

Original Article

Effects of dietary supplements on the Fischer ratio before and after pulmonary rehabilitation

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Recently, efforts in comprehensive pulmonary rehabilitation for COPD have been made, including education, physical therapy, occupational therapy, nutrition, nursing, medication and counseling. Each patient focuses on a different element. Supplying adequate nutrition, among others, is essential for comprehensive pulmonary rehabilitation, as well as survival. In this study, the utility of efficient nutritional supplement therapy before and after pulmonary physical therapy was investigated by adding an amino acid drink with a high Fischer ratio to comprehensive pulmonary rehabilitation. The subjects were eight patients with COPD with obstructive ventilation disorder as severe as $31.5 \pm 6\%$ of FEV 1.0%. Pulmonary physical therapy was performed for eight weeks in a group administered one bottle of dietary supplement with a high Fischer ratio abundant in branched chain amino acids once daily (200 kCal/200 mL, Fisher ratio 40), and in another group without administration. Before and after the physical therapy, six-minute waking examination, QOL assessment (using CRQ), serum protein and serum Fischer ratio were comparatively examined between the two groups. After the eight weeks of pulmonary physical therapy, serum Fischer ratios were evidently reduced and serum protein measurements were also decreased in the group without dietary supplement abundant in branched chain amino acids. Accordingly, more amino acid is needed due to enhanced consumption of muscular protein during pulmonary physical therapy, during which nutrient ingestion including a sufficient amount of branched amino acid is necessary. It is an important element in continuing comprehensive pulmonary rehabilitation for a longer period.

Key Words: chronic obstructive pulmonary disease, branched-chain amino acid, Fisher ratio, nutrition assessment, pulmonary rehabilitation

Introduction

An epidemiological study on "emaciation" or weight loss, one of the clinical characteristics of COPD, reports that patients with weight loss have a high incidence of respiratory failure or high cumulative mortality.¹ In Western counties, it is considered that there is a close relationship between COPT and emaciation. In Japan, there are a number of patients with pulmonary emphysema and emaciation among COPD patients.

Emaciation due to nutritional disturbance severely affects the structure and function of the respiratory muscles.^{2,3} The weight and thickness of the respiratory muscles are reduced and atrophied, attenuating their contractility solely due to weight loss. For example, weight loss has a good correlation with muscle mass reduction of the diaphragm in results from a classical study in human autopsy cases by Arora.⁴ In addition, weight loss affects the diaphragm more significantly than the myocardium. That is, it seems that the myocardium may be resistant to nutritional disturbance, but the diaphragm may be susceptible. Also in animal studies, the weight of the total skeletal muscles including the respiratory muscles such as the diaphragm was decreased, and atrophy of the skeletal muscle fibers in the skeletal muscles (including the diaphragm) was found in fasting hamsters.⁵ More

importantly, dysfunction of the respiratory muscles is more significant with reduction in respiratory muscle weight in a sub-nutritional state. For example, the respiratory muscle tension of a human with weight loss of 71% of the standard weight is reduced as much as 37% compared with a human of normal weight both in the expiratory and aspiratory muscles.⁴ That is, reduction in respiratory muscle tone is far more significant than reduction in body weight or muscle mass. Respiratory muscle reduction in subjects with subnutrition is attributed to disturbance in electrolytes and minerals. Hypophosphatemia, hypocalcemia and hypokalemia reduce the contractive force of the diaphragm muscle.^{6,7} In addition, subnutrition can decrease various enzymes in the glycolysis pathway, oxidases and accumulated phosphorylation energy and increase intracellular calcium levels in the respiratory myocytes, provoking reduction of the respiratory muscles. That is, significant

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Table 1. Patient characteristics

	Ingestion group (4 patients)	No-ingestion group (4 patients)
Age (years)	70.2 ± 6.7	71.5 ± 3.4
Body weight (kg)	50.2 ± 4.8	48.2 ± 12.2
Height (cm)	163 ± 3.8	161.9 ± 7.9
%VC	86 ± 13	83 ± 15
FEV 1.0%	31 ± 5	32 ± 7

subnutrition attenuates energy supply during muscle contraction by reducing glycolytic energy activity in the muscle tissue.⁸ It is also thought that reduction of accumulated energy in the muscular fiber is another cause of muscle power reduction in a subnutritional state. However, in patients with anorexia nervosa, reduced respiratory muscle tone due to subnutrition is recovered by nutrition supply at a much earlier period than muscle mass.⁹ This shows that muscle power reduction associated with subnutrition can be corrected by recovering electrolytes, minerals and the energy generating system by instituting nutrition at an earlier phase (the period before the recovery of respiratory muscle mass).

