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Original Article

Effect of complete high-caloric nutrition on the nutritional status and survival rate of amyotrophic lateral sclerosis patients after gastrostomy

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Abstract: Objectives: Malnutrition is an independent risk factor for the prognosis of patients with amyotrophic lateral sclerosis (ALS). Complete high-caloric nutrition is emerging as an instrument for dietary intervention in disease prevention. Our aim was to evaluate the beneficial effects of complete high-caloric nutrition on nutritional status and prognosis in ALS patients undergoing percutaneous gastrostomy. Methods: Forty patients with ALS following percutaneous gastrostomy were randomized to receive either routine diet alone (the control group) or complete high-caloric nutrition combined with routine diet (the Ensure group) for six months. Body weight, body mass index (BMI), nutritional indicator proteins, lipid levels and total lymphocyte count were measured before intervention and after six months of intervention. At 12 months of follow-up, Kaplan-Meier survival was generated to evaluate the beneficial effects of complete high-caloric nutrition on prognosis. Results: After adjustment for baseline, compared with routine diet, body weight, total lymphocyte count and nutritional indicator proteins including transferrin, albumin, hemoglobin, and prealbumin were significantly increased at six months of intervention (all $P<0.05$). However, we found no significant changes in total cholesterol, triglycerides, low- or high-density lipoprotein cholesterol or BMI during the intervention in either group (all $P>0.05$). Interestingly, the cumulative survival rate of ALS patients in the Ensure group was significantly better than that of ALS patients in the control group ($P<0.05$). Conclusions: The findings of our study suggest that high-caloric nutrition offers potential for improvement of nutritional status and prolonged life. However, no evidence was found for a blood lipid-improving effect of complete high-caloric nutrition.

Keywords: Amyotrophic lateral sclerosis (ALS), complete high-caloric nutrition, gastrostomy, nutritional status, prognosis

Introduction

Amyotrophic lateral sclerosis (ALS), including primary lateral sclerosis, classical amyotrophic lateral sclerosis, progressive bulbar palsy and progressive muscular atrophy, is a selective and progressive chronic degenerative disease of the nervous system, which can involve upper and lower motor neurons [1, 2]. Emerging studies indicate that brain and spinal cord neurons related to movement in ALS patients undergo injury and cell death, which leads to the loss of muscle motor function causing muscle atrophy, and gradually affects the functions of breathing, speaking and swallowing [3]. Eventually, ALS patients lose the ability to swallow and move, leading to respiratory failure and death [4, 5]. Clinical investigation shows that 80%-90% of ALS patients have a poor survival time of only 3-5 years [6, 7]. For example, Pupillo et al [8] evaluated the prognosis of 300 ALS patients and found that the cumulative time-dependent survival at 1, 5, and 10 years from diagnosis was 76.2%, 23.4%, and 11.8%, respectively. Reflecting these findings, the World Health Organization lists ALS as one of five incurable diseases [9].

Extensive studies conducted during the last decade have shown that malnutrition is widespread in patients with ALS [10-12]. According to the new malnutrition criteria of the Global Leadership Initiative for Malnutrition, Jose Lopez-Gomez et al [11] found malnutrition in 48.4% of ALS patients. Multiple factors ac-

Table 1. Demographic features and clinicopathological data at baseline of ALS patients

Variables	The control group (n=20)	The ensure group (n=20)	χ^2/t value	*P* value
Gender (Male/Female)	13/7	15/5	0.119	0.730
Age (years)	56.8±11.52	57.45±12.18	0.1734	0.8633
GUSS score	1.09±0.21	1.05±0.27	0.523	0.604
Respirator wear time (h/d)	15.26±2.94	15.85±2.58	0.6746	0.504
Body weight (kg)	70.15±5.96	70.76±6.06	0.318	0.753
BMI (kg/m^2)	23.6±2.27	23.93±2.8	0.417	0.679
Weight loss before intervention (kg/month)	0.74±0.22	0.72±0.24	0.275	0.785
Duration of disease (years)	12.25±2.94	13.25±3.43	0.7022	0.4868
Body fat (%)	28.14±4.86	27.29±4.42	0.579	0.566
Muscle mass (kg)	22.44±4.79	24.52±5.68	1.252	0.218
Static vital capacity (% of reference value)	62.85±8.44	64.19±6.39	0.566	0.575
Postoperative feeding time (d)	3.59±0.76	3.68±0.0.74	0.3813	0.7051

