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Review article

Body mass index and dietary intervention: Implications for prognosis of amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is an adult onset, neurodegenerative disease that is characterized by the loss of upper (corticospinal) and lower motor neurons. ALS is a multifactorial disease whereby a combination of genetic and environmental factors may contribute to disease pathogenesis. While the majority of studies indicate that the underlying causes for ALS pathology may be due to multiple defects at the cellular level, factors that have recently been identified to be associated with survival could lead to the development of beneficial interventions. In ALS, a higher pre-morbid body mass index (BMI) and the maintenance of BMI and nutritional state is associated with improved outcome. This review will focus on the associations between body composition and adiposity relative to disease duration and risk, and will discuss current evidence that supports the benefits of improving energy balance, and the maintenance of body mass through nutritional intervention in ALS.

Contents

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1. Introduction

1.1. ALS — An aggressive multifactorial disease

Amyotrophic lateral sclerosis (ALS) is an aggressive neurodegenerative disease that is characterized by the concurrent degeneration of upper and lower motor neurons, and associated networks. This results in progressive paralysis and eventual death usually from respiratory failure [1,2]. ALS can be sporadic (90–95%) or familial (5–10%). The clinical presentation of the disease is indistinguishable between sporadic and familial patients.

1.2. Cause of ALS

The primary underlying cause for ALS remains to be determined, but as with all complex diseases, is likely to be due to a combination of genetic and environmental factors. Genes that are causative in ALS have been identified and include copper–zinc superoxide dismutase 1 (SOD1) [3,4], ubiquitin [5], optineurin [6,7], fused in sarcoma protein (FUS) [8–12], TAR DNA binding protein of 43-kDa (TDP-43) [13–15], and C9ORF72 [16,17]. The processes that underlie disease and lead to cell death include abnormal function and/or pathological aggregation of SOD 1 [18], FUS, TDP-43, and ubiquitin, excitotoxicity [19–22], mitochondrial dysfunction [23,24], non-cell autonomous death [25–29], and altered metabolic homeostasis [30–34].

While studies indicate that the underlying causes for ALS pathology may lie at the cellular level, identification of modifiable factors that predict the course of disease could lead to beneficial interventions. Factors that have recently been identified to be associated with survival in ALS include body mass index (BMI) and nutritional state. In this review we will discuss associations between body composition and fatness relative to disease duration and risk, and current evidence that supports the benefits of improving energy balance and nutritional intervention in ALS.

2. ALS — Body mass composition and metabolic considerations

2.1. Body mass index and prognosis in ALS

Weight loss in ALS is universal and is due to loss of muscle mass and a reduction in body fat mass [35], measured as body mass index (BMI, defined as weight in kilograms divided by height squared in meters) [36]. Recent assessment of the relationship between BMI and disease progression in ALS found that patients with a BMI between 30 to 35 had a better survival outcome than those with a BMI below 30, or above 35 [37]. A faster rate of reduction in BMI was also been found to predict shorter length of survival in ALS patients [38]. Most interestingly, recent studies also suggest that higher pre-morbid BMI not only predicts a better result on the ALS Functional Rating Scale (ALSFRS-R) [39], but that increased BMI in earlier life is associated with lower incidence of ALS [40] and decreased risk of ALS mortality [41]. Although these studies suggest that increased body mass (and presumably fatness) in ALS may be protective, they do not entirely confirm that a very high BMI is beneficial in ALS. In fact, the association of BMI with survival in ALS is denoted by a "U" shaped curve, wherein low and high BMIs are detrimental to survival duration [37]. With respect to the detrimental effects of high BMI in ALS, it could be expected that co-morbidities (including cardiovascular disease and type II diabetes) associated with being obese [42] would be the cause of reduced survival. However, Paganoni and colleagues found that while cardiovascular disease occurred at a higher incidence in an ALS cohort with a BMI of >35 (compared to patients with a lower BMI), the increased mortality in this cohort was not directly related to cardiovascular events [37]. Moreover, ALS patients with type II diabetes appear to have later disease onset [43,44]. Thus, factors contributing to poor survival in patients with a BMI above 35 are yet to be elucidated, but do not appear to be due to complications arising from cardiovascular disease or diabetes. Similarly, little is known regarding the factors associated with improved survival in ALS patients with a BMI of 30 to 35. Common theories include provision of higher baseline energy reserves needed to mitigate increased energy requirements associated with ALS, and altered lipid metabolism.