What nutrients are effective for nutrition in COPD patients who are underweight. Odessey and coworkers¹⁰ reported that hydrocarbons were depleted and branched chain amino acids (BCAA) are used 10-20 fold more in the diaphragms of fasting mice than in the diaphragms of normal mice, indicating the importance of BCAA as an energy substrate. Another study¹¹ reported that amino acid imbalance reflecting the reduction of the Fischer ratio (BCAA/AAA) was found in half of patients with stable pulmonary emphysema.

Serum amino acid imbalance in patients with pulmonary emphysema is thought to be a result of using BCAA from muscle protein as energy due to the decomposition of muscle protein including the respiratory muscles themselves in order to cope with the increase in energy consumption in the respiratory muscles due to reduced ventilation efficacy. When amino acids are energy source for protein synthesis, three amino acids called branched chain amino acids are often particularly used. In this case, even though sufficient protein can be ingested from a normal diet, the amino acid balance in the normal diet barely improves the amino acid imbalance in which branched chain amino acids are lacking. Therefore, this study investigates the effect of intake of BCAA-abundant food on the Fischer ratio during pulmonary rehabilitation for eight weeks.

Subjects and method

Subjects

The subjects were eight patients with chronic pulmonary emphysema, who repeatedly visited the respiratory/ allergy medicine clinic and whose symptoms were stable. Seven patients were male and one was female. The mean age was 70.8, the mean body weight was 49.4 kg, and the mean height was 162.5 cm. A once-a-week pulmonary rehabilitation program was performed in these patients under an ambulatory setting for eight weeks. The pulmonary

Table 2. Nutritional status

	Ingestion group (4 patients)	No-ingestion group (4 patients)
%IBW	86 ± 6	83 ± 15
Calories ingested (before)	1600 ± 1500	1650 ± 120
Calories ingested (8 weeks after)	1900 ± 180	1820 ± 110
BEE	1090 ± 52	1076 ± 153
Calories ingested /BEE	175 ± 19	171 ± 21

rehabilitation consisting of a 45-minute lecture and 45-minute physical therapy was performed once a week. The topics of the lecture were nutritional instruction, medication instruction and lifestyle instruction. The patients were then divided into two groups each containing four patients: one was administered a bottle of BCAA enriched dietary supplement once daily and the other was only given nutritional instruction. BCAA enriched dietary supplement is a liquid dietary supplement not necessary to masticate, which can be ingested in a short time. There was emaciation both in the ingestion group and in the no-ingestion group without significant difference in age or body weight. Significant obstructive ventilation disorder was found; the %VC was 86 ± 13 and 83 ± 15, respectively, and the FEV 1.0% was 31 ± 5 and 32 ± 7, respectively (Table 1).

Dietary supplement

BCAA enriched dietary supplement was used as a dietary supplement

BCAA enriched dietary supplement (Clinico, Tokyo, Japan) is mainly used in cirrhosis or hepatitis cases where liver function is depressed. As the Fischer ratio for amino acid composition in a normal diet was limited to the range of about 2 - 4, it is not easy to prevent reduction in the Fischer ratio. Therefore, a bottle of BCAA enriched dietary supplement containing 200 mL per bottle was given once daily. BCAA enriched dietary supplement has 200 kcal per bottle and 4g of protein per 100mL, characterized by the abundance of branched chain amino acids and as high a Fischer ratio as 40. In addition, as the dietary supplement is liquid and does not need to be masticated, it can be ingested in a short time. Essential amino acids are classified into branched chain amino acids such as valine, leucine, isoleucine and aromatic amino acids such as tryptamine, tyrosine and phenylalanine. The Fischer ratio is calculated by dividing the branched chain amino acid value by the aromatic amino acid value among these amino acids.

