Dietary management in COPD

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Dietary management in COPD

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The studies presented in this thesis were performed at the Nutrition and Toxicology Research Institute Maastricht (NUTRIM), which participates in the Graduate School VLAG (Food Technology, Agrobiotechnology, Nutrition, and Health Sciences), accredited by the Royal Netherlands Academy of Arts and Sciences (KNAW).

Dietary management in COPD

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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Chapter 1

General introduction

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a disabling condition with progressive and largely irreversible airflow limitation. The characteristic symptoms of COPD are dyspnoea, coughing and sputum production. Chronic airflow limitation characteristic of COPD is caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contributions of these defects vary from person to person. COPD is mostly caused by a long-term smoking history.¹

Recent guidelines for diagnosis and management of COPD are reported by The Global Initiative for Chronic Obstructive Lung Disease (GOLD).^{1,2} GOLD is conducted in collaboration with the US National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). The aims of GOLD are to increase awareness of COPD and decrease morbidity and mortality from the disease.

COPD causes considerable mortality and morbidity worldwide and is predicted to become the fourth leading cause of death and the fifth leading cause of disability by the year 2020.³ In 2000 the prevalence of COPD in the Netherlands was estimated at 2.4% for men and 1.4% for women.⁴ The prevalence of COPD increases with age, with the highest rates seen in people 75 years and older (16% in men and 4.4% in women).⁵ The future burden of COPD that was assessed by a modeling analysis predicted that the prevalence of COPD in 2015 would be increased in men by 59% and in women by 123%. The higher rise in prevalence in females is predominantly due to changed smoking behavior.⁵

The impact of COPD in an individual patient depends largely on the severity of symptoms, especially breathlessness and decreased exercise capacity. Management of COPD is largely symptom driven, and there is an imperfect relationship between the degree of airflow limitation and the experienced symptomatology.⁶

Exacerbations in COPD

Exacerbations occur commonly in patients with moderate to very severe COPD. An exacerbation of COPD means a worsening of one of the common symptoms, like increased dyspnoea and/or cough and sputum volume. Unfortunately, there is no widely accepted definition of "an acute exacerbation of COPD". For the treatment of mild or moderate exacerbations in COPD antibiotics and/or corticosteroids are advised while severe exacerbations require admission to the hospital for medical treatment. Acute exacerbations of COPD are associated with an increase in health-care utilization, number of hospitalizations, and mortality.⁷ Furthermore, a more impaired health status was found in COPD patients with

frequent exacerbations compared with COPD patients with infrequent exacerbations⁸, indicating that the exacerbation rate has a negative influence on health status in COPD.

Nutrition and COPD

Several studies have showed that nutritional status plays an important role in patients with COPD. An increased risk in mortality was found in COPD patients with nutritional depletion.^{9,10} Furthermore, an increased risk of hospitalization¹¹, an early non-elective readmission in COPD patients previously admitted for an exacerbation¹² and decreased survival time following a disease exacerbation¹³ have been found in depleted COPD patients. Nutritional depletion is associated with decreased muscle mass and muscle strength, in respiratory as well as in peripheral muscles, and an impaired exercise tolerance.¹⁴⁻¹⁶ Nutritional depletion is also related to health status^{17,18} in COPD patients: depleted COPD patients reported poorer health status.

Weight loss occurs frequently in COPD patients and is generally approached as an imbalance between energy expenditure and dietary intake. Altered energy and substrate metabolism and/or reduced dietary intake can cause this disturbed energy balance in COPD patients. Muscle wasting, a result of an imbalance between protein synthesis and protein breakdown, is also frequently reported in patients with COPD.^{19,20} The prevalence of nutritional depletion in moderate to severe COPD patients was 35% in patients admitted to a pulmonary rehabilitation center¹⁹ and 20% in an out-patient COPD population.²⁰ Unfortunately, data of the prevalence of nutritional depletion in COPD patients with mild or moderate COPD are still lacking.

Nutritional depletion is defined as a low body weight or as depletion of fat-free mass in patients with COPD.^{9,19} Nutritional intervention is indicated in COPD patients with nutritional depletion, with the aim to improve dietary intake resulting in gain of body weight and/or improvement of body composition.

