Optimizing oral nutritional drink supplementation in patients with chronic obstructive pulmonary disease

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Nutritional support is indicated in some patients with chronic obstructive pulmonary disease to restore nutritional status and improve functional capacity. However, the efficacy of nutritional supplements is sometimes disappointing, partly owing to a compensatory drop in habitual food intake. We retrospectively studied the effect of nutritional drink supplements, differing in portion size and energy content, on weight gain and body composition. Thirty-nine patients with stable chronic obstructive pulmonary disease, participating in an 8-week pulmonary rehabilitation programme and eligible for nutritional support, were studied. Group A (n 19) received three portions of 125 ml (2380 kJ), whereas group B (n 20) received three portions of 200 ml (3350 kJ) daily. The macronutrient composition of the regimens was similar (20 % protein, 60 % carbohydrates and 20 % fat). Lung function, body weight, body composition (by bio-electrical impedance analysis), habitual dietary intake (by dietary history) and resting energy expenditure (by ventilated hood) were determined. Weight gain was compared with expected weight as predicted by a computer simulation model. Although patients in both groups significantly increased in weight, this increase was higher in group A (A, 3·3 (SD 1·9) kg; B, 2·0 (SD 1·2) kg; P=0·019), while receiving less energy. The observed weight gain in group A was similar to that expected, but in group B it was lower than expected (P<0·001). In both groups, fat-free mass and fat mass were gained in a ratio of 2:1, fat-free mass increasing primarily during the first 4 weeks. This study illustrates that there might be an optimum for the portion size of nutritional drink supplements in chronic obstructive pulmonary disease and that more is not always better.

Chronic obstructive pulmonary disease: Nutrition: Body composition: Therapy: Rehabilitation

Weight loss and muscle wasting frequently occur in patients with chronic obstructive pulmonary disease (COPD), negatively influencing respiratory and peripheral muscle function (Engelen et al. 1994), exercise capacity (Schols et al. 1993; Baarends et al. 1997b), health status (Shoup et al. 1997) and mortality (Schols et al. 1998).

As weight gain has been associated with decreased mortality (Schols et al. 1998), it is of great importance to maintain weight in COPD patients. Weight loss results from an imbalance in dietary intake and energy expenditure. In contrast to an adaptive decreased energy metabolism during (semi) starvation, increased total daily energy expenditure has been measured in ambulatory COPD patients (Baarends et al. 1997c; Slinde et al. 2003). The cause of this COPD-related increase in energy expenditure is not yet clear, although increased $O_2$ cost of breathing and possibly also a decreased mechanical and metabolic efficiency has been suggested to play a role (Baarends et al. 1997a).

Although the dietary intake of stable COPD patients has been shown to be adequate according to the recommended daily allowances (Hunter et al. 1981; Braun et al. 1984), patients can still lose weight owing to an insufficient adaptation of dietary intake to increased energy expenditure. Additional nutritional support is therefore indicated for these patients. Several studies have explored possibilities for reversing weight loss and improving body composition in patients with COPD. Although a Cochrane meta-analysis (Ferreira et al. 2002) previously concluded that nutritional supplementation did not have a significant effect on anthropometric measures, this issue is still under debate because of the limited available number of randomized controlled intervention studies.

In order to improve functional capacity and not only gain fat mass, nutritional support is best combined with an anabolic stimulus. One way to accomplish this is to integrate nutritional supplementation into a pulmonary rehabilitation programme. This approach has been shown to increase weight and fat-free mass (FFM) significantly (Schols et al. 1995; Creutzberg et al. 2003) and to improve respiratory and peripheral muscle function, exercise capacity and health status (Rogers et al. 1992; Creutzberg et al. 2003). However, in the latter circumstances as well, the efficacy of nutritional supplements is sometimes disappointing, at least partly because of a compensatory drop in habitual food intake (Lewis et al. 1987; Knowles et al. 1988; Creutzberg et al. 2003). Voluntary food intake has been shown to be limited by

Abbreviations: COPD, chronic obstructive pulmonary disease; $DL_{CO}$, diffusing capacity of CO; $FEV_1$, forced expiratory volume in 1 s; FFM, fat-free mass; FM, fat mass; REE, resting energy expenditure.

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the volume, frequency and energy density of the food portion, influencing symptoms such as early satiety and bloating (Rettammel et al. 1995; Olin et al. 1996). This suggests that there is an optimum in caloric load and/or portion size in nutritional drink supplements. Nutritional drink supplements are commonly provided in 200 ml packages. We hypothesized that smaller portions of energy-dense nutritional drink supplements administered between regular meals would improve the response to dietary management in COPD patients.

