

Nutritional and pulmonary function assessment in chronic obstructive pulmonary disease: Effects of nutritional supplementation

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We found that with oral supplementation by a liquid soy-based protein hydrolysate in malnourished COPD patients (BMI \leq 20), it possible to increase weight over a 6-week period, and body water and an index of muscle mass (MAMC), but not total body nitrogen (TBN judged by Nitrogen Index) which identifies a particular challenge for nutrition support in COPD patients. There was no associated improvement in pulmonary function but we found that better nourished COPD patients (BMI $>$ 20) had some pulmonary function advantage; it is suggested that TBN may need to improve with nutrition support for pulmonary function to improve.

Key words: Chronic obstructive pulmonary disease, nutritional assessment, pulmonary function assessment, total body nitrogen, nutrition support, formula feed.

Introduction

Weight loss or malnutrition occurs commonly in patients with severe chronic obstructive pulmonary disease (COPD) and those with malnutrition have been shown to have a greater rate of deterioration of lung function and a higher mortality.¹⁻⁴ Malnourished COPD patients have been shown to have more respiratory muscle weakness and a more reduced maximal exercise capacity compared with well-nourished COPD patients with comparable severity of airways obstruction.^{5,6} The work of respiration is much increased in patients with severe COPD and this accounts for their marked increase in O₂ cost of ventilation to levels several times higher than in normal subjects.⁷ The mechanism of malnutrition in COPD is not clear but the main basis is believed to be an inadequate dietary intake to meet the increased energy expenditure from respiratory work. Consequently, many investigators have attempted to increase the dietary intake of COPD patients by adding nutritional supplement to their normal diet in order to improve their weight, respiratory muscle strength, exercise capacity, and ultimately prognosis.^{5,8-11} Results, however, have not been encouraging and most studies of the giving of nutritional supplement to ambulatory patients with COPD have failed to deliver the anticipated benefit.

In addition, instead of using only anthropometric measures as markers of malnutrition, which most studies have adopted, we used the resources of the Body Composition Laboratory of the Monash Medical Centre, Melbourne, Australia, with the techniques of *in vivo* neutron activation analy-

sis (IVNAA) for measuring total body protein (TBP), and bioelectrical impedance analysis (BIA) for measuring body water and fat content.

The aim of this study is to assess the body composition in subjects with severe COPD and low body weight. The effect of nutritional supplementation was reviewed.

A prospective, randomized, double-blind and placebo-controlled study was conducted which considered changes of nutritional and respiratory parameters in malnourished patients with severe COPD in response to nutritional supplementation for 6 weeks. The use of a placebo is unusual in this type of study and this in turn allowed a double-blind design. Sophisticated methods of assessing body composition including *in vivo* neutron activation analysis (IVNAA) to measure total body protein (TBP) and bioelectric impedance analysis (BIA) to measure body water and fat content were applied to accurately assess body composition.

Methods

Patients

Twenty-two malnourished patients with severe COPD were studied (Table 1). These patients had a body weight \leq 90% of ideal body weight as given in the Metropolitan Life Insurance Company standard,¹² or had a BMI of 20 or less. Their

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Table 1. Basic data and baseline pulmonary function (mean \pm SEM)

	BMI \leq 20		BMI $>$ 20
	Treatment group	Placebo group	
No. of patients	11	11	24
Age	68.9 \pm 6.3	62.8 \pm 8.0	62.5 \pm 7.5
Male:female	7:4	8:3	13:11
VC % predicted (pre-bronchodilator)	76.0 \pm 4.5	70.0 \pm 4.9	72.7 \pm 3.1
FEV1 % predicted (pre-bronchodilator)	28.3 \pm 2.5	27.3 \pm 3.6	34.7 \pm 3.4
VC % predicted (post-bronchodilator)	78.0 \pm 4.9	79.5 \pm 4.6	83.0 \pm 3.4
FEV1 % predicted (post-bronchodilator)	29.3 \pm 2.6	29.5 \pm 3.3	38.6 \pm 3.71** ($P < 0.05$)
Diffusing capacity % predicted	44.8 \pm 6.5	39.4 \pm 5.3	47.4 \pm 3.0
MIP % predicted	47.5 \pm 5.0	49.0 \pm 4.8	63.4 \pm 4.8** ($P < 0.01$)
MEP % predicted	66.0 \pm 4.8	58.9 \pm 5.7	66.9 \pm 3.8
Arterial PO ₂ mmHg	68.8 \pm 3.0	68.6 \pm 2.5	not done
Arterial PCO ₂ mmHg	45.4 \pm 1.9	40.5 \pm 1.1* ($P < 0.05$)	not done