Comprehensive pulmonary rehabilitation

Pulmonary rehabilitation was performed in these patients under an ambulatory setting. The program was: a once-a-week visit for pulmonary rehabilitation with respiratory physical therapy for about one hour in hospital, in parallel with additional exercises performed at home. This continued for eight weeks. Physical therapy was performed focusing on breathing instruction and muscle strengthening exercises for the lower limbs.

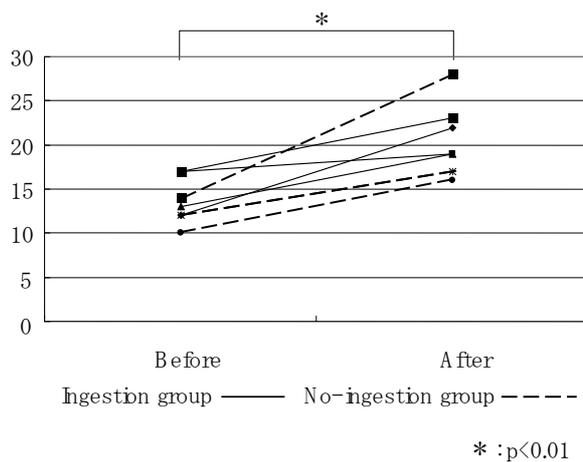


Figure 1. Changes in CRQ before and after pulmonary rehabilitation

Endpoints

Measurement of 6-minute walking distance (6 MWD), QOL assessment using CRQ (Chronic Respiratory disease Questionnaire) and serum tests (serum Fischer ratio and serum protein) were performed before and after the investigation. The HRQL of COPD patients are disturbed to a substantial degree. In the QOL assessment used in the investigation, CRQ was employed including four categories: dyspnea, fatigue, emotional function and mastery. This study approved by the Ethics Committee of Research Council of Kinki University School of Medicine. Informed written consent was obtained by each subject.

Results

There was no difference between the ingestion group and the no-ingestion group in the %IBW and the daily calorie ingestion before the rehabilitation. After the nutritional instruction of the rehabilitation program, the daily calorie intake increased compared to that before the rehabilitation. Although BCAA enriched dietary supplement containing 200 kcal was administered each day, there was no difference between the two groups (Table 2). In this investigation, a dietitian calculated the calorie intake based on the meals described by the patients for three days. The basal energy expenditure (EEE) was calculated using the Harris-Benedict formula. Dyspnea measurement in the QOL assessment by CRQ significantly improved after 8 weeks by performing pulmonary rehabilitation both in the ingestion group and in the no-ingestion group (Fig. 1). In addition, the six-minute walking distance (6MWD) significantly improved after 8 weeks by performing pulmonary rehabilitation both in the ingestion group and in the no-ingestion group (Fig. 2). However, there were evident differences in the Fischer ratio between the ingestion group and the no-ingestion group. That is, in the BCAA enriched dietary supplement-ingestion group, ingestion of the dietary supplement with a high Fischer ratio increased the ratio even after pulmonary rehabilitation. However, in the no-BCAA enriched dietary supplement-ingestion group, the ratio was obviously depressed by performing pulmonary rehabilitation focusing on muscle strengthening exercises for the lower extremities for eight weeks, even though there was

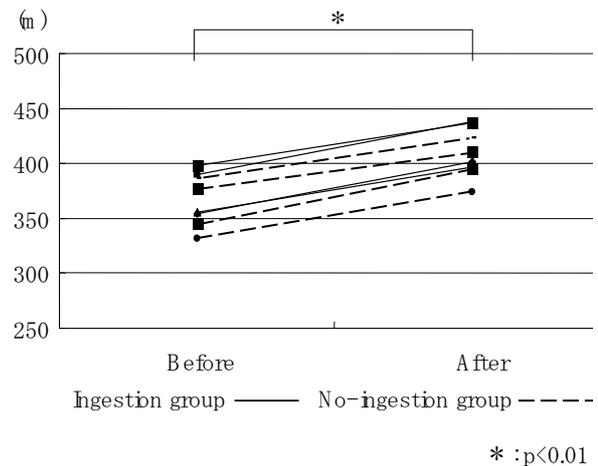


Figure 2. Changes in 6MWD before and after pulmonary rehabilitation

no difference in total calorie ingestion between the two groups (Fig. 3). In addition, serum albumin measurements were not decreased in the BCAA enriched dietary supplement-ingestion group due to the ingestion of a dietary supplement with a high Fischer ratio. However, in the no-BCAA enriched dietary supplement-ingestion group, the serum albumin measurements were depressed by pulmonary rehabilitation focusing on muscle strengthening exercises for the lower extremities for eight weeks because of amino acid deficit (Fig. 4).