GUSS: Gugging Swallowing Screen; BMI: Body Mass Index.

count for malnutrition in ALS patients, including hypermetabolism as well as reduction in caloric and protein intake due to arm weakness or dysphagia, causing an imbalance in energy expenditure. Additionally, malnutrition can have direct consequences on disease duration. Mounting evidence indicates that poor survival in ALS patients is associated with malnutrition and abnormal energy metabolism [11, 13, 14]. Juan Jose Lopez-Gomez et al [11] reported that ALS patients with worse nutritional status had a lower survival median with both Subjective Global Assessment A: 20.5 (10.2-35) months vs SGA B-C: 12 (5.2-23.7) months. Therefore early and frequent nutrition intervention, including implementation of an adequate caloric diet, use of adaptive eating utensils, dietary texture modification, and feeding tube placement, is essential in ALS.

Ensure® complete high-caloric nutrition is a nutrition product produced by Abbott for middle-aged and elderly people. It can provide comprehensive and balanced nutrition, especially suitable for the postoperative rehabilitation of the target population [15]. Therefore, in this study, 40 ALS patients undergoing gastrostomy were given conventional diet or/and complete high-caloric nutrition, to explore a safe, effective and convenient new nutritional treatment scheme, further improving the nutritional status of ALS patients and prolonging their survival.

Materials and methods

Patients

A total of 40 ALS patients who received gastrostomy at Dahua Hospital of Shanghai from January 2019 to March 2020 were included in this study. This study followed the E1 Escorial standard revised by World Neurology Union in 2000 [16], and the protocols were approved by the Ethical Committee of Dahua Hospital (DHYY-20181230-05). Additionally, written informed consent was given by all ALS patients for biospecimen collection, clinical data recording and use in anonymized analysis. After gastrostomy, the 40 ALS patients were randomly divided into the control group (20 patients) and the Ensure group (20 patients) using a computer-generated random number sequence. ALS patients in the control group received a conventional diet. In addition to the above diet, ALS patients in the Ensure group also received complete high-caloric nutrition. ALS patient therapy protocol, demographics, laboratory data, and follow-up records were collected and recorded. A summary of the clinical features of the 40 ALS patients is presented in **Table 1**.

Inclusion and exclusion criteria

The inclusion criteria for ALS patients were: (1) normal digestive function, (2) ability and willingness to comply with doctor's instructions and to complete treatment, and (3) normal routine

Table 2. The main nutritional composition of Ensure® complete high-caloric nutrition

NO.	Nutrients	per 100 g
1	Energy (kj)	1801
2	Protein (g)	15.9
3	Fat (g)	14
4	α-linolenic acid (mg)	310
5	α-linolenic acid energy supply ratio (%)	0.64
6	Linoleic acid (g)	2.5
7	Linoleic acid energy supply ratio (%)	5.14
8	Carbohydrate (g)	57.4
9	Dietary fiber (g)	4.3
10	Vitamin A (μg RE)	410
11	Vitamin D (μg)	4.5
12	Vitamin E (mg α-TE)	6
13	Vitamin K1 (μg)	24.4
14	Vitamin B1 (mg)	0.8 0
15	Vitamin B2 (mg)	0.8 0
16	Vitamin B6 (mg)	0.9
17	Vitamin B12 (μg)	0.9
18	Niacin (mg)	5.2
19	Folic acid (mg)	117
20	Pantothenic acid (mg)	2.88
21	Vitamin C (mg)	54
22	Biotin (μg)	16.2
23	Sodium (mg)	382
24	Potassium (mg)	610
25	Copper (μg)	257
26	Magnesium (mg)	88
27	Iron (mg)	4.5
28	Zinc (mg)	4.7
29	Manganese (μg)	1300
30	Calcium (mg)	410
31	Phosphorus (mg)	270
32	Iodine (μg)	58
33	Chlorine (mg)	540
34	Selenium (μg)	23
35	Chromium (μg)	21
36	Molybdenum (μg)	38
37	Choline (mg)	116

test results, such as blood, liver and kidney function, and electrocardiogram. The exclusion criteria were: (1) loss of follow-up after gastrostomy, (2) history of gastrectomy, and (3) portal hypertension caused by esophageal and gastric varices.