Methods

Patients

Patients with clinically stable COPD, consecutively admitted to an 8-week inpatient pulmonary rehabilitation centre (Asthma Centre Hornerheide, Horn, The Netherlands) during the periods 1995–97 and 2000–02, were included if they were considered eligible for nutritional support and if they met the criteria for COPD of the American Thoracic Society (1995) (see p. 967). Patients who met at least one of the following criteria were considered eligible for nutritional support and included in the study:

1. BMI $\geq$ 21 kg/m$^2$;
2. FFM index $\geq$ 16 (men) or 15 (women) kg/m$^2$;
3. BMI $\leq$ 25 kg/m$^2$ and weight loss $\geq$ 5 % in 1 month or $\geq$ 10 % in 6 months prior to admission to the pulmonary rehabilitation centre.

Patients were excluded if they were prescribed fewer than three cartons of nutritional supplements per d or if they received pharmacological interventions to enhance body composition. Patients were also excluded if they suffered from concurrent diseases such as malignancies, gastrointestinal or kidney abnormalities, metabolic or endocrine diseases and inflammatory diseases.

Research design

To evaluate two different nutritional supplement regimens, we compared nineteen COPD patients (group A, admitted to the rehabilitation centre in 2000–02) receiving three 200 ml cartons daily with a historical group of twenty patients (group B, admitted to the rehabilitation centre in 1995–97) taken from the nutritional intervention study of Creutzberg et al. (2003) (Fig. 1). The historical group was matched with group A in terms of age, gender and oral corticosteroid use and received three 125 ml cartons daily or if they received pharmacological interventions to enhance body composition. Patients were also excluded if they suffered from concurrent diseases such as malignancies, gastrointestinal or kidney abnormalities, metabolic or endocrine diseases and inflammatory diseases.

At baseline and after 8 weeks of intervention, the forced expiratory volume in 1 s (FEV$_1$), body composition, resting energy expenditure (REE), exercise capacity and health status were determined. Body composition was also determined at 2, 4 and 6 weeks of intervention. In addition, habitual dietary intake and diffusing capacity for CO (DL$_{CO}$) were assessed at baseline (Fig. 1). The ethical review board of the University Hospital Maastricht approved the study, and all patients gave their written informed consent.

Body composition

Body height was determined to the nearest 0.5 cm (WM 715; Lamaris, Breukelen, The Netherlands) with subjects standing barefoot. Body weight was measured with a beam scale to the nearest 0.1 kg (model 708; Seca, Hamburg, Germany) with subjects wearing light clothing and no shoes. BMI was calculated as weight divided by height$^2$ (kg/m$^2$). FFM (kg) was estimated using single-frequency (50 kHz) bio-electrical impedance analysis (Xitron Technologies, San Diego, CA, USA), with the subject lying supine. FFM was calculated using the disease-specific equation proposed by Schols and described by Steiner (Steiner et al. 1996). This suggests that there is an optimum in caloric load and/or portion size in nutritional drink supplements. Nutritional drink supplements are commonly provided in 200 ml packages. We hypothesized that smaller portions of energy-dense nutritional drink supplements administered between regular meals would improve the response to dietary management in COPD patients.

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**Fig. 1.** Patient flow and timing of measurements. FEV$_1$, forced expiratory volume in 1 s; DL$_{CO}$, diffusing capacity for CO; REE, resting energy expenditure.

Nutritional intervention was embedded in an 8-week, standardized in-patient rehabilitation programme consisting of a combination of endurance and strength exercise training. The daily programme comprised 2 × 20 min submaximal cycle ergometry, 1 × 20 min treadmill exercise, 1 × 30 min gymnastics and one session of unsupported arm exercise training (consisting of 10 × 1 min exercise, each minute being followed by 1 min rest). A team of experienced physiotherapists based each individual training programme on the patients’ functional impairments in daily living and on their muscular performance. In addition, an educational programme about the disease and medication use was implemented. During rehabilitation, patients received maintenance respiratory medication that in general consisted of inhaled bronchodilators, inhaled corticosteroids and, when indicated, theophylline.

At baseline and after 8 weeks of intervention, the forced expiratory volume in 1 s (FEV$_1$), body composition, resting energy expenditure (REE), exercise capacity and health status were determined. Body composition was also determined at 2, 4 and 6 weeks of intervention. In addition, habitual dietary intake and diffusing capacity for CO (DL$_{CO}$) were assessed at baseline (Fig. 1). The ethical review board of the University Hospital Maastricht approved the study, and all patients gave their written informed consent.