Discussion

Recently, there have been efforts to analyze muscle tissue and serum amino acid kinetics as indices for evaluation of skeletal muscle degeneration or protein catabolic action in COPD. In the skeletal muscles, there were increases in glutamine as well as in arginine, ornithine and citrulline and a decrease in glutamic acid. In the serum, reduction in total amino acids was seen, particularly in alanine, glutamine, glutamic acid, asparagine, etc. In cases where increase was seen in lipopolysaccharide binding protein (LBP), an index of acute inflammatory reaction, enhancement in REE was found and, on the other hand, the total serum amino acid was reduced. Reductions in glutamic acid, glutathione and glutamine in the skeletal muscles increase the levels of lactic acid and pyruvic acid, anaerobic metabolites. These abnormal protein metabolisms in the serum and the skeletal muscles and findings regarding abnormalities in steroids and amino acids are useful in clarifying the pathology of abnormal muscle protein metabolism in COPD, and may possibly prove the validity of the therapy during amino acid nutrition therapy.

Fischer and coworkers¹² reported a reduction of the BCAA/AAA ratio in patients with hepatic encephalopathy, and the Fischer ratio has thereafter been considered as an index showing serum amino acid imbalance. Muto and coworkers¹³ reported that reduction in the Fischer ratio is a highly specific index of protein nutritional disturbance because of the correlation between the reduction in the Fischer ratio and the degree of hypoproteinemia in cirrhosis. The degree of amino acid imbalance in patients with pulmonary emphysema is relatively mild compared

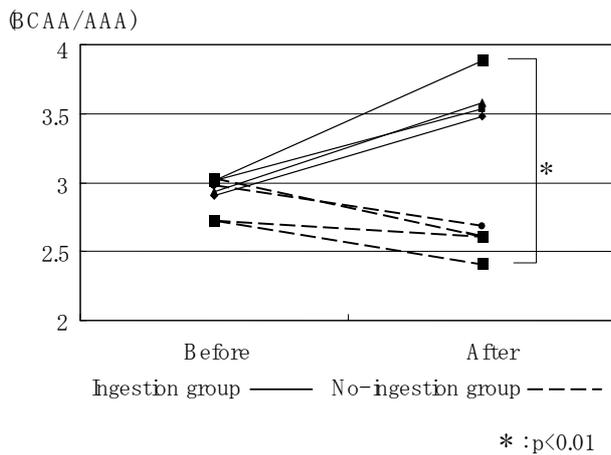


Figure 3. Changes in the Fischer ratio before and after pulmonary rehabilitation

to that in patients with hepatic encephalopathy, but the Fischer ratio correlates with morphometric measurements, and thus, it is assumed that amino acid imbalance is also associated with nutritional disturbance in pulmonary emphysema. Another study¹¹ reported that amino acid imbalance reflects reduction in the Fischer ratio (BCAA/AAA) was found in a half of patients with stable pulmonary emphysema.

According to a report by Yoneda and coworkers¹¹, FEV 1% showed a significant positive correlation with the Fischer ratio. These results suggest the greater association between the progress of respiratory dysfunction and the enhancement of amino acid imbalance and its importance, because the more severe the airway obstruction in patients with pulmonary emphysema, the more significant their amino acid imbalance is.