The GOLD guidelines reported that effective management of COPD should have the following aims: prevention of disease progression, relief of symptoms, improvement of exercise tolerance, improvement of health status, prevention and treatment of complications and exacerbations and reduction of mortality.⁶ As described earlier, several aspects pointed as aims of the treatment, are related with nutritional status. Therefore nutritional screening and intervention should be integrated in a multi-disciplinary approach in patients with COPD.²¹

Nutritional intervention in COPD patients

Several studies have described the effects of nutritional intervention in COPD patients.²²⁻³³ The best effects of nutritional intervention in patients with COPD are

reported when nutritional support was incorporated in a multi-disciplinary pulmonary rehabilitation program.^{9,22,33} Besides weight gain, an increase in FFM was accompanied with improvement of functional performance and better health status.^{22,33} When body weight increased by more than 2 kg during the rehabilitation program of 8 weeks, a decreased risk of mortality was found.⁹ The results about the effectiveness of nutritional support at home in COPD patients are less convincing. When nutritional intervention was started during a hospitalization period and continued at home, the results were better^{27,28} compared with nutritional support in the home setting alone.^{22-24,29,30}

During acute exacerbations of COPD little is known concerning the effectiveness of nutritional intervention. Till now, only one study has described in a controlled design the effects of nutritional intervention during an acute exacerbation in hospitalized COPD patients.³¹ No significant improvement was found in body weight, inspiratory and peripheral muscle strength, but a trend was observed in improvement in well-being score.³¹ Besides a disturbed energy balance, COPD patients may be at increased risk for a negative nitrogen balance during an acute exacerbation, due to an enhanced systemic inflammatory response, high dose of systemic glucocorticoids, immobility and low protein intake. Only two studies have yet measured nitrogen balance in hospitalized COPD patients with an acute exacerbation.^{31,34} Both studies reported a negative nitrogen balance during an acute exacerbation of COPD and a negative correlation between high dose of methylprednisolone and nitrogen balance ($r=-0.73$, $p=0.0048$) was found.³¹ The efficacy of nutritional support during a period of negative nitrogen balance in terms of functional improvement depends on whether predominantly protein synthesis is decreased or whether there is accelerated protein breakdown. Protein supplementation will theoretically increase protein synthesis but not affect protein breakdown. During periods of acute protein breakdown this type of nutritional intervention will therefore not be able to induce a positive protein balance, but could limit the catabolic state.

Ventilation and nutrition are related since oxygen and nutrition are essential for life and participate in oxidative metabolism. Postprandial changes in $\dot{V}O_2$ and $\dot{V}CO_2$ appear after ingestion of nutrition³⁵ and the composition of nutrition may influence the ventilatory load. Nutritional intervention might therefore have adverse effects in patients with COPD and since the current information is limited, further investigation is needed.

Aims of the thesis

Although the importance of nutritional intervention is acknowledged, some important aspects concerning optimal implementation of nutritional support are still lacking in COPD patients.

The aims of the thesis addressed the current lack of dietetic information in COPD patients.

The aims of the thesis were:

1. to investigate the prevalence of nutritional depletion in an out-patient population of COPD patients.
2. to investigate the potential adverse effects of nutritional supplementation in patients with COPD and related factors accompanied with limited effectiveness of nutritional support.
3. to investigate the influence of exacerbations on nutritional profile and the feasibility of nutritional supplementation during hospitalization for an acute exacerbation of COPD.

Outline of the thesis

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In this thesis, firstly the results of the studies during the stable phase of the disease are described (chapter 2-5). Secondly the studies during hospitalization for an acute exacerbation of COPD are presented (chapter 6 and 7).

Stable disease condition

The prevalence of nutritional depletion in COPD patients was investigated in a large multi-centre out-patient COPD population in the Netherlands (chapter 2).

An important issue of nutritional supplements is the postprandial effects of supplements on exercise and symptoms in patients with COPD. For daily clinical practice, it is important to find out the optimal disease-related nutritional support strategy that improves muscle function but minimally interferes with symptoms and activity pattern. We therefore examine in chapter 3 the effects of a liquid oral nutritional supplement in different, but clinically applicable energy contents, on symptoms and exercise capacity. Furthermore the effects of a carbohydrate-rich versus a fat-rich supplement, at the most optimal energy load, on symptoms and exercise capacity in patients with COPD were investigated (chapter 3). Based on the difference in macronutrient content of the supplements described in chapter 3, two test meals were composed to investigate the influence of different solid meals on gastric emptying. We hypothesized that delayed gastric emptying may

occur in COPD patients with severe hyperinflation and this might be more pronounced after a fat-rich meal relative to a carbohydrate-rich meal. Besides rate of gastric emptying, several postprandial signs were measured in COPD patients and compared with a healthy control group (chapter 4).

Nutritional support in COPD patients in the community is less effective and several contributing factors can influence efficacy negatively. For instance, the influence of physical activity rate on energy balance in COPD patients at home is unknown. This issue was evaluated in COPD patients during a period of three months at home and the data are described in chapter 5.