*, Significantly different from treatment group; **, significantly different from the malnourished group (treatment and placebo combined).

lung function tests showed FEV1 $<$ 40% of the predicted normal value, FEV1/VC $<$ 40%, or diffusing capacity $<$ 60% of the predicted normal value, and an increase of FEV1 of 0.3 L or less after aerosol bronchodilator. These patients had been clinically stable for the previous 6 weeks and they did not have other serious medical conditions likely to affect this study. The 22 patients were randomized into two equal groups with one group receiving the placebo and the other group receiving the nutritional supplement.

Twenty-four COPD patients with a BMI $>$ 20 were also studied, as a control group, on one visit for lung function and nutritional measurements (Table 1). These subjects received no supplement, placebo or nutritional advice prior to their assessment.

Study design

The study was double-blind until all data were collected. The patients visited our laboratories on four occasions. The first was for recruitment and for familiarization with the lung function test procedures. The second visit, regarded as week 0, and the fourth visit 6 weeks later were for full nutritional and lung function assessment. The third visit at end of week 3 was for body weight measurement and quality of life assessment.

Diets and dietary assessment

Under the supervision of the clinical nutritionists, the patients were taught to keep a 4 day record of their food intake the first (week 0) and final weeks (week 6) of the study. The records were coded by a dietitian, and converted using Nutritionist III software (N Squared Computing), to allow calculation of mean daily intakes of total energy and protein. The patients in the treated group each day consumed two 250 mL aliquots of

Top-up (Novo, Copenhagen, Denmark), a chemically defined liquid enteral supplement, based on a low pH, soluble non-bitter soy protein hydrolysate. Patients in the placebo group consumed a similar quantity of non-calorigenic dextrans, which had the same appearance, taste and consistency as Top-up. The 100 mL of Top-up contained 5 g protein, 2.98 g fat, 0.59 g essential fatty acids and 11.89 g carbohydrates, providing an energy density of 1 kcal/mL. The sodium content was 120 mmol/L. Body composition was assessed during weeks 0 and 6 of the study. Anthropometric measurements included weight, height, skinfold thicknesses at the triceps, biceps, subscapular and suprailiac sites, mid-arm, umbilical and hip (at the suprailiac level) circumferences. Measurements were performed in the Body Composition Laboratory, by trained personnel, using standard equipment including Harpenden skinfold callipers. The sum of the skinfold thicknesses was converted into body fat content using the equations developed by Durnin and Womersley (1974).

BIA (bioelectrical impedance) was performed using a single (50 kHz) frequency analyser (RJL systems, Detroit). Whole body electrical resistance was converted into body water and fat content, using regression equations developed by Lukaski *et al.*,¹³ and assumed a fat-free mass (FFM) hydration of 73%. The error of the electrical resistance is 3%.

Total body protein using IVNAA was performed in the Body Composition Laboratory on equipment developed 'in-house'.¹⁴ The neutron source is Cf²⁵², and the technique has been validated with an error of 4%.¹⁴ Results were also expressed as a 'Nitrogen Index' (NI) to allow standardization and comparison of TBP with respect to an apparently healthy population. An NI $<$ 0.8 (normal 1.0 \pm 0.1) was considered evidence of TBP wasting.

Measurement of lung function

Arterial blood gases were measured at rest prior to the other lung function tests. Vital capacity (VC) and forced expiratory volume 1 (FEV1) see before and after aerosol salbutamol, and the single breath diffusing capacity (DLCO) were measured using a SenorMedic model 2400 Pulmonary Laboratory. Measurement of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were based on the method of Black and Hyatt, with modifications as described by Clausen.^{15,16} Cycle ergometry was performed, but at a predetermined fixed workload, with recording of minute ventilation, heart rate and the duration of exercise. A steady workload had been found previously to be better tolerated and more reproducible than an incremental workload.

