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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; $P=0{\cdot}019$), 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 ($P<0{\cdot}001$). 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.* 1997*b*), 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.* 1997*c*; 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.* 1997*a*).

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 $\leq 21\,kg/m^2$;
2. FFM index ≤ 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 125 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 200 ml cartons per d.

Group A (*n* 19) received three 125 ml cartons of Respifor (2380 kJ = 6·35 kJ/ml; 20 % energy from protein, 60 % from carbohydrate, 20 % from fat; Nutricia BV, Zoetermeer, The Netherlands), whereas group B (*n* 20) received three 200 ml cartons (one Ensini, one Fortimel, one Nutridrink = 3350 kJ = 4·19 kJ/ml; 22·3 % energy from protein, 59·7 % from carbohydrate, 18 % from fat; Nutricia BV) daily for 8 weeks. The supplements were labelled with the name of each individual patient and handed out between regular standardized meals three times per d at standardized times in order to have control over their intake. Except for the nutritional supplement regimens, all circumstances were the same for both groups during rehabilitation. In addition, during the first 2 weeks after admission and before the 8 weeks of rehabilitation, patients received only regular meals from the rehabilitation centre in order to create a standardized starting point for both groups.

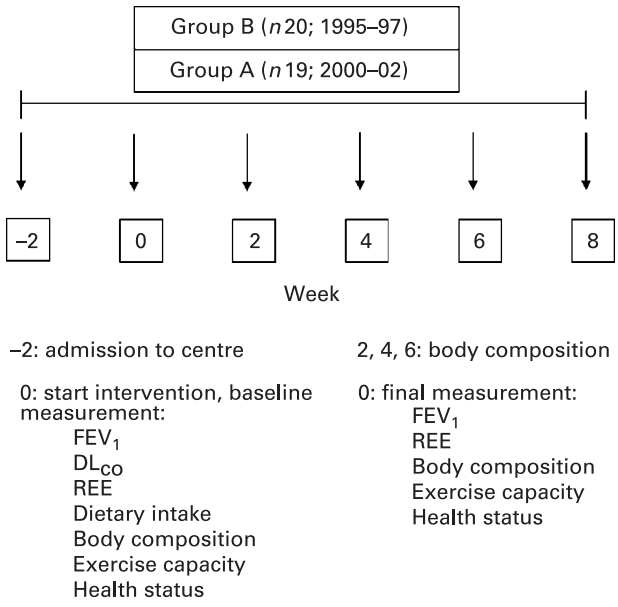

Fig. 1. Patient flow and timing of measurements. FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity for CO; REE, resting energy expenditure.

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.

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. 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 dietitian. Computer nutrient analysis was performed with 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 ($P=0{\cdot}030$). 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 $P<0{\cdot}001$) and FFM (group A, $P<0{\cdot}001$; group B, 0·004) (Table 2). FM was significantly increased in group A ($P=0{\cdot}002$) but not in group B. The patients in group A, however, gained more weight than those in group B ($P=0{\cdot}019$; 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, $P<0{\cdot}001$ *v.* group B 1·2 (SD 2·4) kg, $P=0{\cdot}035$; between groups). FM was primarily gained during the second half of the rehabilitation (group A, 1·1 (SD 1·0) kg, $P<0{\cdot}001$ *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.*

Table 1. Baseline characteristics of groups A and B

	Group A		Group B		
	Mean	SD	Mean	SD	*P*-value
n (M/F)	19	14/5	20	16/4	NS
Age (years)	62·0	11·1	63·5	8·0	NS
FEV_1 (% predicted)	35·7	15·2	35·0	7·3	NS
DL_{co} (% predicted)	44·1	16·5	47·4	20·2	NS
Weight (kg)	57·5	7·7	56·8	5·2	NS
BMI (kg/m^2)	20·1	1·9	19·7	1·8	NS
FFM index (kg/m^2)	15·3	1·0	15·1	1·3	NS
FM (%)	23·6	5·2	23·0	8·0	NS
REE/FFM (kJ/kg)	128	16	140	31	NS
Dietary intake (kJ)	8193	2379	7886	2934	NS
Intake/ REE	1·49	0·49	1·33	0·32	NS
Peak load (W)	57	31	52	15	NS
SGRQ-Symptom (points)	58	16	54	22	NS
SGRQ-Activity (points)	59	22	59	23	NS
SGRQ-Impact (points)	31	11	35	16	0·030
SGRQ-Total (points)	44	12	45	16	NS

FEV_1, forced expiratory volume in 1 s; DL_{CO}, Diffusing capacity for CO; FFM, fat-free mass; FM, fat mass; REE, resting energy expenditure; SGRQ, St George's Respiratory Questionnaire.

(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, −0·7 (SD 5·6) kcal/kg, within-group change $P=$NS; group B, −3·1(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 (Vermeeren *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

	Group A	Group B	*P*-value
n (M/F)	19 (14/5)	20 (16/4)	
Weight gain (kg)	3·3** (1·9)	2·0** (1·2)	0·019
Fat-free mass (kg)	2·2** (2·0)	1·4* (1·9)	NS
Fat mass gain (kg)	1·1* (1·3)	0·6 (1·6)	NS
Non-response (%)	10·5	20·0	NS

Within-group change (baseline to 8 weeks): *$P<0·005$; **$P<0·001$.