Acute disease exacerbations

In chapter 6 the metabolic profile of COPD patients admitted to the hospital for an acute exacerbation are described. In addition, the next step was a study to improve energy and protein intake in depleted COPD patients admitted to the hospital for an acute exacerbation. This study was performed in a randomized double-blind, placebo-controlled clinical trial in two centers and is presented in chapter 7.

In chapter 8 the results and conclusions presented in this thesis are discussed and implications for future investigations are given in the general discussion.

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Chapter 2

Prevalence of nutritional depletion in a large out-patient population of patients with chronic obstructive pulmonary disease

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Submitted

Abstract

Introduction

Nutritional depletion and muscle dysfunction commonly occur in patients with chronic obstructive pulmonary disease (COPD). The present study focuses on the prevalence of nutritional depletion in relation to functional performance, airflow limitation, experienced dyspnoea and health status in a large multi-center out-patient population with moderate to severe COPD.

Methods

In 39 out-patient centers in the Netherlands, 389 patients with moderate to severe COPD (217 men) were recruited. The study evaluated baseline characteristics of the COSMIC study. Measurements included lung function by spirometry, body composition by bio-electrical impedance analysis, dyspnoea by MRC-score and peripheral muscle function by isometric handgrip strength. Disease-specific health status was assessed by St. George Respiratory Questionnaire (SGRQ).

Results

The prevalence of nutritional depletion (defined as body mass index (BMI) ≤ 21 kg/m² and/or fat-free mass index (FFMI) ≤ 15 (females) or ≤ 16 (males) kg/m²) was high (27%). Prevalence of different categories of depletion, 73% normal BMI and normal FFMI, 15% only low FFMI, 1% only low BMI and 11% low BMI and low FFMI. The prevalence of low BMI as well as low FFMI was significantly higher in female than in male COPD patients, 18% and 40% versus 10% and 20% respectively (both $p < 0.01$). No differences in FEV₁ %predicted, dyspnoea score and health status were observed between depleted and non-depleted COPD patients. Multiple regression analysis in the total group, showed that handgrip strength correlated with FFMI after correction for sex distribution and age ($r = 0.22$, $p < 0.001$), but not FEV₁ %predicted.

Conclusions

The prevalence of nutritional depletion was high in a large out-patient COPD population in the Netherlands, especially in female COPD patients. Depletion of FFM was associated with impaired peripheral muscle strength, independently of disease severity.

Introduction

Nutritional depletion commonly occurs in patients with chronic obstructive pulmonary disease (COPD). Its prevalence is increasing from 20% in clinically stable out-patients¹ up to 35% in patients eligible for pulmonary rehabilitation.² Whole body muscle wasting, and in particular muscle wasting of the extremities frequently occurs in patients with COPD.³ Furthermore, depletion of fat-free mass (FFM) may even occur in normal-weight COPD patients.² Loss of FFM, as an indirect measure of muscle mass, adversely affects respiratory and peripheral muscle function¹, exercise capacity², health status⁴, and even mortality rates.⁵ Thus nutritional depletion has an important impact on COPD.

At this moment, most studies concerning the prevalence of depletion in COPD patients have been performed in selected populations such as patients eligible for pulmonary rehabilitation, hospitalized patients, patients undergoing lung volume reduction surgery (LVRS) or treated with long-term oxygen therapy.^{2,6-11} Only Engelen et al has described the prevalence of depletion in an out-patient population.¹ However, this study had a small sample size and was performed in a single-center.

To our knowledge, no data have been published on the prevalence of muscle wasting in COPD in a large out-patient multi-center setting. Furthermore it is yet unclear if nutritional depletion and thereby reduced muscle function are associated with the severity of airflow limitation or with other factors like gender, age and clinical symptoms or quality of life.

The present study therefore investigates the prevalence of nutritional depletion in relation to functional performance, airflow limitation, dyspnoea, and health status in a large out-patient COPD population. This study was applied on the baseline characteristics of the COSMIC (COPD and Seretide: a multi-center intervention and characterization) study; a double-blind, parallel group study on the efficacy of the salmeterol/fluticasone combination product in comparison with salmeterol alone in patients with moderate to severe COPD.

Methods and materials

Patients

In 39 out-patient centers in The Netherlands, patients were recruited to participate in the COSMIC study. Inclusion criteria were:

1. age 40-75 years
2. an established clinical history of COPD

3. current or ex-smokers with ≥ 10 pack years
4. pre bronchodilator FEV_1 %predicted: 30-70 %predicted
5. reversibility after inhalation of a β_2 -agonist (400 μ g salbutamol): $< 10\%$ FEV_1 %predicted
6. history of at least two COPD exacerbations in the last year requiring oral corticosteroids and/or antibiotics.