Clinical treatment

The patients in both groups were treated with percutaneous gastrostomy under local anesthesia. The puncture site was the center of the gastric bubble or the maximum curvature. Before the puncture, 500-1500 ml of air was injected to expand the stomach, which brought it close to the abdomen. Under DSA perspective, the gastric wall fixator was punctured into the stomach cavity, and the stomach wall and abdominal wall were tightly sutured. The same method was used to fix the stomach and abdominal walls at the lower right 1 cm of this point. Under DSA perspective, the PS needle was used to puncture vertically between the two fixed points. The T-guided sheath was placed into the stomach cavity and then the PS needle was withdrawn. The fistula was inserted into 15 F through the T-Guide sheath and fixed on the abdominal skin. Twenty-four hours after the operation, the fistula was observed making port closely. If no leakage, bleeding, plugging or infection of the fistula was found, the patients could eat through the fistula. The skin of the fistula mouth was cleaned and sterilized daily, and the dressing was replaced. Suture removal was performed in the sinus after two weeks. The control group received routine diet after the operation, progressing gradually from fluid to semi fluid then to general food, in gradually increased amounts. Twice daily, patients in the Ensure group were given a high-caloric nutrient solution (TY20195005) of total safety hormone consisting of 53.8 g of total safety hormone in 195 ml of warm water stirred well before feeding through the fistula. The main nutritional composition of Ensure® complete high-caloric nutrition was shown in **Table 2**. All patients were given a half seat for 30 min to help digestion. The fistula was washed with 30-50 ml of warm water before and after the food injection.

Index detection

Body mass index (BMI), transferrin, albumin, hemoglobin, prealbumin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total lymphocyte count were measured in the week before gastrostomy, as well as six months after gastrostomy.

Venous blood samples were collected and initially isolated into serum by centrifugation (400 g, 15 min) at 4°C then stored at -80°C for analysis. Transferrin, albumin, hemoglobin, and prealbumin were detected using a Human Transferrin (TF) enzyme linked immunosorbent assay (ELISA) Kit (Sangon Biotech (Shanghai) Co., Ltd., Shanghai, China), Human Serum Albumin EIA Kit (Cayman Chemical Company, Michigan, USA), Human hemoglobin ELISA Kit (Beijing Leagene Biotechnology Co., Ltd., Beijing, China) and Human prealbumin test kit (Beijing Leagene Biotechnology Co., Ltd., Beijing, China), respectively. TC and TG were detected using a Micro Total Cholestenone (TC) Content Assay Kit (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) and Triglyceride (TG) Content Assay kit (Beijing Boxbio Bioengineering Technology Co., Ltd., Beijing, China), respectively. Low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) were tested using relevant test kits (Zhejiang ERKN Biotechnology Co., Ltd., Wenzhou, China). Total lymphocyte count was tested using CytoFLEX S flow cytometry (Beckman Kurt International Trading (Shanghai) Co., Ltd., Shanghai, China).

Follow-up

Follow-up was completed by May 31, 2021. Overall survival (OS) time of ALS patients was verified by hospital records or by phone contact with patients' relatives. The OS time was calculated from the date of eating after the operation to the date of death. All ALS patients were followed up regularly each month after percutaneous gastrostomy.

Statistical analysis

The statistical analyses were performed using SPSS software (Version 21.0, IBM Corp., Armonk, NY, USA). Chi-square tests were used to examine Count data. Measurement variables are presented as mean ± standard deviation. Student-t test and covariance analysis were used to compare the statistically significant measurement variables. Survival curves were constructed using the Kaplan-Meier method and compared using log-rank tests. Furthermore, a Cox proportional-hazards regression model was used to analyze prognostic significance of each variable. Two-tailed P<0.05 was considered to indicate a statistical significance.

Results

Characteristics of the study population

A total of 40 ALS patients were involved in this study including 28 men and 12 women with a median age of 57.13±11.71 years. To evaluate the effect of Ensure high-caloric nutrient on nutritional status and prognosis of ALS patients undergoing gastrostomy, all patients were randomly assigned to two groups: the control group (20 patients) and the Ensure group (20 patients). Demographic features and clinicopathological data of ALS patients in the control and Ensure groups are shown in **Table 1**. In the control group, 13 were male and 7 were female, the average age was 56.8±11.52 years. In the Ensure group, the average age of 20 patients including 15 males and 5 females was 57.45±12.18 years. No significant differences in gender, age, Gugging Swallowing Screen (GUSS) score, respirator wear time, BMI, duration of disease, weight loss before the intervention, body fat, muscle mass, static vital capacity and postoperative diet time were found between the two groups (P>0.05).

