



Applied nutritional investigation

Should patients with ALS gain weight during their follow-up?



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ABSTRACT

It was recently postulated that a nutritional intervention aiming at achieving weight gain might increase survival in ALS patients. This article discusses the effect of nutritional status and weight gain on survival, respiratory status and physical function. Based on the available literature, it remains unknown whether weight gain during the progression of the disease improves survival whatever the baseline body weight is. A high body mass index may impair respiratory muscle function and passive mobilization of paretic patients. Future research should evaluate the effect of changes in weight and body composition on clinical outcome while taking into account respiratory muscle strength and physical function.

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a life expectancy of 2 to 5 y. Effective treatment for ALS is lacking. A multidisciplinary approach [1], non-invasive ventilation [2], riluzole, and enteral nutrition via percutaneous endoscopic gastrostomy have been shown to improve survival and quality of life to some extent [1]. In a recently published article, it was postulated that a nutritional intervention, aiming at achieving weight gain, might be a therapeutic option for patients with ALS [3]. These assumptions relied on the increased survival with a high-calorie diet in an ALS mouse model [4] and on the lower risk for ALS in overweight or obese individuals [5].

Here we summarize the effect of initial nutritional status and weight gain during follow-up on survival and respiratory and physical function to explore whether weight gain is beneficial for patients with ALS.

Weight and body mass index at diagnosis and survival

Few studies related baseline weight to survival in ALS. In clinical routine, weight often is expressed as body mass index (BMI). A BMI <18.5 kg/m² defines underweight and a BMI ≥30 kg/m² defines obesity [6].

A study of 92 patients with ALS demonstrated that a history of weight loss at diagnosis was significantly associated with survival [7]. After adjustment for age, sex, bulbar versus non-bulbar onset, ALS functional rating scale (ALSFRS), manual muscular testing, forced vital capacity, and diagnostic delay, the study found a 30% increase in risk for death for each 5% weight loss and a 20% increase in risk for death for each BMI unit loss.

In the same study population, undernutrition at diagnosis, defined as a BMI <18.5 kg/m² if <70 y or <21 kg/m² if ≥70 y (n = 8), was not associated with survival, after the aforementioned adjustments [7]. Effect of obesity was not assessed. A larger study stratified 285 patients with ALS according to BMI categories at baseline [8]. BMI categories were not predictive of survival or rate of progression. However, only 3 patients were undernourished and 65 were obese. A shorter survival in patients with ALS and a baseline BMI <18.5 kg/m² (n = 9) than in those with a higher BMI was reported in univariate Cox regressions [9]. One group of researchers studied 427 patients with ALS [10]. A decreased survival was seen in patients with a BMI >35 or <18.5 kg/m² at diagnosis; thus a U-shaped relationship between BMI and survival was established. This finding was confirmed in the PRO-ACT (Pooled Resources Open Access ALS Clinical Trial) database, which pooled data from 16 Phase II/III trials and 1 observational study (n = 8635) [11]. Obese and overweight patients with ALS, respectively, showed a 54% and

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35% lower risk for dying compared with those with a BMI <25 kg/m².

Thus, studies generally agree that undernutrition at diagnosis decreases survival, whereas a BMI of 25 to 35 kg/m² may be protective in this patient population.

Weight change and survival

Several studies highlighted that weight loss increases the risk for mortality in patients with ALS [7–9,12–14]. As a corollary, interventions aiming at preventing weight loss, such as hypercaloric nutrition, should be beneficial. The tolerance and safety of such an intervention was tested in 24 patients under enteral nutrition, randomized to hypercaloric high-carbohydrate (HC) nutrition, hypercaloric high-fat nutrition, or isocaloric (C) nutrition, for 4 mo and followed up to 5 mo [3]. At baseline, patients had a BMI in the normal range but a body weight loss of almost 20%. Patients on the HC diet had fewer adverse events (e.g., dyspepsia, bloating, diarrhea, etc.), fewer serious adverse events (e.g., hypoxia, dyspnea, bronchoaspiration, etc.) and a higher ALSFRS after the intervention than controls. Weight gain and mortality were not significantly different between groups. The authors suggested that HC nutrition might be a therapeutic option in patients with ALS, although they could not highlight a difference in weight gain, probably because of difficulties in determining energy balance.

