³ hyperexcitability or bistability of spinal motor neurons,⁷⁴ or through impairments in inhibitory mechanisms of interneuron activity.⁷⁵ Muscle cramping in ALS can be persistent and can cause debilitating pain. Various drugs have been proposed to treat cramps in ALS, including antispasmodics such as Baclofen or Zanaflex.⁷⁶ To manage cramping, patients report the use of quinine and increased consumption of dietary supplements including vitamin E and magnesium.

Quinine

Quinine is used for the treatment of malaria.⁷⁷ While showing some benefits in managing nocturnal leg cramps,⁷⁸ the occurrence of life-threatening complications⁷⁹ has resulted in a ruling by the FDA to prohibit the use of quinine for the treatment of cramps. Promotion of quinine for treatment of leg cramps has been prohibited in the USA since February 1995, with the marketing of quinine-containing preparations banned by the FDA since December 2006 (FDA, Docket No. 2006N-0476). ALS patients report reduced muscle cramps following the consumption of quinine as tonic water, with amounts of quinine ingested per liter of tonic water estimated to be ~25-fold lower than the proposed daily dosage for the treatment of malaria.⁷⁷

Vitamin E

Vitamin E is a group of lipid-soluble antioxidants commonly found in plant products.⁸⁰ Investigation of the effects of vitamin E on dermatological conditions led to the suggestion of treatment benefits on nocturnal leg cramping in individuals with possible vitamin E deficiency.⁸¹ While vitamin E deficiency in ALS is not universal,^{82–84} a potential reduction in risk for ALS is suggested in those with higher vitamin E levels,⁸² or those with low baseline vitamin E levels who are receiving vitamin E supplementation.^{85–87} Despite these positive associations, oral administration of vitamin E does not impact ALS survival or the quality of life.^{88–91} A randomized crossover trial to assess the impact of vitamin E on the number, duration, and severity of cramps was initiated in 2006 (NCT00372879). While this trial is now complete, the results have not been made public.

Magnesium

Magnesium deficiency can lead to neuronal excitability, enhancing neuromuscular transmission.⁹² Accordingly, magnesium supplementation has been proposed for the treatment of cramps. A recent systematic review of randomized controlled trials with meta-analysis found no evidence for effective management of cramps using magnesium. A small

effect in reducing nocturnal cramps was observed in pregnant women only.⁹³ Comparing the results from five large cohort studies, recent observations found no association between magnesium intake and ALS risk, or protective effects of magnesium on ALS,⁹⁴ although modest effects had been suggested previously.⁹⁵ We could not identify any studies assessing the specific use of magnesium to manage cramps in ALS.

Dietary modification for spasticity and stiffness

Spasticity, an increase in tonic stretch reflexes due to hyperexcitability, is observed in a number of neurological disorders as a result of loss of upper motor neurons.⁹⁶ Symptoms include increased tone, spasms, and/or clonus, and spasticity can lead to severe disability, pain, or incapacitation.⁹⁷ Pharmacological treatments include Baclofen, alpha-2 agonists such as clonidine, or use of anticonvulsants such as benzodiazepines.⁹⁶ Given the possible side effects of pharmacological treatment,⁹⁸ a multidisciplinary approach combining medication and physical therapy is recommended.⁹⁶ Use of nutraceuticals including L-threonine and CBs can be considered for treatment of spasticity.

L-Threonine

L-Threonine is an essential α -amino acid, acting as a glycine precursor to increase glycine levels in the central nervous system.⁹⁹ Potential use of glycine to treat spasticity has led to the assessment of L-threonine as a possible treatment for spasticity in ALS.¹⁰⁰ A double-blind, placebo-controlled, crossover study of oral L-threonine to treat spinal spasticity found a modest antispasmodic effect.¹⁰¹ Similar treatment effects were not observed in ALS, with a pilot observation¹⁰⁰ and a double-blind, placebo-controlled, crossover study of L-threonine showing no improvements in ALS.¹⁰² These observations were unexpected, given suggested positive treatment effects following short-term L-threonine treatment of ALS.¹⁰² A recent Cochrane review found evidence for the effective use of L-threonine in the treatment of ALS to be of low quality,¹⁰³ and thus the use of L-threonine for treatment of spasticity in ALS remains unsupported.