2.2. Evidence that adiposity and lipids influence disease progression in ALS

Above we presented evidence demonstrating an association between BMI and the risk of developing ALS, disease outcome and disease progression. We now discuss the role of adiposity and lipids in ALS.

Whilst BMI is influenced by fat mass, BMI is determined by all components of the body including lean muscle mass. Accordingly, fat mass may largely determine BMI in obese individuals, whilst muscle mass may greatly contribute to BMI in a lean individual. In this regard, a decrease in BMI in ALS may not be due solely to a loss in fat mass, but rather rapid weight loss and the resulting reduction in BMI may result from muscle atrophy due to denervation [45]. Loss of motor function resulting in difficulty in feeding due to upper limb weakness, and a reduction in food intake due to dysphagia in ALS [46] may result in malnutrition and contribute to this reduction in muscle mass (proteolysis). Consequently, measures of BMI may not specifically address the role of fat mass in ALS survival, and thus should be treated accordingly.

Detailed measures of adiposity and survival in ALS are limited, however existing observations provide some insights to delineate the potential beneficial role of fat mass and ALS survival. Assessment of ALS patients within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of individuals revealed that an increase in pre-morbid body fat mass was associated with decreased risk of ALS mortality [41]. While limited by the extrapolation of fatness through assessment of BMI, this study included comparisons between ALS survival and waist to hip ratio (WHR). This is important, as WHR is considered to be a predictor of abdominal adiposity [47]. While demonstrating a non-significant trend showing reduced risk of ALS relative to an increase in WHR, the data highlighted a potential divergence in risk between males and females. In men, no relationship between WHR and ALS survival was observed, while a significant reduction in risk was observed in women relative to an increase in WHR. Given that the deposition of adipose in the waist and hip varies between males and females [48], it would seem relevant that future studies would also consider gender specific analysis of waist and hip circumference with respect to the risk of developing ALS.

To our knowledge, Lindauer et al. (2013) conducted the only comprehensive study that specifically assesses the relationship between adipose mass and ALS survival. Lindauer and colleagues used MRI-based methodologies to quantify fat distribution, and presented observations relative to visceral (fat located around organs) and subcutaneous fat mass (fat underlying the skin). While demonstrating a trend for improved duration of survival of ALS patients relative to increased total and visceral fat mass, a significant relationship was only observed relative to subcutaneous fat mass. Importantly, these observations were specific to male patients, suggesting a potential gender specific difference in the role of adipose mass in the prediction of survival in ALS. Given that adipose tissue represents the primary store of energy, and there are known alterations in energy demands associated with ALS (see below), one may conclude that altered fat mass infers a survival advantage through the sustained provision of energy. Of course, this assumes mechanisms that mediate the movement of energy out of storage, and that facilitate the use of fat as energy remain intact.

While there is good evidence that higher BMI is a predictor of ALS risk and survival, other studies have assessed the levels of lipids in circulation in relation to the prognosis of ALS. Although some studies show prolonged survival in patients with elevated levels of total cholesterol, low-density lipoprotein (LDL), LDL/high-density lipoprotein (HDL) ratio, or triglycerides [49,50], conflicting observations suggest that total cholesterol, triglycerides, LDL, HDL and the LDL/HDL ratio between

ALS patients and controls remain unchanged [43]. Moreover, it has also been found that cholesterol and LDL are unchanged in ALS patients throughout the course of disease [37]. Thus, whether dyslipidemia exists in ALS, and whether dyslipidemia is related to or able to predict survival in ALS remains to be confirmed. Given that hyperlipidemia may be beneficial, and as lipid-lowering statins may cause neuromuscular damage and upper motor neuron lesions or an ALS-like syndrome [51], it would seem prudent to be cautious about the treatment of hyperlipidemia, especially with statins, in ALS patients.