Patients were excluded if they were suffering from respiratory diseases other than COPD or other disorders, if they required regular oxygen therapy or maintenance systemic corticosteroids or if there was evidence for alcohol, drug or solvent abuse.

The study was approved by a central medical ethics committee in The Netherlands and by the local medical ethics committees of the participating centers. All subjects gave written informed consent.

Lung function

Forced expiratory volume in one second (FEV_1) was calculated from the flow volume curve measured by spirometry. The highest value from at least three technically acceptable spirometric maneuvers was used and expressed as percentage of reference value.¹²

Disease severity

Disease severity was defined according to the currently published GOLD guideline¹³ and updated supplement.¹⁴ We divided our patients on base of post bronchodilator FEV_1 into stage 2, moderate COPD: FEV_1 50-80 %predicted and with or without symptoms; and stage 3, severe COPD: FEV_1 30-50 %predicted and with or without symptoms. According to the inclusion criteria, patients with GOLD stage 1 and 4 did not participate in the study.

Body weight and body composition

Body height was determined to the nearest 0.5 cm with subjects standing barefoot. Body weight was assessed with the beam scale to the nearest 0.1 kg, with subjects standing barefoot and in light clothing. Body mass index (BMI) was calculated as body weight in kg/(height in m)². Depletion of body weight was defined as $BMI \leq 21$ kg/m².⁵ Body composition was estimated using single frequency (50 kHz) bio-electrical impedance analysis (Bodystat 1500, Bodystat Ltd., Douglas, Isle of Man, Britian) while subjects were in supine position. The measurements were performed by trained personnel. FFM was calculated from COPD- and gender-specific regression equations.¹⁵ FFM depletion was defined as FFM index (FFMI: FFM in kg/(height in m)²) ≤ 15 (females) or ≤ 16 (males) kg/m².² Fat mass (FM) was calculated by subtracting FFM from body weight. FM index (FMI) was calculated as FM in kg/(height in m)². Patients were divided in four different categories based on BMI and FFMI: normal BMI and normal FFMI; normal BMI and low FFMI; low BMI and normal FFMI; low BMI and low FFMI.²

Peripheral muscle function

Peripheral muscle function was assessed by isometric handgrip strength using a hand-held dynamometer (JAMAR, Preston, Jackson, Michigan, USA). The isometric grasp was determined by measuring the maximally developed strength of the flexors of the right and left hand respectively. The highest value of three maneuvers was used. The mean of the highest value per hand was used in the analysis.

Dyspnoea

Experienced breathlessness was assessed by the Medical Research Council (MRC). The MRC dyspnoea scale is a validated and simple questionnaire (16) that consists of five statements: grade 1, "I only get breathless with strenuous exercise"; grade 2, "I get short of breath when hurrying on the level or up a slight hill"; grade 3, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"; grade 4, "I stop for breath after walking 100 meter or after a few minutes on the level"; grade 5, "I am too breathless to leave the house". The patients selected the grade that applied to them. MRC-score 3, 4 and 5 were classified as having severe dyspnoea, corresponding with moderate to severe disability.¹⁶

Disease-specific health status

Disease-specific health status was measured by the St. George's Respiratory Questionnaire (SGRQ), with the domains: symptoms, activity, impact and total.¹⁷ The SGRQ is a broadly used and well validated questionnaire for the assessment of health status in COPD. A higher score of SGRQ means greater impairment in health status.

Statistics

To analyze possible associations between the different parameters, Pearson product moment correlation coefficients were calculated. When appropriate, partial correlation coefficients were calculated to control for the influences of gender distribution and age. ANOVA was used with age and sex as covariates to explain the differences between depleted and non-depleted COPD patients in handgrip strength and health status. A linear stepwise regression model was applied on the data to reveal which variables independently contributed to the variation in handgrip strength in the patients.

A p-value of less than 0.05 was considered statistically significant. Data were expressed as mean $\pm$ SD or as median (range) in the text and tables. The statistical analyses were performed using the Statistical Product and Service Solutions (SPSS, version 11.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

The study group consisted of 389 patients with COPD (271 men, 70%); table 2.1 shows the characteristics of patients with COPD. According to the GOLD guidelines, the study group represented 214 patients with GOLD stage 2 (55%) and 175 patients with GOLD stage 3 (45%).