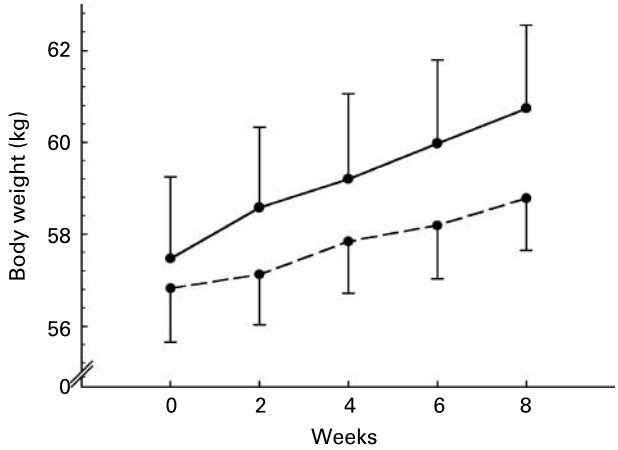

Fig. 2. Course of body weight per 2 weeks during 8 weeks of nutritional therapy. The change in body weight of group A (—; 3·3 (SD 1·9) kg) was significantly higher than that of group B (- - - -; 2·0 (SD 1·2) kg; $P=0·014$).

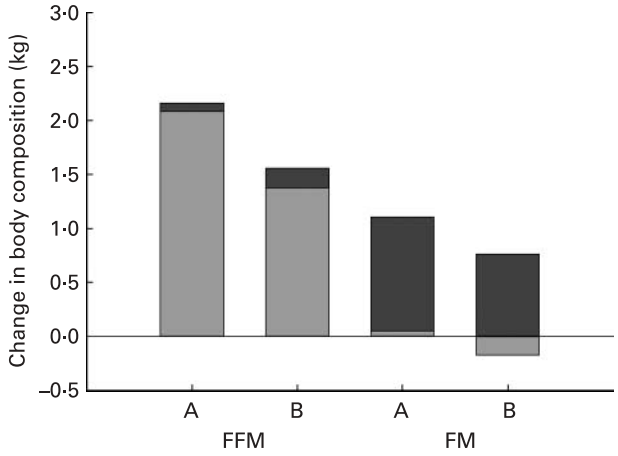

Fig. 3. Change in fat-free mass (FFM) and fat mass (FM) after 4 and 8 weeks of rehabilitation in groups A and B. Patients in group A gained more weight than patients in group B ($P=0{\cdot}019$; see also Table 2). Almost all the FFM was gained during the first 4 weeks of rehabilitation (■). FM was primarily gained during the second half of the rehabilitation (▤).

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

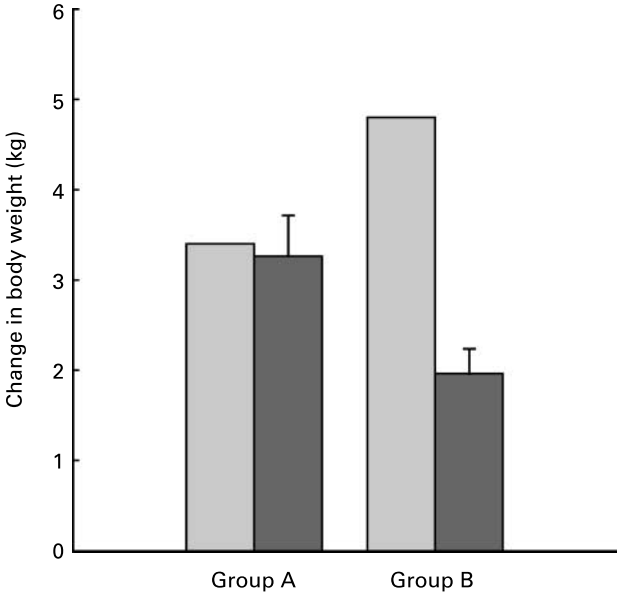

Fig. 4. Observed weight gain (▤) compared with expected weight gain (■) after 8 weeks of nutritional supplementation. The observed body weight gain (3·3 (SEM 1·9) kg) of group A was similar to the expected weight gain (3·4 kg; $P=$NS). In group B, the observed body weight gain (2·0 (SEM 1·2) kg) was significantly less than the expected weight gain (4·8 kg; $P<0{\cdot}001$). Data are presented as mean and SEM.

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

Change in	Group A	Group B	*P*-value
SGRQ-Symptom (points)	−9·9† (16·9)	−15·8† (12·9)	NS
SGRQ-Activity (points)	−7·0‡ (15·2)	4·1 (20·8)	NS
SGRQ-Impact (points)	−2·7 (13·4)	−0·0 (13·9)	NS
SGRQ-Total (points)	−5·4‡ (10·7)	−1·4 (13·0)	NS

SGRQ, St George's Respiratory Questionnaire.
Within-group change (baseline to 8 weeks): †$P<0{\cdot}05$; ‡$P<0{\cdot}08$.

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 postprandial 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-

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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