From the aforementioned studies, it is uncertain whether weight loss increases the risk for mortality independently of baseline body weight. It is possible that weight loss is not as detrimental in obese patients as it is in lean patients because it improves mobilization and ventilation and thus quality of life. Additionally, the timing of nutritional support is still unclear. Should health care providers wait until patients with ALS have lost 10% of their body weight before providing nutritional support by percutaneous endoscopic gastrostomy [15], or aim at increasing weight as of initial follow-up evaluation? Health care providers also must realize that achieving weight gain in a patient with ALS may be difficult because of large variations in energy expenditure [16].

Thus, weight gain during follow-up may decrease mortality; however, the effect of changes in body composition, physical activity, and timing and composition of nutritional support remains largely unknown.

Body weight versus body composition

Body composition measurements allow separating body mass into fat mass (FM) and fat-free mass (FFM), which includes muscle mass. Because low FFM, a hallmark of undernutrition, has been related to several negative outcomes (increased hospital length of stay, mortality) [17], assessment of body composition, in addition to BMI, may provide useful information for treatment and follow-up, as suggested elsewhere [18].

A low FFM has been linked to mortality in older and obese patients [19,20]. Thus, it would seem logical to consider that FFM at diagnosis may predict survival. As physical activity is among the main anabolic drives, individuals who are physically active at baseline may have a higher muscle mass and function and may survive longer than those who already have physical limitations. If baseline FFM is a key factor for estimating survival, the best methodology for body composition assessment must be determined. Because ALS generally does not affect the limbs symmetrically, methodologies that do not rely on assumptions

integrating a symmetrical distribution, such as dual energy x-ray absorptiometry (DXA), may be the most appropriate.

Changes in body composition may, in fact, be better predictors of mortality than body weight changes. An increase in FM predicts a better survival [7]. Using DXA, one study showed that patients who gained weight increased FM and FFM, whereas those who lost weight lost FFM but increased FM [3]. This suggests that loss of FFM may be a better predictor of mortality than loss of FM. Recently, one study demonstrated the negative effect of FFM loss on mortality [21]. Consequently, every effort should be directed toward maintaining FFM. This may be achieved to some extent through physical activity, if feasible for the patient, or by increasing intake of energy (Fig. 1). In healthy individuals, a positive energy balance leads to an increase of both FM and FFM. In patients with ALS, gain in FFM seems unlikely due to the disease, but weight gain could offset loss of FFM.

However, the advice to maintain FFM through weight gain probably should take into account the patient's BMI. It likely applies to patients with ALS who have a low or normal BMI but not to those with a BMI in the overweight or obese range. In the latter group, weight gain may worsen physical and respiratory function, and passive mobilization, as detailed later.

To summarize, in ALS, an increase in FM predicts a longer survival. The increase in FM may just reflect a better preservation of FFM.

Nutritional status and respiratory function

Progressive loss of upper and lower motor neurons involving respiratory muscles in ALS leads to respiratory failure and is a major determinant of prognosis. Nutritional status may affect respiratory function in ALS through several pathways.

In patients with non-bulbar onset of ALS, hypercapnic respiratory failure occurs relatively late in the course of the disease. Decrease in peripheral muscle strength and FFM is associated with a simultaneous loss in inspiratory muscle strength. Longitudinal noninvasive follow-up of inspiratory muscle strength using Sniff nasal inspiratory pressure [22] shows a linear slope of decline that may be a better predictor of the need for ventilator support than conventional parameters such as forced vital capacity or PaCO₂ [23]. The relationship between peripheral muscle mass, muscle strength, and respiratory muscle mass (mainly the diaphragm) has been well established in healthy individuals [21] and in patients with chronic hypercapnic respiratory failure. In a descriptive study, hypercapnic patients with restrictive or obstructive lung disease were more likely to have a low FFM index when compared with age- and sex-matched controls [24]. In this report, estimation of nutritional status by BMI alone clearly underestimated the prevalence of FFM index depletion. Furthermore, correlation between respiratory muscle strength and FFM was stronger than with BMI. A positive association between Sniff nasal inspiratory pressure and BMI also was reported in patients with chronic hypercapnic respiratory failure who survived an episode of respiratory failure in the intensive care unit [25]. The authors hypothesized that higher BMI values were associated with increases in FM and FFM. These findings provide a possible explanation for the prevailing opinion that prognosis may be better in critically ill patients with obesity ("obesity paradox").

Based on these observations, it is logical to surmise that in ALS, progressive peripheral muscle wasting assessed by FFM depletion—related or not with changes in BMI—may be associated with a proportional and simultaneous decrease in respiratory muscle strength, leading to dyspnea and respiratory failure.

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