Statistical methods

Paired Student's *t*-test was used to compare the mean levels between weeks 0 and 6 in both placebo and active groups. Paired Student's *t*-test was used to compare the means of the placebo group and the treatment group at week 0. A level of $P < 0.05$ was considered significant.

Results

Table 1 shows the demographic and pulmonary function of the treatment (BMI \leq 20) and control (BMI $>$ 20) COPD subjects. Compared with the placebo, the treatment group had a higher arterial CO₂ tension consistent with more severe pulmonary function. The normal BMI group showed a general

trend towards better lung function and had a significantly higher post bronchodilator FEV1 and MIP.

All 22 patients tolerated the placebo or supplement, and dietary record did not show any significant reduction in their usual diet intake during the 6 weeks of the study.

In terms of nutritional measurement, there was no significant difference between the treatment and the placebo group at week 0 (Table 2). The changes in nutritional parameters from weeks 0 to 6 in the placebo and the treatment groups are shown in Table 2. There was no significant change of nutritional parameters in the placebo group after 6 weeks of supplement. In contrast, the treatment group showed a significant increase in body weight, BMI, total body water content, and mid-arm muscle circumference, but no change in nitrogen index or total body fat content.

The differences between the means of the nutritional parameters of the COPD patients stratified according to BMI (Table 2).

In terms of lung function, which included exercise heart rate, ventilation and duration, there was no significant change after 6 weeks of placebo or supplement, with two exceptions. In the treatment group receiving supplement, there was a slight deterioration after 6 weeks in pre-bronchodilator FEV1 (from 28.3 ± 2.5 (SEM) to 26.1 ± 1.8) and arterial O₂ tension (from 68.8 ± 3.0 to 64.6 ± 2.7 ; $P = 0.05$).

Both of the individual and total visual analogue scores for quality of life for each patient were assessed in the placebo and the treatment group in weeks 0 and 6. In addition, control subjects VAS were assessed and compared with BMI < 20 subjects. There was no significant difference between the groups or between weeks 0 and 6 in each group, for total scores or individual parameters.

For the COPD patients with BMI > 20, as expected nutritional variables were superior to the ≤ 20 group. For the BMI > 20 group, FEV, and MIP, were also superior.

Discussion

Starved animals lose weight and striated muscle mass. The muscle mass of the diaphragm, which is a striated muscle, is reduced in starved animals after 4–6 weeks.^{17,18} Refeeding of subjects results in increase in muscle mass.^{2,19} Because weight loss in COPD is mainly due to an inadequate intake to match the increased energy expenditure from respiratory work and because there is evidence of loss of both skeletal and diaphragm muscle mass in COPD,^{19–21} it is conceivable

that the weight loss in COPD may be reversed. This will result in a rebuilding of the skeletal and respiratory muscles if energy and nutritional intake can be made to exceed the daily energy requirement. A recent short-term study on hospitalized patients have shown such recovery through maintaining a high nutrition intake.¹¹ In this study, handgrip strength and respiratory muscle function of these patients improved and muscle rebuilding was implied by the increase in muscle strength. Total body protein in this study was not measured to confirm this increase. Furthermore, this small study was not controlled with no placebo group evaluated.

In the present study, the 24 COPD patients with a BMI > 20 had a body composition characterized by a normal fat, water and TBP content. Although not measured in our study, BMI mass may be reduced in COPD,²² but, at most, would contribute 1–1.5 kg of weight loss if total bone mass were about 4 kg. Since we studied COPD patients with reduced body weight (BMI < 20), it is not surprising to find that compared with the control COPD group, these patients are depleted in fat content, measured by anthropometry and BIA, as well as TBP measured by TBP. This suggests that underweight patients with COPD have body composition changes likely to contribute to reduced respiratory muscle effort, and an increased susceptibility to infections.²³