Table 2.1 Characteristics of the total out-patient COPD population

	n = 389
Male/female	271 / 118
Age, years	63 ± 7
FEV ₁ , %predicted	51 ± 11
Body Mass Index, kg/m ²	26.1 ± 4.3
Fat-free mass index, kg/m ²	17.2 ± 2.2
Fat mass index, kg/m ²	8.8 ± 2.8

Data are mean±SD; FEV₁: forced expiratory volume in one second post bronchodilator

Prevalence of depletion

The prevalence of nutritional depletion (defined as BMI ≤21 kg/m² and/or FFM I ≤15 (females) or ≤16 (males) kg/m²) was 27% in the total study population. When assessing different types of depletion, 73% of the COPD population had normal BMI and normal FFM I, 15% normal BMI and low FFM I, 1% low BMI and normal FFM I and 11% low BMI and low FFM I. No differences in the prevalence of nutritional depletion between GOLD stage 2 and GOLD stage 3 were observed. The prevalence of the different nutritional depletion combinations in male and female COPD patients is presented in figure 2.1. Depletion of body weight was significantly more present in female (18%) than in male (10%) COPD patients, p<0.01. The prevalence of FFM depletion was significantly higher in female COPD patients (40%) than in males (20%), p<0.001. In 25% of the female COPD patients FFM depletion with body weight preservation occurred, which was significantly higher than in males (11%), p<0.05.

Figure 2.1 The prevalence of different depletion categories stratified by gender

Factors related to nutritional depletion

FEV₁ %predicted and age were similar in depleted COPD patients relative to non-depleted COPD patients. Gender distribution was significantly different between depleted and non-depleted COPD patients ($p<0.01$). Therefore adjustment for gender distribution was applied in further analyses.

Table 2.2 Characteristics of COPD patients stratified by nutritional depletion

	Non-depleted COPD patients	Depleted COPD patients
	n = 283	n = 106
Male/female	215 / 68	56 / 50*
Age, years	63 ± 7	62 ± 7
FEV ₁ , %predicted	51 ± 11	51 ± 12
Handgrip strength, kg	38 ± 11	31 ± 9**
Severe dyspnoea, % of patients	40	41
	n = 273	n = 102
SGRQ – symptoms	57 (11-91)	54 (22-91)
SGRQ – activity	58 (0-100)	59 (11-100)
SGRQ – impact	26 (0-68)	26 (3-73)
SGRQ – total score	40 (1-76)	40 (16-72)

Data are mean±SD and median (range); FEV₁, forced expiratory volume in one second post bronchodilator; severe dyspnoea defined as score of 3-5 by MRC scale; * $p<0.01$ for gender distribution, ** $p<0.01$ after adjustment for gender distribution and age

Patients suffering from depletion were characterized by a significantly lower handgrip strength compared to non-depleted patients, as shown in table 2.2. Dyspnoea score and health status did not significantly differ between depleted and non-depleted COPD patients.

Factors related to handgrip strength

Mean handgrip strength significantly correlated with FFMI after adjustment for gender and age, $r=0.22$, $p<0.001$ (figure 2.2).

Stepwise regression analyses showed that gender, age and FFMI independently explained 51% of the variation in handgrip strength in the total patient group, while FMI and FEV₁ %predicted were excluded from the model (table 2.3).

Figure 2.2 The correlation between handgrip strength and FFMI, after correction for gender distribution and age, $r=0.22$, $p<0.001$. Open circles, females; closed circles, males

Table 2.3 Stepwise regression analysis to assess independent variables to explain the variation in handgrip strength (kg)

Prediction variables	Effect	Cumulative R ²	p-value
Sex, male/female	15.2	0.43	<0.001
Age, years	-0.35	0.48	<0.001
Fat-free mass index, kg/m ²	0.8	0.51	<0.001
Fat mass index, kg/m ²			NS
FEV ₁ , %predicted			NS

Discussion

This study shows that the prevalence of nutritional depletion in a large out-patient COPD population in The Netherlands is high: in 27% of the COPD patients, recruited with FEV₁ between 30-70 %predicted, body mass and/or fat-free mass was depleted. Independently of disease severity, depletion of FFM was significantly correlated with impaired peripheral muscle strength. In this study, the prevalence of nutritional depletion in female patients with moderate to severe COPD was more pronounced.

The prevalence of nutritional depletion in a large out-patient COPD population by body compositional analysis has not been reported previously. Compared with the study of Engelen et al¹, the prevalence of nutritional depletion was quite similar (21%), but lower relative to the prevalence found in the study of Schols et al (45%).² The latter discrepancy can be due to more severe COPD being present in the study of Schols et al. Remarkably, the 26% prevalence of FFM depletion in combination with BM preservation in our study was higher than in the study of Engelen (18%).¹ This may be explained by different inclusion criteria of the