Changes in body weights and BMI in the two groups

The mean body weights at the conclusion were 74±5.64 kg in the control group and 77.83± 6.12 kg in the Ensure group, respectively, indicating a significant increase in body weight in the Ensure but not the control group compared with at the onset (P<0.01, P=0.057; respectively). After adjustment for baseline body weight, our data showed a slight increase in body weight in the Ensure group compared with the control group (F=3.763, P=0.06), as shown in **Figure 1A**. The increase in BMI was higher in ALS patients in the Ensure than the control group (P<0.01), however, this difference was not significant (F=1.45, P=0.24), as shown in **Figure 1B**.

Changes in nutritional indicator proteins in the two groups

Transferrin data are presented in **Figure 2A** and show a significant increase during the intervention in both groups (P<0.01; P<0.01). After

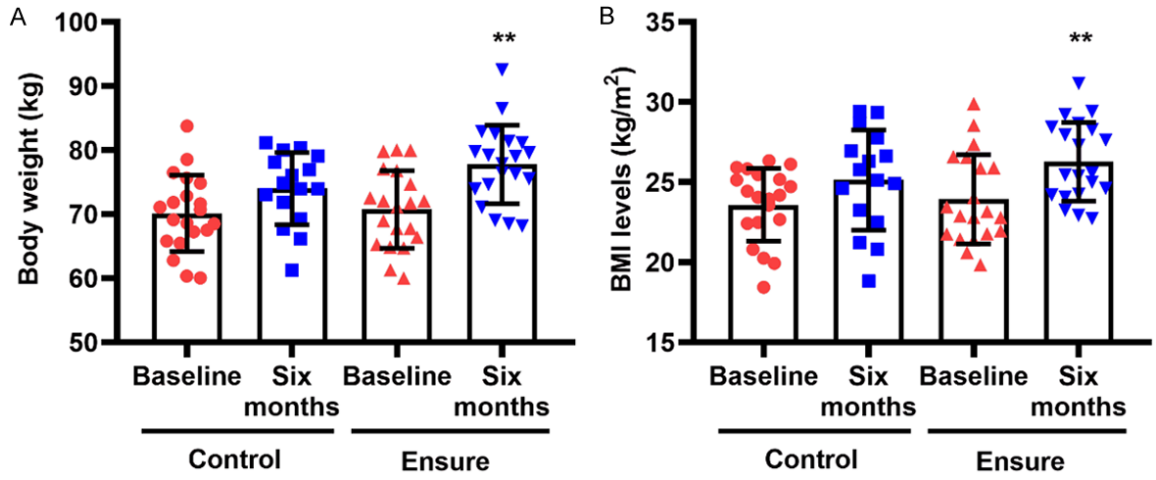


Figure 1. The changes in body weight (A) and body-mass index (BMI) (B) of 40 amyotrophic lateral sclerosis (ALS) patients on conventional diet or/and Ensure® complete high-caloric nutrition. *VS* Baseline, **P<0.01.