Cannabis

Clinical use of cannabis and CBs in treating spasticity originates from observations in multiple sclerosis (MS), where synthetic THC treatment transiently improved spasticity scores.¹⁰⁴ This observation is in line with studies that implicate the endocannabinoid system in the pathophysiology of MS.¹⁰⁵ The use of CB agonists to ameliorate spasticity in MS

is established.^{106,107} Evidence supporting the use of cannabis or cannabis-derived compounds in treating ALS is mostly limited to animal studies, and in particular observations of delayed disease progression following treatment of SOD1^{G93A} mice with a CB1/CB2 agonist.¹⁰⁸ Moreover, the upregulation in CB2 receptor expression¹⁰⁹ and potentiation of CB1 receptors controlling glutamatergic and GABAergic transmission in ALS mice¹¹⁰ suggest the involvement of the endocannabinoid system in the pathophysiology of ALS. Unlike MS, clinical evidence showing positive treatment effects of CB use in ALS is mostly limited to patient self-reports of subjective improvement in spasticity.⁵¹ These patient reports are contradicted by a small randomized double-blind crossover trial, where twice-daily treatment with THC did not improve cramp intensity.¹¹¹ Given the lack of evidence, use of THC in treating spasticity in ALS is not clinically supported, and more studies are needed to explore other treatment effects.¹¹²

Dietary modification for low energy, fatigue, and weakness

Caffeine

Caffeine is a commonly consumed stimulant, acting within the central nervous system via various mechanisms to promote alertness, memory, performance, and coordination.¹¹³ Chronic consumption of caffeine in the SOD1^{G93A} mouse model negatively influenced motor performance and reduced survival duration,¹¹⁴ prompting fears that caffeine might worsen disease survival. However, subsequent studies in humans found no association between caffeine and risk for developing ALS.¹¹⁵ This contradicts findings from a case-control study, observing a reduction in ALS risk relative to increased coffee consumption.¹¹⁶ Recent reviews discuss the possible mechanisms of action and perceived benefits of caffeine in ALS and other neurodegenerative diseases.^{117–119}

Ketogenic diet

Introduced in 1921 for the treatment of epilepsy,¹²⁰ the ketogenic diet is a regimen that encompasses high dietary intake of fat alongside the restriction of protein and carbohydrates.¹²¹ The ketogenic diet has been trialed as a nonpharmacological therapeutic approach across a number of neurological conditions.^{122–124} While its neuroprotective effects are proposed to range from mitigating inflammation to alleviating neuronal excitotoxicity, data remain contentious.¹²³ In ALS, the most pertinent mechanism by which the ketogenic diet could exert neuroprotection is through the provision of fat, which is converted into ketone bodies for use as a fuel substrate for the generation of cellular energy.¹²⁵ In light of defective mitochondrial

function in skeletal muscle^{126–130} of ALS patients, and mouse data highlighting muscle weakness in the presence of defective skeletal muscle glucose metabolism,^{131,132} the ketogenic diet offers an avenue through which skeletal muscle can bypass mitochondrial dysfunction and the need for glucose to sustain function. Improved motor performance in SOD1^{G93A} mice fed a ketogenic diet implies that this may be the case. However, given that improved motor performance was observed alongside the attenuation of motor neuron death,¹³³ it remains unknown whether the ketogenic diet has direct effects on muscle to mitigate weakness. To date, there is limited mouse data, and no human data to support the adoption of a ketogenic diet in ALS. While a clinical trial to assess the safety and tolerability of the ketogenic diet in ALS (NCT01016522) was initiated in 2009, the study was terminated, and no data have been disseminated. Critically, since the ketogenic diet promotes weight loss by reducing appetite and increasing the breakdown of endogenous fat stores,¹³⁴ this could exacerbate malnutrition and weight loss in ALS. Further research is needed to clarify the clinical efficacy of the ketogenic diet in ALS.

Deanna protocol

The Deanna protocol is a commercially available dietary supplement cocktail. Components of the Deanna protocol are thought to target pathophysiological processes of ALS including glutamate excitotoxicity and oxidative stress.¹³⁵ In addition, the key components of the Deanna protocol are L-arginine, which improves blood flow to promote protein synthesis,¹³⁶ and alpha-ketoglutarate, a fuel substrate that can be fed directly into mitochondrial pathways for the generation of cellular energy.^{135,137} Thus, it is plausible that L-arginine and alpha-ketoglutarate could have positive effects in ALS by promoting skeletal muscle growth and bypassing defects in skeletal muscle glucose metabolism¹³¹ to improve energy production to sustain muscle function. Congruent with this, a 2014 study in SOD1^{G93A} mice found that supplementation with arginine-alpha-ketoglutarate led to improved motor function.¹³⁷ However, this mouse data has not been independently replicated, and there are no published clinical trials on the use of the Deanna protocol in ALS. Given that the current clinical value of the Deanna protocol rests solely on anecdotal patient reports¹³⁵, further research into the adoption of the Deanna protocol in ALS is needed.