2.3. Hypermetabolism in ALS

Hypermetabolism, defined as a significant increase in metabolic rate at rest [52], is observed in ALS patients at the whole body level [30,32–34] and within the brain [31]. Consistent with hypermetabolism and negative energy balance, reduced total body weight is seen in ALS [53,54]. In part, this may underlie the close association between survival and the aggregation of adipose stores. The mechanisms that underlie the development of hypermetabolism in ALS remain unknown. It has been proposed that mitochondrial defects inherent to ALS could drive the hypermetabolic phenotype [23,24,55]. Reduced mitochondrial capacity, leading to increased reactive oxygen species may alter pH [56], which may in turn contribute to metabolic dysfunction [57].

Attempts have been made to further understand hypermetabolism in ALS. In this regard, efforts to alter systemic metabolism or efforts to balance energy homeostasis may modify disease outcome. Hypermetabolism in mouse models of ALS (SOD^{G93A} and SOD^{G86R}) is demonstrated by an increase in resting energy expenditure [58,59]. Comprehensive assessment of the metabolic profile of SOD^{G86R} mice at the asymptomatic and symptomatic stages of disease reveals depletion of lipid stores, altered carbohydrate metabolism, and glucose accumulation in skeletal muscle [58]. Complimentary to this, altered glucose flux and lipid metabolism is observed in SOD^{G93A} mice, and there is an increased tendency for the peripheral clearance of lipids in response to high fat feeding [57,60]. By compensating for an increase in energy demand through high fat feeding, Dupuis and colleagues were able to extend mean survival in SOD^{G86R} mice [58]. Taken together, these studies provide compelling evidence to suggest that hypermetabolism in ALS is of skeletal muscle origin, and that increased energy demand may partially underlie the mobilization and eventual depletion of fat mass (and body weight/BMI) that is observed in ALS. Considering this, close associations between adiposity and survival in ALS may simply be reflective of a capacity or tendency to compensate for the hypermetabolic state.

2.3.1. Altered energy supply during periods of negative energy balance in ALS

In both health and disease, energy metabolism and the maintenance of body composition are tightly regulated to sustain energy homeostasis (Fig. 1). During periods of energy surplus (healthy population), endocrine mechanisms promote the movement of energy into storage for future use. Conversely, during periods of negative energy balance (ALS), endocrine factors may act to preserve protein (muscle) by promoting the mobilization and use of fat as the preferential energy substrate. Prolonged negative energy balance results in a gradual depletion of energy stores. This is followed by a reduction in circulating blood glucose levels, while glycogen stores in the liver and muscle are rapidly consumed as an alternative energy substrate [61]. Following the depletion of glycogen stores, energy demands are met through the use of triglycerides, which are stored in the liver (short-term use) and in adipose tissue (long-term use). The breakdown of triglycerides results in free fatty acid release. These non-esterified free fatty acids (NEFAs) are then used by the liver and by muscle to sustain continued energy supply. Following prolonged negative energy balance, NEFAs are converted to ketone bodies; the energy supply of last resort used by critical organs such as the brain, heart and kidneys. Prolonged catabolism of triglycerides during extended periods of negative energy balance results in a significant loss in body fat mass [62,63]. Given that maintenance of optimal nutrition is central to survival in health and in disease, it comes as no surprise that numerous intricate systems work in synergy to sustain energy supply during periods of negative energy intake. Comprehensive investigations targeting endocrine components specifically underlying metabolic responses in ALS patients are yet to be conducted, however attempts to modify disease progression through altered endocrine function in preclinical models of ALS have been attempted.