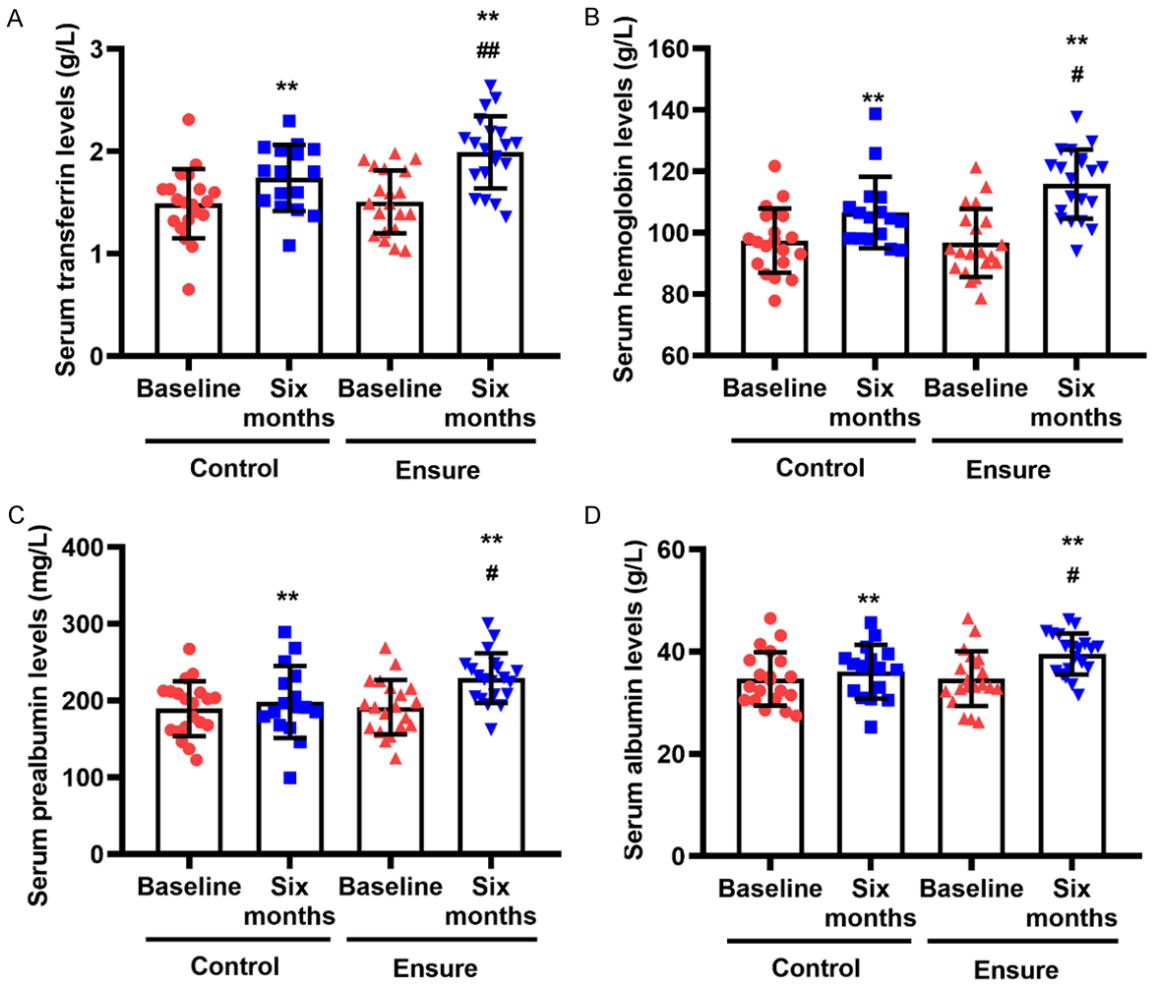


Figure 2. The changes of nutritional indicator proteins of 40 amyotrophic lateral sclerosis (ALS) patients undergoing conventional diet or/and Ensure® complete high-caloric nutrition, including transferrin (A), hemoglobin (B), prealbumin (C) and albumin (D). *VS* Baseline, **P<0.01; *VS* Three months in control group, #P<0.05, ##P<0.01.

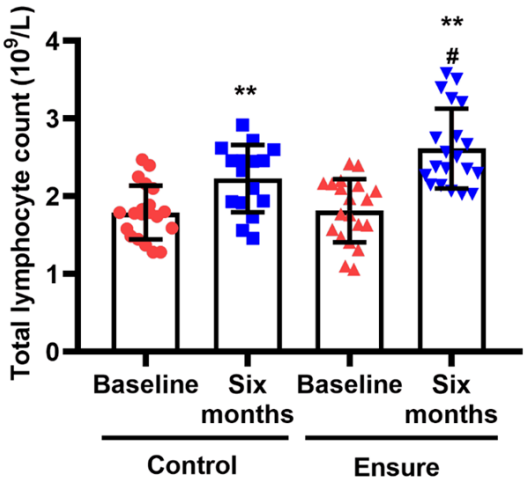


Figure 3. The changes in total lymphocyte count of 40 amyotrophic lateral sclerosis (ALS) patients on conventional diet or/and Ensure® complete high-caloric nutrition. *VS* Baseline, **P<0.01; *VS* Three months in control group, #P<0.05.