Creatine

Creatine is a naturally occurring guanidine derivative that is synthesized in the liver and found predominantly in muscle and the brain.¹³⁸ Dietary supplementation with creatine is thought

to increase energy output during anaerobic activity, increasing phosphocreatine availability¹³⁹ and stimulating mitochondrial respiration.¹⁴⁰ Creatine is also thought to act as an antioxidant, stabilizing mitochondrial membranes.¹⁴¹ Study outcomes in SOD1^{G93A} mice are mixed. Initial studies found that creatine was able to extend survival¹⁴² while reducing glutamate excitotoxicity;¹⁴³ however, improvements in muscle function were not observed.¹⁴⁴ Creatine use by ALS patients was reported to lead to improvements in muscle function,¹⁴⁵ with reduced muscle fatigue and improved endurance. Comprehensive studies, however, showed no positive outcomes on strength.^{146,147} A recent Cochrane review of trials in ALS found no improvement in ALSFRS-R scores following the use of creatine, suggesting no functional benefits of creatine use. The same review found no significant benefit of the use of creatine in ALS survival, noting studies are needed to assess the potential benefits of creatine when taken earlier in the disease course.¹⁴⁸

Protein

Few studies have assessed the impact of protein supplementation in ALS, despite the belief that protein supplementation could aid muscle recovery and slow loss of muscle mass. Supplementation with milk whey protein in a small cohort of ALS patients prevented weight loss, contributing to a modest but significant rise in BMI. Maintenance of body weight was associated with a stable ALSFRS-R score over the 4-month assessment period, whereas ALSFRS-R scores declined in individuals not supplemented with protein.⁴⁵ These results suggest that whey protein supplementation can improve the nutritional status of patients; specific effects of increased protein supply versus calorie supplementation remain unclear.

Vitamin D

Vitamin D is a secosteroid (fat-soluble sub-class of steroid-derived hormones) involved in a range of biological processes including calcium regulation. While some foods contain vitamin D, it is primarily produced endogenously following direct sun exposure to the skin.¹⁴⁹ Vitamin D supplementation alone, or in combination with calcium in aged individuals, improves musculoskeletal function,¹⁴⁹ suggesting possible benefits for treatment in ALS. Supplementation of vitamin D in SOD1^{G93A} mice show mixed results, with studies documenting improvements in functional capacity but not survival. Treatment was found to be toxic in female mice.^{150,151} In patients, low vitamin D status correlates with a faster functional decline, with reduced life expectancy observed in those with vitamin D deficiency.¹⁵² Assessment of ALS patients found vitamin D levels <30 ng/mL in ~80% of patients, and vitamin D levels

<20 ng/mL in ~40% of patients. Noting a modest slowing of functional decline following vitamin D supplementation, the authors concluded that vitamin D supplementation was safe and may have some benefits.¹⁵³ Additional prospective control trials are required to study the effect of vitamin D on the progression of disability in ALS patients.

Dietary interventions that address pathological mechanisms in ALS

Antioxidants

A balance between oxidation/reduction states (redox homeostasis) allows for the generation of reactive oxygen species (eg, free radicals) and reactive nitrogen species that play essential roles in regulating cellular pathways that maintain function and survival. Naturally occurring antioxidant defense systems in cells protect against cell damage by preventing the oxidation of molecules and by scavenging free radicals. When the balance between free radical production and antioxidant defenses becomes unfavorable, oxidative stress ensues.¹⁵⁴ With oxidative stress considered to be one of the primary pathogenic mechanisms in ALS,¹⁵⁵ it is not surprising that dietary supplements with antioxidant effects are commonly used. Common antioxidants include vitamins, carnitine, and coenzyme Q10 (CoQ₁₀). Despite the lack of bona fide clinical trial data to demonstrate positive effects in ALS for the majority of antioxidants,^{156,157} high tolerance and safety combined with ease of availability do not discourage their use by patients.