Thyroid hormones play an important role in regulating metabolism [64,65]. Thyroxine (T4) is the main hormone produced by the thyroid gland and undergoes conversion in tissues to tri-iodothyronine (T3) [66]. T3 directly regulates mitochondrial uncoupling proteins 1 and 3, and thus control energy production and thermogenesis [67,68]. Accordingly, reductions in T3 levels results in increased coupling and reduced

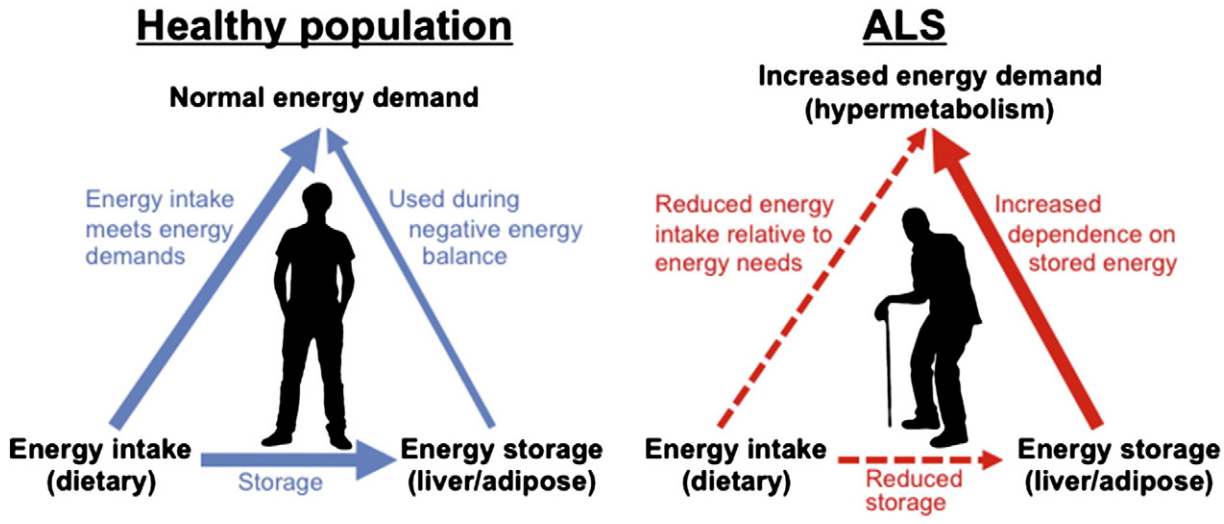

Fig. 1. Potential implications of increased energy requirements in amyotrophic lateral sclerosis (ALS). In the healthy population, and under periods of normal energy demand, energy homeostasis is maintained within a healthy range. Energy intake (from dietary sources) is used to meet energy demands. Excess energy is shunted into the liver and adipose for storage. An inability to maintain energy intake results in negative energy balance. During negative energy balance, energy reserves in the liver and adipose are used in order to supply energy demands. Hypermetabolism in ALS is defined by an increase in energy demand. In ALS, decreased energy intake results in decreased storage of energy in the liver and adipose, and an increased dependence on the use of stored energy. This allows for the continual supply of energy substrates to meet energy requirements. Hypermetabolism and negative energy balance in ALS results in a decrease in body mass index. The capacity to sustain energy requirements (from dietary sources or through release of endogenous stores) may predict survival duration in hypermetabolic ALS patients.

systemic metabolism, whereas an elevation in T3 levels drives a reduction in coupling and increased metabolism. Pharmacological induction of hypothyroidism with methimazole was unable to prolong survival in SOD^{G93A} mice [69]. These observations suggest that the alleviation of systemic hypermetabolism by targeting T4 does not modify disease outcome. However, results from this study must be interpreted with caution, because of the limited number of animals and the lack of information to describe improved metabolic balance. Serum levels of thyroid hormones in ALS patients are within a normal range [70,71], and thus it seems unlikely that altered thyroid function underlies hypermetabolism in ALS. In line with this, thyrotropin-releasing hormone (TRH) treatment does not represent a viable therapeutic option for ALS patients [72]. However, these results do not negate the potential therapeutic value of other endocrine regulators of metabolism.