While it is possible that the hydration state of the FFM, assumed to be 73%, is different in COPD, the significant increase in weight in the treated group is most likely due to the increase in total body water (TBW) measured by BIA, since fat content and TBP did not change over the course of the 6 weeks. This is the more likely since the error of the BIA technique is less than that of the IVNAA. In retrospect, the time course of the study (6 weeks) may have been too short for changes in TBP to develop, an indication of the length of time required for nutritional rehabilitation in these patients. An increase in the extracellular component of the TBW possibly explains the total increase in TBW, but this was not measured in the present study. Swept-frequency BIA, in a future study, may help clarify this aspect. We attribute the increase in TBW to an increase in intracellular water associated with an increase in muscle glycogen. Russell *et al.* showed that, in protein–energy malnutrition, energy repletion is associated with an initial increase in intramuscular glycogen stores, which occurs before any demonstrable increase in TBP, as measured by IVNAA.²⁴

Table 2. Nutritional parameters before and 6 weeks after supplement or placebo (mean \pm SEM)

	BMI ≤ 20				BMI > 20
	Supplement treatment		Placebo		
	Week 0	Week 6	Week 0	Week 6	
Weight (kg)	50.9 \pm 1.7	52.3 \pm 1.7 ($P < 0.001$)*	50.9 \pm 2.1	51.5 \pm 2.3	69.4 \pm 2.2
BMI (kg/m ²)	18.9 \pm 0.5	19.5 \pm 0.5 ($P < 0.01$)*	18.1 \pm 0.5	18.3 \pm 0.6	24.9 \pm 0.7
Nitrogen Index	0.78 \pm 0.02	0.76 \pm 0.03	0.72 \pm 0.04	0.74 \pm 0.04	0.92 \pm 0.03
Mid-arm muscle circumference (cm)	20.5 \pm 0.7	21.7 \pm 0.6 ($P < 0.05$)*	20.6 \pm 0.6	20.2 \pm 0.6	24.3 \pm 0.5
Total body water content (L)	31.0 \pm 1.6	32.0 \pm 1.5 ($P < 0.03$)*	32.3 \pm 1.5	32.4 \pm 1.7	36.9 \pm 1.1
Total body fat content (%)	19.3 \pm 2.3	19.1 \pm 2.6	18.6 \pm 1.8	18.0 \pm 1.9	28.1 \pm 1.3

*, significant difference from Week 0.

In the present study, the recorded normal NI, TBW and fat contents of these 24 well-nourished patients with COPD are presented to highlight the reduced values of these measurements in our 22 malnourished COPD patients. The contrasting findings of NI, TBW and fat content in the well-nourished group and the malnourished group are in support of the usefulness of such tests for monitoring changes in body composition.

Despite the relatively small number of patients studied and the short period of supplementation, a significant increase in body weight, BMI, mid-arm muscle circumference and TBW content were demonstrated. Because we were unable to show any improvement in maximal inspiratory and expiratory pressure and exercise tolerance, one may question whether the demonstrated changes in nutritional parameters in the treated group represent an early stage of muscle rebuilding which would be beneficial, or represent merely fluid retention which would be detrimental. The lack of change in NI in our subjects is evidence against muscle rebuilding. On the other hand, from other studies, there is evidence that muscle rebuilding in malnourished patients with marasmus may initially go through a period of increased intramuscular water and glycogen deposition before the rebuilding of muscle protein.^{24,25} Our data are relatively compatible with this early phase of muscle rebuilding. In order to resolve this question, future studies of nutrition should have a much longer period of supplementation and they must include objective measurement of total body nitrogen.

The use of a placebo and a double-blind design in the present study is of considerable importance to avoid subject and observer bias because measurements that depend on maximal effort by the subject, and strong urging by the investigators (such as the measurement of maximal inspiratory and expiratory pressures and exercise capacity) may be influenced if the subject or the observer is aware that the subject is receiving the nutritional supplement. The advent of dextran technology has allowed the preparation of a placebo for the present study which has the same taste, colour and consistency as the nutritional supplement. The use of a placebo and a double-blind design should become an important component of future studies of nutritional supplement.