Vitamin B12

Vitamin B12 is a water-soluble vitamin that plays an essential role supporting the health of the nervous system.¹⁵⁸ Humans are unable to synthesize vitamin B12, and hence must obtain it through dietary sources.¹⁵⁹ Methylcobalamin, an active form of vitamin B12, has been trialed at high doses in ALS. In a double-blind controlled trial, Kaji et al found that compared to low-dose methylcobalamin, high-dose methylcobalamin was able to prevent the deterioration in the amplitude of the compound muscle action potential after 4 weeks of treatment.¹⁶⁰ A randomized double-blind, Phase III clinical trial (NCT00444613) conducted by the same group found that patients receiving high-dose methylcobalamin (intramuscularly) had a lesser decline in ALSFRS-R and prolonged survival if the compound was administered within 12 months of symptom onset.¹⁶¹ Based on current clinical data, ALSUntangled have provided recommendations to encourage the replication of findings and the validation of the use of vitamin B12 in ALS.¹⁶²

Carnitine

Carnitine is an essential nutrient that plays an integral role in fatty acid metabolism. L-carnitine, the biologically active form of carnitine, can be synthesized endogenously and obtained through dietary sources. As an antioxidant, L-carnitine is proposed to protect against oxidative stress and damage.¹⁶³ A randomized double-blind placebo-controlled trial assessing the effects on disability and mortality of acetyl-L-carnitine in combination with riluzole showed that there was a slower decline in ALSFRS-R and an increase in median survival.¹⁶⁴

Coenzyme Q10 (CoQ10)

CoQ10, also known as ubiquinone, is a lipid-soluble antioxidant. Serving as a diffusible electron carrier in the mitochondrial electron transport chain, CoQ10 plays a vital role in cellular energy production.¹⁶⁵ Hence, CoQ₁₀ could exert beneficial effects in ALS by boosting mitochondrial function, and by scavenging free radicals to protect against oxidative stress. In an open-label dose-escalation trial, doses of up to 3000 mg/day of CoQ10 were found to be safe and tolerable in ALS.¹⁶⁶ However, a subsequent Phase II double-blind randomized controlled trial assessing daily CoQ10 at 2700 mg/day demonstrated no significant benefit of CoQ10 over placebo.¹⁶⁷

Mitoquinone (MitoQ)

A synthetic derivative of CoQ₁₀, MitoQ is a strong antioxidant that was designed to accumulate in and protect against oxidative damage in mitochondria.¹⁶⁸ Administration of MitoQ to symptomatic SOD1^{G93A} mice slowed the decline in mitochondrial function in skeletal muscle and spinal cord, improved hindlimb strength, and extended survival.¹⁶⁹ These data suggest that specific targeting of antioxidants to mitochondria could be beneficial in ALS. A previous trial of MitoQ in Parkinson's disease demonstrated no positive effects,¹⁷⁰ and there have been no clinical trials of MitoQ in ALS.

Edaravone

Currently being developed by Mitsubishi Tanabe Pharma Corporation (Japan), edaravone (MCI-186, Radicut®) is a potent antioxidant that scavenges reactive oxygen species.¹⁷¹ Preclinical studies demonstrate that edaravone improves motor function, slows symptom progression, and attenuates motor neuron degeneration in rodent models of ALS.^{172,173} A confirmatory double-blind, parallel-group, placebo-controlled study of edaravone in ALS patients demonstrated a smaller reduction in ALSFRS-R in patients receiving edaravone over a 24-week treatment period.¹⁷⁴ More recently, Tanaka et al presented results from a 24-week, Phase III, double-

blind, parallel-group study of edaravone in a defined cohort of patients (NCT01492686), revealing a lesser decline in ALSFRS-R at 6 months and less deterioration in quality of life.¹⁷⁵ Radicut® (The Japanese Pharmacopoeia Edaravone injection) is currently approved for use as a treatment for ALS in Japan and South Korea. Radicava™ (intravenous) received FDA approval for use in ALS in the USA in May 2017. A Phase I trial of an oral formulation of edaravone (TW001) in the Netherlands has returned positive results, and a Phase II/III trial is in progress. For a more detailed overview of Edaravone, we encourage the reader to consult a recent review.¹⁷⁶

Concluding remarks

In the absence of effective treatments for ALS, patients are increasingly adopting dietary regimens and using dietary supplements with the view to alleviate symptoms and to improve quality of life and disease outcome. While data suggest that the adoption of high-calorie or high-protein diets may have some benefit, larger clinical trials are needed to validate the effectiveness of these approaches in ALS. Although the majority of dietary supplements reviewed here have not been clinically validated, preliminary data from some trials suggest the potential usefulness of supplements that target specific pathogenic mechanisms in ALS. In these instances, further studies are needed.

Acknowledgments

STN acknowledges the support of a Scott Sullivan MND Research Fellowship funded by The MND and Me Foundation, The Royal Brisbane & Women's Hospital Foundation, and the Queensland Brain Institute. The authors would like to acknowledge the valuable funding/salary support of Wesley Medical Research (Project number 2016-32) and The Motor Neurone Disease Research Institute of Australia.

Disclosure

The authors report no conflicts of interest in this work.

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