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et al. 2002). FFM index was calculated as FFM divided by height$^2$ (kg/m$^2$). Fat mass (FM) was calculated as total body weight minus FFM. Body weight, FFM and FM were measured at baseline and after 2, 4, 6 and 8 weeks of intervention. Treatment non-response was defined as a body weight gain <2% (Creutzberg et al. 2000).

Lung function

COPD was defined, according to the criteria for COPD of the American Thoracic Society (1995), as a FEV$_1$ below 70% of the predicted value with reversibility after inhalation of a bronchodilator of less than 200 ml or 10% of the reference value. FEV$_1$ was assessed from the flow-volume curve using a spirometer (Masterlab; Jaeger, Würzburg, Germany). The highest value of at least three measurements was used. FEV$_1$ was also assessed 15 min after inhalation of a bronchodilator (β-agonist) via a metered-dose inhaler to determine reversibility. DL$_{CO}$, which is an indirect measure of emphysema, was determined using the single-breath method (Masterlab, Jaeger). Instruments were calibrated twice per d. Lung functional parameters were expressed as a percentage of reference values (Quanjer, 1993). FEV$_1$ was determined at baseline and after 8 weeks of intervention, and DL$_{CO}$ was determined at baseline.

Energy balance

REE was measured in the early morning (08.30 hours) at baseline and after 8 weeks of intervention by indirect calorimetry using a ventilated hood (Oxycon Beta; Jaeger). The system was calibrated daily at the start of the experiment, accuracy being regularly assessed using a methanol combustion test. Patients were in a fasting state for at least 10 h and had a period of at least 30 min bed rest prior to the measurement. When patients were receiving additional oxygen during hospitalization, the oxygen was temporarily withdrawn 30 min before and during the measurement of REE. The patients lay comfortably on a bed in the supine position. REE was calculated from O$_2$ consumption and CO$_2$ production using the abbreviated Weir formula (Weir, 1990). The ratio of REE and FFM was used for analysis.

Habitual dietary intake was assessed at baseline using the dietary history method with cross-checking. All interviews were performed by the same trained dietician. Computer nutrient analysis was performed by a program based on food tables (Becel Nutrition Program 96; Nederlandse Unilever Bedrijven BV, Rotterdam, The Netherlands).

Exercise capacity

An incremental bicycle ergometry test was performed at baseline and after 8 weeks on an electromagnetic braked ergometer (Corival 400; Lode, Groningen, The Netherlands) under supervision of a chest physician to investigate maximal leg exercise capacity. After 2 min rest and 1 min unloaded cycling, the power was increased every minute by 10 W until exhaustion. Peak workload was used in the analysis.

Health status

At baseline and after 8 weeks of intervention, disease-specific health status was measured by the St George’s Respiratory Questionnaire (Jones et al. 1991). The patients completed the fifty items themselves, after which subscores were calculated for the categories of symptoms (distress owing to respiratory symptoms), activity (disturbance of physical activity) and impact (overall impact on daily life and well-being), as well as the total score (the weighted mean of the three scores). Subscores ranged from 0 to 100, a high score denoting greater impairment. A change of four or more points in total score is considered clinically significant, decreases being beneficial (Jones, 1995).

Data handling and statistical analysis

Results are presented as means and standard deviations for normally distributed variables. Differences between the baseline characteristics of separate groups were tested using the Student’s t test for independent samples when normally distributed. Changes within the groups between baseline and 8 weeks were tested using the Student’s paired t test. The changes in body composition were compared between groups using linear regression with baseline value, age, gender and assigned intervention group as predictors. The percentage of non-responders between the groups was compared using the χ$^2$ test. Data were analysed using SPSS (Statistical Package for the Social Sciences, version 11 for Windows; SPSS Inc., Chicago, IL, USA). Significance was assumed at a P-value of 0.05.

A computer model taking into account the patient’s gender, age, height, body composition and dietary intake (Westerterp et al. 1995) was used for estimating the predicted weight gain on the basis of a net rise in dietary intake after nutritional supplementation. Changes in body composition were performed separately for men and women, and the weighed mean was taken for analysis.

Results

At baseline, patients in group A and B did not differ significantly in terms of age, gender, lung function and body composition. Energy balance at baseline, as determined by REE and dietary intake, was also not significantly different between the two groups, the same being true for baseline peak workload. Patients in group B had a worse score on the impact dimension of the St George’s Respiratory Questionnaire (P=0.030). The other three dimensions, were not, however significantly different (Table 1).