Serum amino acid imbalance in patients with pulmonary emphysema is thought to be a result of using BCAA from muscle protein due to the decomposition of muscle protein including the respiratory muscles themselves in order to cope with increase in energy consumption in the respiratory muscles due to reduced ventilation efficacy. The two findings, the correlation between respiratory muscle power and muscle mass and the correlation between FEV 1% and amino acid imbalance, suggest that metabolic enhancement in the respiratory muscles associated with obstructive ventilation disorder may provoke amino acid imbalance, which in turn may enhance respiratory fatigue.¹¹

In order to compensate energy that is insufficient from meals, muscular protein is decomposed in the body and used as an energy source, and thus, the muscles become emaciated. When amino acids are used as an energy source, as the three amino acids called branched chain amino acids are often particularly used, the branched chain amino acids are consumed more than the other amino acids, resulting in the disturbance of balance among the 20 amino acids in the body. Thus, the ability to synthesize the necessary proteins is reduced and various harmful effects such as immuno-suppression develop. In this case, even though sufficient protein can be ingested from a normal diet, amino acid balance in the

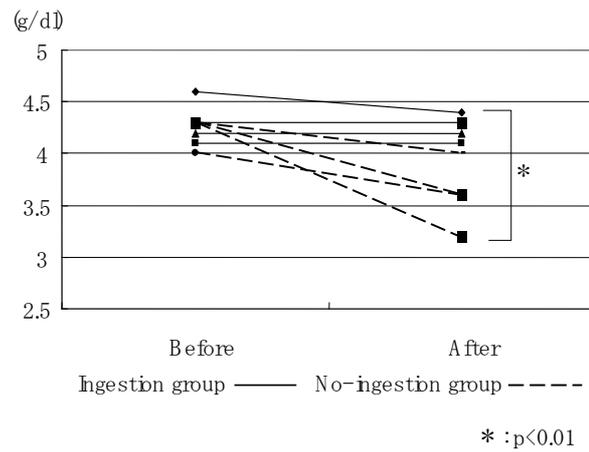


Figure 4. Changes in serum albumin before and after pulmonary rehabilitation

normal diet barely improves the amino acid imbalance in which branched chain amino acids are lacking.

Thus, efficiently administrating branched chain amino acids with a high Fischer ratio during exercise therapy leads to reinforcement of the respiratory muscles, but on the other hand, exercise therapy solely might reduce the Fischer ratio and affect protein synthesis in patients with COPD, leading to the development of amino acid imbalance. Therefore, amino acid imbalance develops in COPD, and comprehensive pulmonary rehabilitation should be performed in parallel with exercise therapy as well as appropriate branched amino acid substitution. However, nowadays, the importance of nutritional management is barely recognized in daily medical practice. Nevertheless, eating is an essential requirement for the survival of human beings, and is performed more frequently by humans than taking medicine. If we recognize and clarify the importance of nutrition in the prognosticate of COPD, a new treatment strategy can be developed.

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膳食補充劑對肺部復健前後 Fisher ratio 的影響

最近，針對慢性阻塞性肺部疾病(COPD)的全面性肺部復健已經有相當的努力，包括教育、物理治療、職能治療、營養、護理、藥物及諮詢。每一個病人雖有不同的重點，其中供應足夠的營養對全面的肺部復健以及存活則是必須的。本研究利用增加含高 Fisher ratio 的胺基酸飲料，探討肺部物理治療前後營養補充劑治療的可用性。八名 COPD 合併阻塞性呼吸失調的病人，其嚴重度為 FEV1.0% 只有 $31.5 \pm 6\%$ 。肺部物理治療共進行八週，其中一組每日服用一瓶高 Fisher ratio 並富含支鏈胺基酸(200 大卡/200 毫升，Fisher ratio 40)的膳食補充劑；而另一組則沒有服用。物理治療前後會進行 6 分鐘的清醒評估、QOL 評估(使用 CRQ)、血清蛋白質及血清 Fisher ratio，並比較兩組的結果。八週肺部物理治療之後，沒有補充支鏈胺基酸的組別其血清 Fisher ratio 明顯的降低，而血清蛋白質也下降。據此，在進行肺部物理治療時由於肌肉蛋白的消耗，所以需要更多的胺基酸，而在營養素攝取時，包含足量的支鏈胺基酸是需要的。這對於長期且連續的全面性肺部復健而言是個重要的因素。

關鍵字:慢性阻塞性肺部疾病、支鏈胺基酸、Fisher ratio、營養評估、肺部復健。