adjustment for baseline transferrin, we found that levels were significantly higher in the Ensure group than in the control group (F= 5.28, P=0.03). As shown in **Figure 2B**, the hemoglobin at six months of intervention was 106.64±11.64 in the control group and 115.87±11.28 in the Ensure group, both significantly increased from baseline (P<0.01; P<0.01). Intriguingly, after adjustment for baseline levels, this increase was significantly higher in the Ensure group than in the control group (F=5.79, P=0.02). In agreement with these data, significant increases in albumin and prealbumin were also observed in the Ensure group at six months after percutaneous gastrostomy (F=4.86, P=0.04; F=5.39, P=0.03, respectively, **Figure 2C** and **2D**). Total lymphocyte count (**Figure 3**) was significantly raised by intervention in the Ensure and control groups (P<0.01, P<0.01, respectively) and after adjusting for baseline levels, this increase was higher in Ensure than in the control group (F=5.34, P=0.03). Together, these results offered new insights into the role of Ensure® high-caloric nutrient supplement in improving the nutritional status of ALS patients.

Lipid level changes in ALS patients

Figure 4 provides a comparison of lipid levels in the control and Ensure groups. Analysis showed that TC and TG serum levels were not significantly increased following Ensure treatment (P=0.13; P=0.07, respectively) or routine diet (P=0.82; P=0.11, respectively). Further analysis revealed that serum TC and TG levels were not significantly different between the two groups at six months of intervention (F=1.23, P=0.28, **Figure 4A**; F=0.03, P=0.86, **Figure 4B**, respectively). Consistent with these data, we found no significant changes in serum HDL and LDL during the intervention in the Ensure or control group (F<0.01, P=0.99; F=0.62, P=0.44, respectively; **Figure 4C** and **4D**). These results collectively indicate that Ensure high-caloric nutrient is not conducive to improving lipid levels of ALS patients.

Ensure® high-caloric nutrient supplement improves the survival rates of ALS patients

To examine whether Ensure® high-caloric nutrition correlated with the survival of ALS patients after percutaneous gastrostomy, we obtained the clinical records and calculated the overall survival rate over one year. The survival rates of the Ensure group were 100%, 100% and 80% at 3, 6 and 12 months after gastrostomy respectively, and the control group rates were 80%, 70% and 55%, respectively, as shown in **Figure 5**. Kaplan-Meier survival analysis was conducted and showed that the cumulative survival rate of ALS patients in the Ensure group was significantly better than that of ALS patients with routine diet (P=0.049), as shown in **Figure 5**. No serious adverse events occurred in either group. Two patients in the Ensure group had minor adverse events including diarrhea and dyspepsia. One patient in the control group had diarrhea, and no other adverse events were observed in this group. The frequency of minor adverse events was therefore slightly higher in the Ensure group but this result was not significant (P>0.05).

Discussion

Our findings show that Ensure® complete high-caloric nutrition, one of the adult nutrition products produced by Abbott, provides supplementary nutrients and energy, stabilizing body weight [17]. As demonstrated by the results of recent studies, ALS patients suffer from weight loss and catabolism [18]. Therefore, we sought to explore whether complete high-caloric nutrition improves nutritional status and survival rate of ALS patients after gastrostomy. We