After 8 weeks of nutritional intervention combined with pulmonary rehabilitation, both groups showed a significant gain in weight (both groups P<0.001) and FFM (group A, P<0.001; group B, 0.004) (Table 2). FM was significantly increased in group A (P=0.002) but not in group B. The patients in group A, however, gained more weight than those in group B (P=0.019; Fig. 2 and Table 2). The proportional increases in FFM and FM were similar in both groups (group A, 66% FFM, 34% FM; group B, 70% FFM, 30% FM). Fig. 3 shows the change in FFM and FM after 4 and 8 weeks of rehabilitation. It is remarkable that almost all the gain in FFM was obtained during the first 4 weeks of rehabilitation (group A 2.1 (sd 1.9) kg, P<0.001 v. group B 1.2 (sd 2.4) kg, P=0.035; between groups). FM was primarily gained during the second half of the rehabilitation (group A, 1.1 (sd 1.0) kg, P<0.001 v. group B 0.8 (sd 1.8) kg, P=NS; between groups: P=NS). Fig. 4 shows the observed increase in body weight compared with the expected increase in body weight, as predicted by the Westerterp et al.
(1995) model. In group A, the observed rise in body weight was similar to the expected rise (3.3 (SD 1.9) kg v. 3.4 kg). In group B, however, the finally achieved rise in body weight was lower than the expected value (2.0 (SD 1.2) kg v. 4.8 kg; \( P, 0.001 \)).

Changes in health status during the intervention are shown in Table 3. No significant differences in change in health status were found. However, only in group A did the total score decrease by more than four points, which is considered a clinically significant improvement.

There were no differences in functional response between the two groups. Peak workload during the incremental bicycle ergometry test increased similarly in both groups (group A, 8.3 (SD 17.1) W, within-group change \( P=0.062 \); group B, 9.0 (SD 9.4) W, within-group change \( P=0.002 \); between-group change, \( P=NS \)). FEV\(_1\) did not change significantly (group A, 0.7 (SD 8.4) % predicted, within-group change \( P=NS \); group B, 2.3 (SD 5.5) % predicted, within-group change \( P=NS \); between-group change \( P=NS \)), and nor did REE/FFM (group A, 2.0 (SD 6.0) kcal/kg, within-group change \( P=NS \); group B, \(-3.1(\text{SD } 6.0)\) kcal/kg, within-group change \( P=0.048 \); between-group change \( P=NS \)).

**Discussion**

The present study shows a remarkable difference in response to two different nutritional supplement regimens. Although patients in group A received less energy, they gained more weight than did the patients receiving the commonly used 200 ml portions. Since both nutritional support regimens were incorporated into a pulmonary rehabilitation programme, the proportional gain of FFM was higher than the gain of FM and similar in both groups. FFM was primarily gained during the first 4 weeks of rehabilitation.

The most likely explanation for the difference in weight response between the different portion sizes is a load-related drop in habitual dietary intake. Previous nutritional intervention studies in COPD have shown that patients tend to eat less of their regular meals during nutritional support consisting of liquid supplements (Lewis et al. 1987; Knowles et al. 1988; Creutzberg et al. 2003). Unfortunately, it is virtually impossible to measure changes in dietary intake accurately (Schoeller, 1990), especially during a prolonged intervention period and in conditions such as COPD (Goris et al. 2001) that are characterized not only by clinically stable periods, but also by acute exacerbations that may cause a temporary drop in dietary intake (Vermeer et al. 1997). We therefore did not measure the

### Table 2. Change in body weight, fat-free mass and fat mass and percentage of non-response of the patients during 8 weeks of intervention and rehabilitation

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n ) (M/F)</td>
<td>19 (14/5)</td>
<td>20 (16/4)</td>
<td></td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>3.3** (1.9)</td>
<td>2.0** (1.2)</td>
<td>0.019</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>2.2** (2.0)</td>
<td>1.4* (1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass gain (kg)</td>
<td>1.1* (1.3)</td>
<td>0.8 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-response (%)</td>
<td>10.5</td>
<td>20.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Within-group change (baseline to 8 weeks): *\( P<0.005 \); **\( P<0.001 \).
change in daily dietary intake in the present study. However, as patients from group A increased in weight as predicted by the model of Westerterp et al. (1995), it is not likely that these patients compensated in terms of their habitual intake. On the other hand, the increase in weight in patients from group B was significantly smaller than the predicted value. This may point towards a compensatory adaptation of the regular meals in the patients receiving the 200 ml packages.