studies. The COSMIC study population was selected by more than 2 exacerbations accompanied with corticosteroid or antibiotic treatment in the previous 12 months. It can be hypothesized that frequent treatment with systemic corticosteroid may induce protein catabolism adversely affecting skeletal muscle function. In cross sectional studies no relationship was found between depletion of FFM and systemic corticosteroid use^{18,19}, but Bernard and coworkers showed that the ratio muscle function and muscle mass tended to be lower in COPD patients exposed to systemic corticosteroids.²⁰ Little is known about changes in body composition due to exacerbations in COPD patients. There are two studies reporting body composition during hospitalization for an acute exacerbation in COPD patients^{21,22} and it seems that FFM depletion with preservation of BM occurs frequently in hospitalized COPD patients.^{21,22} An acute exacerbation has been shown to be accompanied with higher levels of inflammatory mediators^{22,23} and different reports suggested a relationship between the presence of depletion and increased systemic inflammatory status.^{24,25} The observed higher prevalence of nutritional depletion in our study might thus possibly be explained by the higher exacerbation rate accompanied with an impaired chronic inflammatory response and altered body composition. Otherwise, the exacerbation rate in our population is not exceptional high, since a comparable exacerbation rate of 2.4 per patient per year has been previously reported in a cohort of 101 COPD patients with mean $\pm$ SD FEV₁ of 42 $\pm$ 19 %predicted.²⁶ Still we cannot fully rule out that the inclusion criterion is a confounder of the reported prevalence in the current study.

Nutritional depletion has been shown to be associated with adverse effects on respiratory and peripheral muscle function, on exercise capacity and on health status.^{1,2,4,27-30} In the current study the association between nutritional depletion and peripheral muscle strength was confirmed and appeared to be independent of disease severity. Besides FFM depletion, age and especially gender were found to be independent predictors of muscle weakness in COPD. Further, in contrast to the studies concerning impaired health status in depleted COPD patients^{4,30}, we found no significant or clinically relevant differences in any score of SGRQ nor in the dyspnoea score between depleted and non-depleted COPD patients. The former could be explained by the less impaired airflow limitation in the majority of our study population. A recent study in COPD showed that the threshold for worsening of health status lies at FEV₁<50 %predicted.³¹

Till now, COPD is predominantly considered as a "male" disease, but the prevalence of COPD will become even higher in females than in men, predominantly due to the changed smoking behavior.³²⁻³⁴ Given this increased prevalence of COPD in females, it is worthwhile to consider possible gender differences in COPD patients, as has been proposed by other authors.^{35,36} An increased risk of hospitalization has been reported previously in female COPD patients.³⁷ We found in our study that FFM depletion occurred more frequently in female than in male COPD patients. Gender differences in body composition have been found in earlier studies.^{1,2} Engelen and coworkers also reported a higher prevalence of nutritional depletion in women (35%) than in men (16%)¹ and values in the study of Schols et al printing in the same direction i.e. 42% and 34%,

respectively.² A higher nutritional depletion in females could also exist if females had more severe COPD. However, in our study the female COPD patients had even a better mean FEV₁ %predicted (54 ± 13 %predicted) compared to males (49 ± 12 %predicted). Recently, several systemic effects in patients with COPD have been described.³⁸ Nutritional depletion has been associated with lower diffusion capacity³⁹ and with systemic inflammation in COPD patients.³⁹⁻⁴¹ Therefore female COPD patients in our study might have lower diffusion capacity or increased inflammatory response, underlying the observed gender difference. Further research is required to unravel gender differences and its consequences in patients with COPD.

The prevalence of FFM depletion in our study (26%) is higher than in the other study, reporting values of 18% in an out-patient COPD population.¹ This discrepancy can be explained by differences in disease severity, but also by differences in the used formula to calculate FFM. We used a disease and gender specific formula¹⁵ and in earlier reported studies^{1,2} a disease specific formula was used.⁴² In comparison with reference values of FFMI in healthy female subjects⁴³ the FFMI cut-off point in female COPD patients might be high, 15 versus 14.6 kg FFM/m² (10th percentile of healthy female subjects).⁴³ However, using the FFMI cut-off point of healthy female subjects (14.6 kg FFM/m²)⁴³, the prevalence of FFM depletion in our study population remains high, namely 30%.

In conclusion, the prevalence of nutritional depletion in our COPD population is high, and especially so in female COPD patients. The presence of nutritional depletion was not associated with lower levels of FEV₁ %predicted. Peripheral muscle weakness was associated with nutritional depletion and gender and age were also found as independent predictors of muscle weakness. Assessment of body composition additional to body weight is therefore necessary in all patients with COPD, independently of the stage of disease severity. Since depletion of FFM is an important determinant of functional capacity in COPD patients, (early) detection is essential in clinical practice.

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Chapter 3

Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease

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Abstract

Background

Use of nutritional supplements in depleted patients with chronic obstructive pulmonary disease (COPD) requires optimization between positive effects on outcome and potential acute adverse effects on metabolism and exercise performance.

