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Review article

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

S.T. Ngo [a,b], F.J. Steyn [a,*], P.A. McCombe [b,c]

[a] School of Biomedical Sciences, University of Queensland, St Lucia, Queensland, Australia
[b] University of Queensland Centre for Clinical Research, University of Queensland, Herston, Queensland, Australia
[c] Department of Neurology, Royal Brisbane & Women's Hospital, Herston, Queensland, Australia

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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

* Corresponding author at: School of Biomedical Sciences, University of Queensland, St Lucia 4072, Queensland, Australia. Tel.: +61 7 3365 1409.
E-mail address: f.steyn@uq.edu.au (F.J. Steyn).

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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