A compensation in habitual food intake can result from increased or prolonged satiety after the ingestion of the drink supplements in COPD patients, who already suffer from an increased feeling of bloating and early satiety because of hyperinflation, a flattened diaphragm and a reduction in abdominal volume (Donahoe & Rogers, 1990). Vermeeren et al. (2001) showed that post-prandial satiety sensation was indeed adversely affected by the energy load of nutritional supplements in COPD patients. In elderly hospitalized patients, it has been shown that volume rather than energy density limits the voluntary energy intake of food (Olin et al. 1996), which could largely be overcome by reducing portion size and increasing meal frequency (Barton et al. 2000). A similar observation has also been made in a study in adult patients with cystic fibrosis, which reported that reducing the volume and increasing the frequency of oral nutritional supplements relieved symptoms such as fullness, nausea and bloating (Rettammel et al. 1995).

One of the reasons that smaller portions lead to less satiety may be related to gastric emptying, as more volume in the stomach leads to a prolonged gastric emptying time. Another factor influencing gastric emptying is the fat content of the food ingested, as high-fat meals have been shown to delay gastric emptying in COPD patients (Akrabawi et al. 1996). In the present study, although the macronutrient content was similar in both supplementary regimens, patients in group B received more fat in absolute terms owing to the larger portion size. In addition, the extra volume of the 200 ml supplements could theoretically have had a significant influence on the time needed to empty the stomach and therefore on prolonged feelings of satiety, leading to a drop in intake of regular meals.

The proportion of non-responders defined as patients with a body weight gain of less than 2% (Creutzberg et al. 2000) was not significantly different in the two groups. The in-patient setting of the rehabilitation centre provided the same control over adherence to the nutritional therapy and over the standardization of exercise training for both groups. Creutzberg et al. (2000) previously characterized non-responders by a higher age, an enhanced systemic inflammatory response and a decreased spontaneous dietary intake. In the present study, groups A and B did not differ in the parameters of age, lung function, baseline habitual dietary intake, BMR, relative anorexia and systemic corticosteroid use. Unfortunately, no markers of systemic inflammation were included in this study.

Groups A and B gained FFM and FM in the same ratio, which is indicative of a similar anabolic stimulus. Another indication for this is a similar outcome of the rehabilitation programme, as reflected by a comparable improvement in peak workload during incremental cycle ergometry. Improvements in exercise capacity are, however, not necessarily reflected in increases in FFM, as was observed in the present study (Young et al. 1983; Bernard et al., 1999). To measure improve-

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**Table 3.** Change in exercise capacity and health status during 8 weeks of nutritional intervention as part of pulmonary rehabilitation

<table>
<thead>
<tr>
<th>Change in</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ-Symptom (points)</td>
<td>-9·9† (16·9)</td>
<td>-15·8† (12·9)</td>
<td>NS</td>
</tr>
<tr>
<td>SGRQ-Activity (points)</td>
<td>-7·0‡ (15·2)</td>
<td>4·1 (20·8)</td>
<td>NS</td>
</tr>
<tr>
<td>SGRQ-Impact (points)</td>
<td>-2·7 (13·4)</td>
<td>0·0 (13·9)</td>
<td>NS</td>
</tr>
<tr>
<td>SGRQ-Total (points)</td>
<td>-5·4† (10·7)</td>
<td>-1·4 (13·0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

SGRQ, St George’s Respiratory Questionnaire.
Within-group change (baseline to 8 weeks): †P<0·05; ‡P<0·08.
ments in skeletal muscle function related to increases in FFM, sensitive tests of the lower limb function, such as isokinetic strength testing or magnetic simulation, should be used (Polkey, 2002; Gosker et al. 2003).

This difference in gain in FFM between the two food regimens was most pronounced in the first 4 weeks of rehabilitation. A higher increase in FFM in the first 4 weeks has also been reported in a prior publication by our group (Schols et al. 1995). During the second 4 weeks, a gain predominantly in FM was seen in both studies. This indicates that the timing and harmonization of training to nutritional intervention, for example, by switching the intensity or type of exercise, may be of importance to further optimize the efficacy of nutritional support.

As weight loss is a predictor of mortality in COPD and weight gain has been associated with increased survival (Schols et al. 1998; Prescott et al. 2002), the weight gain of nutritionally depleted patients is of the utmost clinical importance. In the present study, we show that simply decreasing the portion size of nutritional drink supplements from 200 to 125 ml is a useful strategy to increase the efficacy of supplemental nutrition in terms of weight gain in depleted patients with COPD.

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References