Objective

The aim of this study was to investigate the acute effects of nutritional supplements on metabolism and exercise capacity in stable COPD patients.

Design

In part 1, the effects of 3 different energy loads (placebo, 1046 kJ, and 2092 kJ) with a normal distribution of macronutrients were investigated in 14 COPD patients. In part 2, the effects of a fat-rich compared with a carbohydrate-rich supplement (both 1046 kJ) were studied in 11 COPD patients. The study was performed in a randomized, double-blind, cross-over fashion. Metabolic and ventilatory variables were measured postprandially and during a submaximal cycle endurance exercise test.

Results

Overall, no immediate negative effects of the supplements were found in part 1. A slight but significant postprandial increase in respiratory quotient was found after the 1046 kJ and 2092 kJ supplements compared with placebo. There was no significant difference in metabolism or exercise capacity after a fat-rich or carbohydrate-rich supplement. Surprisingly, the change in shortness of breath (postprandial compared with preprandial) was significantly greater after the fat-rich supplement.

Conclusions

An energy load up to 2092 kJ had no adverse immediate effect in COPD patients compared with placebo. The subjects who consumed the fat-rich supplement experienced more shortness of breath than did the subjects who consumed the carbohydrate-rich supplement.

Introduction

The association between weight loss and chronic obstructive pulmonary disease (COPD) has long been recognized. In the 1960s, several studies reported that a low body weight and weight loss were negatively associated with survival in COPD.¹ Adverse effects of weight loss and, in particular, loss of the fat-free mass component on skeletal muscle function and exercise capacity were reported extensively.² Weight loss results from an imbalance between dietary intake and energy expenditure. An elevated resting energy expenditure (REE)³ is reported in COPD, as well as an elevated total daily energy expenditure.⁴ The latter is related to the increased oxygen cost of breathing and possibly also to a decreased mechanical and metabolic efficiency.⁵ Therefore, patients with COPD can lose weight despite an apparently normal dietary intake. Besides, symptoms that occur frequently, such as dyspnoea and fatigue, as well as an elevated systemic inflammatory response, are reported in relation to a decreased appetite and dietary intake.^{6,7} So when optimal adaptation of dietary habits fails to improve dietary intake to preserve body weight, nutritional supplements are commonly indicated. To improve functional capacity, nutritional support should be combined with an anabolic stimulus. Indeed, nutritional support as an integrated part of a pulmonary rehabilitation program results in improvements in muscle function, exercise capacity and health status.⁸

In supplemented COPD patients, potential adverse effects on the ventilatory system of the nutritional support strategy also have to be considered. Nutrition and ventilation are intrinsically related because oxygen is required for optimal energy exchange. Meal-related dyspnoea and limited ventilatory reserves may restrict the quantity and composition of nutritional support in patients with respiratory disease.

It was suggested that carbohydrate-rich supplements would induce greater ventilation as a result of a higher respiratory quotient (RQ). In clinically stable patients with COPD, 3 studies⁹⁻¹¹ compared the acute effects of high-energy (3849 kJ) nutritional supplements with high and low carbohydrate contents, respectively, on immediate postprandial energy metabolism at rest and during exercise. For instance, Efthimiou et al⁹ found adverse effects of supplements on exercise performance. However, the energy content of the supplements was even higher than that of a normal meal and would therefore be difficult to incorporate into the daily pattern of meal consumption without affecting spontaneous food intake.

It is important in daily clinical practice to find out the optimal disease-related nutritional support strategy that improves muscle function but interferes minimally with symptoms and activity pattern. The first aim of the present study was therefore to examine the effects of liquid oral nutritional supplements with different, but clinically applicable, energy contents on symptoms and exercise capacity. The second aim was to compare the effects of a carbohydrate-rich with a

fat-rich supplement, at the most optimal energy load, on symptoms and exercise capacity in patients with COPD.

Subjects and methods

Study population

The study group consisted of patients with COPD participating in an in-patient pulmonary rehabilitation program. The patients were in a clinically stable condition, patients with signs of an airway infection were excluded. Other exclusion criteria were cardiovascular, neurologic, or endocrine diseases or locomotor limitations and a resting arterial oxygen tension <7.3 kPa or the need for oxygen supplementation. In part 1, 14 patients (10 men) and in part 2, 11 patients (9 men) participated in and completed the study. Patient characteristics are summarized in table 3.1. No subject participated in both studies. All subjects were fully informed of the aims and the procedures of the study and gave written informed consent. The ethical committee of Maastricht University approved the study. The procedures followed were in accord with the Helsinki Declaration of 1977, as revised in 1983.