Recent observations demonstrate elevated levels of circulating growth hormone in SOD^{G93A} mice at a time representative of the onset of disease symptoms [73]. While patients are growth hormone deficient at the latter stages of disease (as is seen in the SOD^{G93A} mouse [74]), the role and the release of growth hormone relative to disease progression in patients remain unknown. Of interest, growth hormone is a key anabolic hormone that facilitates the use of fat to preserve muscle during periods of negative energy balance [75]. Thus, altered growth hormone release at disease onset in SOD^{G93A} mice may represent an endogenous response to altered metabolic demands, and may thus drive the mobilization of NEFAs to meet energy requirements. Given that clinical trials relying on growth hormone treatment demonstrate no beneficial effects in patients [76,77], the implications of altered growth hormone release throughout disease progression in ALS remains unknown. Thus, at the time of assessment of the potential benefits of growth hormone treatment in ALS, the physiological actions of growth hormone had not been assessed in context to its role specific to disease progression. More importantly, whether altered growth hormone release exacerbates hypermetabolism requires further assessment. This is important, given that growth hormone and associated endocrine factors not only mediate energy flux, but also determine the utilization of energy by organs, including muscle [78–80].

3. Maintaining BMI in ALS: measures that may counteract weight loss and hypermetabolism in ALS

3.1. Nutrition in ALS

Caloric restriction in healthy individuals (defined as 30% to 60% decrease in *ad libitum* food intake exclusive of malnutrition) increases lifespan by delaying the onset of age-associated diseases [81–84]. In individuals with metabolic disorders (e.g. obesity and diabetes mellitus), calorie restriction improves lifespan by reducing both subcutaneous and visceral fat mass [85,86]. Given the observed benefits of caloric restriction on lifespan in these groups, the benefits of caloric restriction have been assessed in rodent models of ALS [87–89]. In these models, caloric restriction provided a transient improvement in motor performance. This might be attributed to an increase in nicotinamide adenine dinucleotide/sirtuin mediated pathways that improve metabolic balance during caloric restriction [90,91]. However, it is unlikely that there are prolonged benefits of the activation of these pathways in ALS since caloric restriction resulted in alarming reductions in body weight, and an overall reduction in mobility and fore-paw grip endurance. Most strikingly, caloric restriction induced faster onset of clinical symptoms, and shortened lifespan [87–89]. While the negative impact of caloric restriction on disease progression in ALS rodents is attributed to lipid peroxidation, inflammation, and apoptosis [89], it is well known that reduced body weight contributes negatively to ALS [53,92], and that reduced deposition of subcutaneous fat mass is associated with poorer ALSFRS-R [93]. Thus, caloric restriction may accelerate disease progression by aggravating conditions associated with malnutrition in ALS, thereby exacerbating the decrease in BMI that is seen in ALS patients throughout the course of disease. Given the prevailing hypermetabolic state of ALS patients, coupled with existing energy deficits, further restrictions in food intake are highly likely to aggravate disease progression and should be approached with extreme caution. More importantly, these studies demonstrate the value of optimal nutrition and sustained calorie intake in ALS.

In ALS, malnutrition at the time of diagnosis or during the course of disease is associated with shorter duration of disease [94] and increased mortality [95]. Consequently, the American Academy of Neurology and the European Federation of Neurological Societies advocate regular nutritional evaluation in ALS [96,97]. Factors that contribute to impaired nutrition and weight loss include dysphagia [98–103], loss of appetite [104], impaired chewing and deficits in tongue muscles [101], muscle wasting in the hands resulting in impaired capacity to for unassisted preparation and consumption of food [105], and hypermetabolism [30,31]. More importantly, the adverse physiological consequences of hypermetabolism dictate that hypermetabolic individuals need to increase food consumption in order to sustain energy substrates. However, ALS patients do not consume enough calories to compensate for increased energy need [35]. Given the implications of the loss of fat mass and reduced BMI in ALS disease progression, a number of interventions have been developed in order to ensure adequate nutrition in ALS. Interventions include changing food consistency and assisted feeding [106], enteral nutrition (eg. percutaneous radiological gastrostomy/radiologically inserted gastrostomy (PRG/RIG) [107–109] or percutaneous endoscopic gastrostomy (PEG)) [54,106,110,111] or, nutritional supplementation with high-calorie diets [112] or nutriceuticals [113,114]. These considerations will be discussed below.