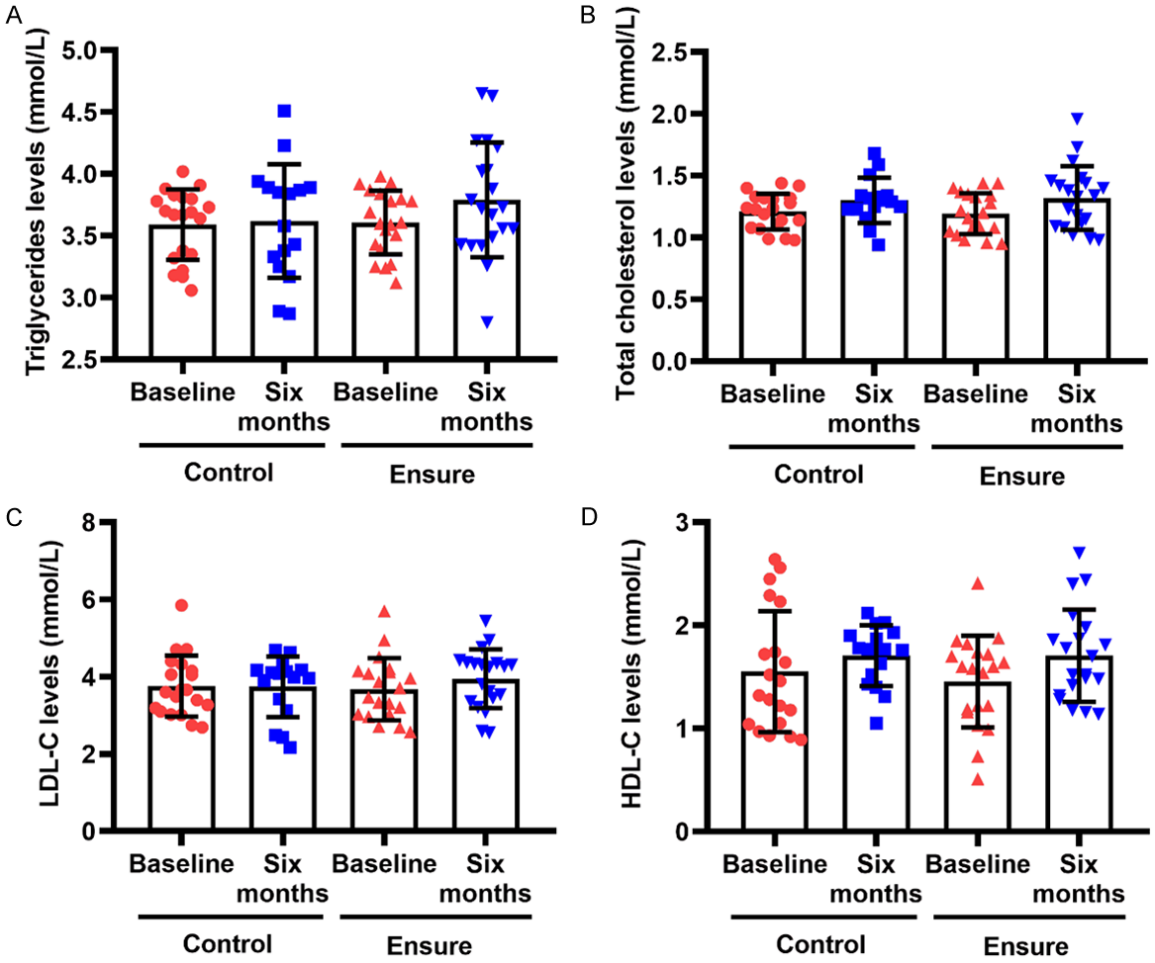
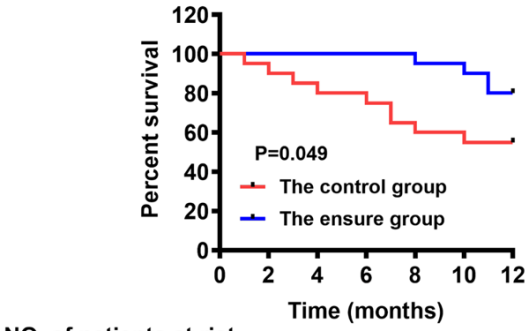


Figure 4. The changes in lipid levels of 40 amyotrophic lateral sclerosis (ALS) patients on conventional diet or/and Ensure® complete high-caloric nutrition, including triglycerides (A), total cholesterol (B), low-density lipoprotein cholesterol (LDL-C; C) and high-density lipoprotein cholesterol (HDL-C; D).



NO. of patients at rist							
The control group	20	19	17	16	13	12	11
The ensure group	20	20	20	20	20	19	16

Figure 5. Cumulative survival estimate to death from intervention of 40 amyotrophic lateral sclerosis (ALS) patients.

found that it caused a significant increase in nutritional status, including body weight, transferrin, albumin, hemoglobin, prealbumin and total lymphocyte count, at different periods after percutaneous gastrostomy. However, we found no significant changes in total cholesterol, total triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or BMI during the intervention in either group. Furthermore, we provide convincing evidence for a life-prolonging effect of complete high-caloric nutrition for ALS patients.

Importantly, multiple retrospective studies have observed positive correlations of survival with BMI or body weight in ALS patients. Additionally, animal studies support the notion that high-caloric intake and weight gain in ALS patients may increase survival [19, 20]. Here, we found that complete high-caloric nutrition significantly increased body weight but not BMI compared with routine diet, inspiring us to use