We do not consider that the slight, albeit significant, reduction in prebronchodilator FEV1 and arterial O₂ tension (which was also measured before bronchodilator) in the treatment group represented deterioration of lung function due to nutritional supplementation. First, the changes were slight and occurred only before bronchodilator, and such minor changes of lung function are not unexpected in patients with severe COPD. For instance, changes in air pollution can easily cause such minor changes. Second, other studies of nutritional supplement in COPD have not shown significant change in spirometry or blood gases. In particular, there has been no observed change in arterial CO₂ tension in ambulatory patients as a result of an increased carbohydrate load during supplementation. Third, our treatment group of patients tended to be older and had a higher arterial CO₂ initially and they may be expected to be more likely to show periodic minor exacerbations. It should be pointed out that even major periodic exacerbations among COPD patients are not uncommon. In this study, six patients completed the studies for week 0, but could not complete the studies at

week 6 due to clinically evident exacerbation of COPD. Their data was not used for this report.

One may argue, however, that our patients who had supplement for 6 weeks may have developed a degree of cor pulmonale with fluid retention, leading to some worsening in FEV1 and arterial O₂. Our nutritional data may support this view as there were increases in body weight, BMI, mid-arm muscle circumference and TBW content, but not in total body nitrogen or fat content. Clinically, there was no evidence of cor pulmonale but clinical signs are probably not sensitive tests for mild cor pulmonale.

Of the studies of nutritional supplementation in ambulatory malnourished patients with COPD,^{8-10,26} only one showed improvement in body weight, triceps skinfold thickness, mid-arm muscle circumference, maximal inspiratory and expiratory pressures, hand grip strength, and sternomastoid muscle function, as well as improved symptoms and walking distance whether 6 min or 12 min.⁵ In this study, the period of supplementation was 3 months. However, similar supplementation studies by other investigators have failed to show such benefits, and a possible explanation for this lack of benefit is the common observance that the subjects often replace part of the normal diet with the liquid nutritional supplement instead of taking both. Therefore, they did not achieve a high nutrition intake in sufficient excess above the energy expenditure to achieve weight gain and muscle recovery.

Finally, because of the conflicting results from previous reports and the difficulty in interpreting results of the present study, a definitive study of nutritional supplement in patients with COPD is much needed. Such a study should recruit a much larger number of malnourished COPD patients than in the present study, and the supplementation should be for a period of at least 3 months to allow time for possible muscle protein synthesis. The use of a placebo and a double-blind design is essential to prevent subject and observer bias. The study should be supervised closely by a dietitian to ensure that the supplement given has not replaced part of the normal diet. Regular home visits by the dietitian are probably useful. In addition to traditional anthropometry, the study should use the more sophisticated methods of measurement of nutritional parameters such as *in vivo* neutron activation analysis to quantitate total body protein and the measurement of bioelectric impedance to quantitate TBW and fat content, so that more detailed information on the changes of body composition may be gained.

Another possibility has emerged from the recent study of combined and separate nutrition support and skeletal muscle strength training in the aged,²⁸ that unless muscle training takes place, nutrition support may be of limited value in improving performance, but may do so, with combined therapy, ahead of evidence of body compositional improvement. Perhaps this could be tested in relation to respiratory muscle performance with physiotherapy as part of the combined therapy with nutrition. Again, since growth hormone has been shown to improve nitrogen status in malnourished COPD patients given TPN, growth hormone combined with oral nutrition support in COPD may lead to improved respiratory function.²⁷

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**慢性阻塞性肺病(COPD)病人營養和肺功能的評估：
營養補充的影響**

摘 要

我們發現給營養不良的慢性阻塞性肺病 (COPD) 病人 (體重指數 BMT \leq 20) 口服大豆蛋白質水解液經過六個星期, 可能使體重增加, 也可能使人體水份和肌肉質量指數 (MAMC) 增加, 但總體氮 (TBN , 用氮指數判斷) 不變, 作者沒有發現肺功能有所改善, 但他們發現獲得較好營養的慢性阻塞性肺病 (COPD) 病人 (BMI>20) 對肺功能改善有一些好處。最後作者指出營養支持改進 TBN 對肺功能的改善也許是需要的。

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