3.2. Percutaneous radiological gastrostomy and percutaneous endoscopic gastrostomy

Enteral feeding is recommended in ALS patients who lose more than 10% of their baseline body weight, or in those who have reduced respiratory function [97]. Assisted feeding by gastrostomy is also indicated in ALS patients who have bulbar symptoms, lower dietary intake, fatigue or anxiety associated with eating, sialorrhea, dehydration, and dysphagia with aspiration [106]. PRG is better tolerated than PEG and has not been associated with major complications. While PRG reduces aspiration, studies do not indicate a significant improvement in survival in patients using PRG over PEG [107–109,115]. PEG feeding in ALS is not associated with major short or long-term complications. Assisted feeding by PEG has been shown to stabilize or increase patient body weight after use, improve survival, and improve quality of life [110,111,116,117]. However, heterogeneity in the presentation of disease and variable disease course in ALS is associated with difficulties in the identification of patients who have sufficient respiratory function with minimal weight loss, modest dysphagia, and who are psychologically prepared for enteral feeding. Consequently, other means of nutritional management are considered for maintaining body weight in ALS.

3.3. High caloric diets in ALS

ALS patients are reported to consume 15–16% fewer calories than recommended [35]. Since inadequate nutrition and weight loss contribute negatively to disease, it is recommended that ALS patients consume calories in excess of their calculated daily needs [35,113,118]. Studies that assess the benefits of high protein or high carbohydrate diets in ALS are limited. However, a number of studies have suggested that supplementation with high fat diets is associated with reduced risk of ALS [119–121]. Whether improved outcomes are associated with specific dietary substrates, or simply the provision of excess calories remains to be determined. Studies assessing the potential therapeutic value of specific dietary components, including protein, carbohydrates and fat are discussed below.

3.3.1. Protein

Few studies have assessed the benefits of a high protein diet on ALS progression. A study of 6 months of supplementation with protein (18 g protein and 275 kcal) in 20 ALS patients reported no significant improvement on disease progression or alleviation in the loss of muscle mass [122]. More recently, a study that provided supplementation with 70%:30% of milk whey proteins:modified starch in 16 ALS patients over a 4 month period, reported a small increase in body weight, and a slight increase in body mass index (BMI) when compared to those patients who did not receive supplementation. Patients receiving milk whey protein:modified starch had stabilization of the ALSFRS-R, whilst the ALSFRS-R declined throughout the study in patients not receiving supplementation [123]. While suggesting that a diet with increased protein content may be favorable in maintaining nutritional state and/or BMI in ALS, it remains unclear whether this is due to supplementation with protein or simply due to an increase in caloric consumption.

3.3.2. Carbohydrates

As with high protein diets, limited information exists regarding the benefit of a high carbohydrate diets in ALS patients. High carbohydrate supplementation (0% fat, 89% carbohydrate, and 11% protein; 900 kcal/day) has been assessed in a cohort of 14 ALS patients over a 3-month period. Outcomes demonstrate a stabilization of body weight, but no improvement in muscle mass or ALSFRS-R [112]. These observations are hard to interpret, given the small patient cohort, a high drop-out rate (38%), and high levels of non-compliance. Furthermore, whether outcomes from this study were due to supplementation with carbohydrates, or an increase in caloric consumption also remains to be determined. More recent observations provide promising evidence supporting improved prognosis following intervention with a high-calorie high-carbohydrate diet [148]. Future trials that include a larger group of patients are needed to provide more definitive information regarding the efficacy of high carbohydrate diets in ALS.