complete high-caloric nutrition to improve the nutrition of ALS patients. Emerging evidence supports the notion that transferrin, albumin, hemoglobin and prealbumin can be used as clinical biochemical parameters for nutritional assessment [14, 21]. Additionally, previous studies suggested that ALS patients have lower levels of transferrin, albumin, hemoglobin and prealbumin, indicating inadequate protein intake [14, 22]. In the present study, levels of these proteins were higher in the Ensure group than in the control group, indicating that complete high-caloric nutrition can help increase ALS patients' intake and nutritional status. The cumulative mouse and human ALS data suggest that increasing the levels of regulatory T lymphocytes in ALS patients at early stages in the disease process may be of therapeutic value, slow the rate of disease progression and stabilize patients for longer periods of time [23, 24]. After adjustment for baseline difference in T lymphocytes, we found that complete high-caloric nutrition can promote T lymphocytes. These findings, in conjunction with the results presented above for BMI and nutritional indicator proteins, confirm the beneficial effects of complete high-caloric nutrition on nutritional status. Complete high-caloric nutrition contains several nutrients (such as high quality protein, dietary fiber, linoleic acid, and α-linolenic acid) related to nutritional recovery. Among them, high quality protein provides amino acids needed by malnutrition patients to enhance polyamine synthesis. Moreover, dietary fiber promotes the gastrointestinal movement of ALS patients and helps to absorb nutrients [25]. These nutritional functions may reflect the mechanism by which complete high-caloric nutrition improves nutrition in ALS patients.

Several studies indicated that lipids might be beneficial as energy substrates by compensating for any associated weight loss as well as increasing metabolic rate [26]. Moreover, some studies have reported positive effects of highly caloric fat supplements in ALS patients [7]. For example, Dorst J et al [27] reported prolonged survival in amyotrophic lateral sclerosis patients with elevated triglyceride and cholesterol serum levels. Here, we investigated the serum levels of TC, TG, LDH and HDL, and found no role for complete high-caloric nutrition in the regulation of these lipid factors. Such observation is in fact consistent with previous reports in which both a high-caloric food supplement with high carbohydrate content and a high-caloric food supplement with high fat content do not increase serum cholesterol and triglycerides [28]. Accumulating evidence shows that linoleic acid and α-linolenic acid may inhibit the metabolism of TC, TG, LDH and HDL [29, 30]. Therefore, it is necessary to supplement extra nutrition to improve TC, TG, LDH and HDL levels.

A population-based study from Pupillo [8] showed that the cumulative time-dependent survival at 1, 5, and 10 years from diagnosis of ALS was 76.2%, 23.4%, and 11.8%, respectively. In this paper, we first evaluated the prognostic relevance of complete high-caloric nutrition in ALS patients who had undergone percutaneous gastrostomy. We found that the survival rates of ALS patients given complete high-caloric nutrition were 100%, 100% and 80% at 3, 6 and 12 months, consistent with Kirstein's report [31]. Kaplan-Meier survival analysis showed that ALS patients in the Ensure group had significantly better survival status. Similar patterns were also observed in Wills' study [32], where the death rate of patients in a high-carbohydrate hypercaloric diet group was significantly lower than that of patients in a replacement calories group during a five-month follow-up schedule. These findings suggested that complete high-caloric nutrition may be suitable for nutritional supplementation in ALS patients. Additionally, Ludolph et al [33] reported no difference in survival of ALS patients on placebo and high-caloric fatty diets. We speculated that improved survival in patients on complete high-caloric nutrition might not be due to improved blood lipid levels. Similarly, previous studies have demonstrated that dyslipidemia is not an independent predictor of survival in ALS [28, 34].

Some limitations in this study will need to be addressed in the future. First, the follow-up period should be extended to further clarify the beneficial effects of complete high-caloric nutrition. Another limitation is the small sample size, expansion of which will increase the reliability of future research on the Ensure diet. Moreover, the potential of other high-caloric supplements including high-fat and high-carbohydrate nutrition to improve blood lipids needs to be explored. Finally, the clinical symp-

toms of the ALS patients included in this study were severe. It is necessary to further explore the effect of complete high-caloric nutrition on the survival of ALS patients without gastrostomy.

Conclusion

In summary, we reported for the first time that complete high-caloric nutrition significantly increased nutritional indicator proteins and has a life-prolonging effect. However, complete high-caloric nutrition did not affect blood lipid levels. These findings provide reference resources for improving nutritional status and increasing the survival rate of ALS patients after gastrostomy.

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Written informed consent for the biological studies was obtained from each patient involved in the study, and the study was approved by the Ethics Committee of the Dahua Hospital of Shanghai (DHYY-20181230-05).

Disclosure of conflict of interest

None.

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