3.3.3. Fat

The possible benefit of high fat diets in ALS is attracting significant interest. In the SOD^{G86R} mouse model of ALS, supplementation with 21% butter fat (animal fat) and 0.15% cholesterol (wt/wt) led to an increase in body weight, an increase in retroperitoneal and epididymal fat pad mass, and an extension in survival from 102.3 $\pm$ 1.6 days to 122.5 $\pm$ 4.5 days [58]. Likewise, supplementation with 47% animal fat, 38% carbohydrates, and 15% protein (calorie content) in the SOD^{G93A} mouse model was able to increase body weight, and extend survival from 180 days to between 220 and 270 days [124]. While the mechanisms by which high fat diets improve body weight and survival in mouse models of ALS remains to be elucidated, excess energy substrate provided in the form of fat may compensate for the hypermetabolism [125], and altered lipid metabolism [60] observed in ALS mice. Compared to high protein or high carbohydrate diets, high fat diets may provide an easier way to sustain greater calorie intake (given the higher energy content of high fat foods).

Dorst and colleagues assessed the effects of high fat diet supplementation in ALS patients [112]. In 12 ALS patients, dietary intervention with a food supplement consisting of 35% fat, 50% carbohydrates, and 15% protein (900 kcal/day) promoted an increase in body fat and stabilization body weight [112]. However there was no reported improvement in ALSFRS-R and there was no direct comparisons with non-supplemented participants. Again, whether increased body fat and maintenance of body weight in this cohort of patients resulted from dietary supplementation with fat, or is due to an increase in overall caloric consumption remains to be resolved. Current observations in mouse models of ALS, and in ALS patients provide compelling evidence to support further research that aims to ascertain the potential therapeutic benefits of a high fat diet regimen in ALS. In this regard, a Phase II clinical trial aimed at assessing the benefit of a high fat/high calorie diet in ALS patients has recently been completed (Clinicaltrials.gov ID NCT00983983). In the same vein, given the importance of maintaining nutrition and appetite in ALS, a Phase II/III clinical trial that aims to investigate the effectiveness of olanzapine in promoting appetite and weight gain and/or stabilization in ALS has also been developed (Clinicaltrials.gov ID NCT00876772). Results from these clinical trials are pending.

3.3.4. Alternate approaches: ketogenic diets and medium chain triglycerides

3.3.4.1. Ketogenic diet. The ketogenic diet is a calorie-restricted, high fat, low protein, low carbohydrate diet. Because mitochondrial dysfunction is thought to be involved in ALS pathogenesis [23,24,126], ketogenic diets may be beneficial as they may serve to promote the production of ketones from the liver, which in turn may act to improve mitochondrial metabolism and biogenesis [127,128]. Though no improvement in survival has been observed in SOD^{G93A} mice supplemented with a ketogenic diet (caloric composition: 60% fat, 20% carbohydrate, 20% protein/caloric composition), an improvement in motor performance, increased body weight, and reduced motor neuron death was observed when compared to SOD^{G93A} mice on a control diet (caloric composition: 10% fat, 70% carbohydrate, 20% protein/calorie consumption) [129]. Although compliance with the strict and unpalatable ketogenic diets is difficult [130–132], results in ALS mouse models are fairly promising. Accordingly, a clinical trial (NCT01016522) that aims to test the safety and tolerability of the ketogenic diet (80% fat, 3% carbohydrate, 17% protein) in ALS was initiated in 2009. To our knowledge, the outcomes of this trial have not been revealed.

3.3.4.2. Medium chain triglycerides. Oral medium chain triglycerides are highly ketogenic [133,134]. The effects of the medium chain triglyceride, caprylic triglyceride (octanoate), on disease outcome have been assessed in SOD^{G93A} mice [135]. While dietary supplementation with 10% caprylic triglyceride in SOD^{G93A} mice resulted in improved motor performance and protection against motor neuron death, no improvement in survival outcome was apparent [135]. Overall, a ketogenic diet and octanoate may improve motor performance and rescue motor neurons [129,135], although they seem to provide minimal benefit in modifying the duration of disease. Whether supplementation with higher amounts of medium chain triglycerides is advantageous in ALS remains to be determined.

3.4. Nutriceuticals/dietary supplements in ALS

Nutriceuticals [113,114] are defined as *"a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease"* [136]. The use of nutriceuticals is common in ALS patients, with 54.5% of ALS patients reporting regular intake of dietary supplements, and up to 44.8% of these patients reporting the consumption of a cocktail of multiple supplements [53]. Nutriceuticals and dietary supplements are popular amongst ALS patients as it is suggested that they may provide benefits by targeting the mechanisms that underlie disease pathophysiology including oxidative stress, glutamate excitotoxity, mitochondrial dysfunction, inflammation, and protein and RNA toxicity. Commonly used supplements include vitamin E, vitamin B6 and B12, folate, green tea extract, coenzyme Q10, zinc, melatonin, and creatine, amongst many others. The rationale underlying the use of supplements, and studies that assess their benefits in ALS has been reviewed previously [106,114]. Briefly, few observations exist to support the benefits of these substances in the pathogenesis of ALS, however some promising observations exist regarding the potential therapeutic benefits of Vitamin E [121,137,138]. It is of critical importance that benefits and potential side effects of existing nutriceuticals and dietary supplements in ALS are assessed, given their widespread use by patients. Second to this, it is critical that we consider the potential benefits of nutriceuticals shown to be effective in *in vitro* and *in vivo* models of ALS.

Resveratrol is a natural phytocompound that is produced by several plants [139]. It has been described to have a number of health promoting benefits in cancer [140] and cardiovascular disease [141]. The protective effects of resveratrol have been attributed to its activation of sirtuin 1 [142]. In 2011, two independent studies demonstrated an attenuation of neuronal death by resveratrol; motor neuron-like cultures harboring the mutant human SOD^{G93A} displayed increased viability and increased energy production [143], and rat cortical motoneurons were protected from calcium-mediated death that was driven by ALS cerebral spinal fluid [144]. Most recently, dietary supplementation with resveratrol in SOD^{G93A} mice prior to, and after the onset of symptoms resulted in an attenuation of motor neuron death, improved motor function, and an extension in survival [145]. While this was attributed to an increase in the expression of sirtuin 1 and improved metabolic capacity, the low oral bioavailability of resveratrol [146] may necessitate high oral dosage to achieve similar beneficial effects in humans. We are not aware of any current clinical trials that are assessing the potential benefits and side effects of resveratrol in ALS.

4. Conclusion

There is increasing evidence to suggest that higher pre-morbid BMI, maintenance of BMI, dyslipidemia, and improved nutrition is associated with improved outcome in ALS. While current data assessing the impact of dyslipidemia on survival outcome in ALS is contradictory, the benefit of increased pre-morbid BMI, a stably maintained BMI, and a high-fat diet regimen in ALS is more consistent. Despite these observations, the mechanisms by which elevated/maintained BMI and improved high caloric intake improve the prognosis in ALS remain to be determined. One plausible mechanism may be the provision of increased energy substrates to account for increased energy needs in ALS [147]. Indeed, higher BMI may be associated with increased levels of baseline energy stores, or increased readily available energy substrates associated with food intake. This is consistent with observations that declining BMI throughout the course of disease, which may be resultant of hypermetabolism and negative energy balance, is associated with shorter survival, and that the preservation of adequate nutrition is associated with maintenance of body weight, better survival outcome and improved quality of life. Future work that dissects out the mechanisms by which BMI or nutritional/dietary management contribute to better survival in ALS will provide essential knowledge to allow successful translation of adoptive practices into the clinic. This is of particular importance, given potential benefits, the relatively low cost to benefit ratio, and the relative ease through which improved dietary habits may be adopted. Ultimately, the improvement of metabolic balance in patients, and potentially the improved progression of disease outcome, depend on rigorous assessment of the mechanisms through which dietary supplementation may modify the course of disease, and the identification of critical dietary factors essential to survival in ALS.

Conflict of interest

The authors have nothing to disclose.

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