Table 3.1 Physiological, pulmonary and metabolic characteristics of the study group

	Part 1 n = 14	Part 2 n = 11
Male / female	10 / 4	9 / 2
Age, years	65 $\pm$ 11	62 $\pm$ 8
Weight, kg	58.9 $\pm$ 6.1	66.5 $\pm$ 7.2*
BMI, kg/m ²	20.6 $\pm$ 1.4	22.6 $\pm$ 2.3*
FFMI, kg/m ²	16.0 $\pm$ 1.3	16.6 $\pm$ 1.8
FEV ₁ , %predicted	36 $\pm$ 7	34 $\pm$ 12
IVC, %predicted	86 $\pm$ 16	90 $\pm$ 16
FVC, %predicted	82 $\pm$ 14	87 $\pm$ 19
TLC, %predicted	127 $\pm$ 24	125 $\pm$ 23
ITGV, %predicted	161 $\pm$ 24	166 $\pm$ 44
Raw, %predicted	225 $\pm$ 82	230 $\pm$ 113
DLco, %predicted	45 $\pm$ 13	64 $\pm$ 42
PaO ₂ , kPa	9.5 $\pm$ 1.4	10.1 $\pm$ 1.2
PaCO ₂ , kPa	5.6 $\pm$ 1.2	5.5 $\pm$ 0.5
SaO ₂ , %	94.7 $\pm$ 1.2	94.8 $\pm$ 1.7
Wmax, watt	61 $\pm$ 20	71 $\pm$ 30

Data are mean $\pm$ SD; * $p < 0.01$ (independent student's t-test). FEV₁, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; FVC, forced vital capacity; TLC, total lung capacity; ITGV, intrathoracal gas volume; Raw, airways resistance; DLco, diffusion capacity of carbon monoxide; Wmax, maximal power on cycle ergometer test

Study design

The first aim of the study was to test the effects of 2 different clinically applicable energy loads (1046 and 2092 kJ compared with placebo) on symptoms, lung function, and exercise capacity (part 1). Second, the effects of a high-carbohydrate compared with a high-fat supplement on symptoms, lung function and exercise capacity were investigated at the most optimal energy load (1046 kJ) (part 2). The nutritional supplements were administered in a randomized, double-blind and cross-over fashion. The composition of the nutritional supplements, which were given as drinks with an equal volume of 200 mL are shown in table 3.2.

Table 3.2 Energy profile and composition of the different food supplements

	Part 1		Part 2	
Composition	Normal ^a	Normal ^b	CHO-rich ^c	Fat-rich ^d
Energy profile	1046 kJ	2092 kJ	1046 kJ	1046 kJ
Energy% protein	21	21	20	20
Energy% fat	34	36	20	60
Energy% CHO	45	43	60	20

Ingredients: ^a154 g nutridrink®, 10 g protifar®, ^b117 g nutridrink®, 35 g protifar®, 40 g maltodextrin/fat mixture®, ^c179 g respifor®, ^d90 g pulmocare®, 12 g protifar®, 17 g solagen®

The placebo was a mixture of coffee creamer and lemon syrup with an energy load of 209 kJ. There was no more than 1 day between the study days. The measurements were done within 2 weeks after the patients completed an incremental bicycle ergometer test. The administration of medication was standardized on the study days. Also, a breakfast with the same composition was given every study day at the same time (07.30h). The study design for both studies is shown in figure 3.1.

Part 1

The experiment started 2 hours after breakfast, at 9.30h. Patients had to ingest the supplement in 15 minutes. Fifteen minutes after the supplement was consumed pulmonary function was measured and 30 minutes after the supplement was finished the exercise test began.

Part 2

The procedure followed in part 2 was exactly the same as that in part 1, except that blood glucose was analyzed as well. Furthermore, the patients had to ingest the supplement in a 5 minutes because differences in gastric emptying might have influenced the results if patients drank the supplements at different speeds.

Pulmonary function

The flow-volume curve was measured by using a flow screen (Masterlab, Jaeger, Wurzburg, Germany). Forced expiratory volume in 1 second (FEV₁), inspiratory

vital capacity (IVC), forced vital capacity (FVC), mean expiratory flow (MEF), and peak expiratory flow (PEF) were calculated from the flow-volume curve. The highest value of ≥ 3 measurements was used for analysis. The values were expressed as a percentage of the reference value.¹²

Symptoms

Using a visual analogue scale (VAS), the patients reported about the following symptoms: shortness of breath, satiety, and pain in the legs. The severity of the symptoms was assessed before and after administration of the supplements and before and after the exercise test. The symptom pain in the legs was scored only before and after the exercise test.

Oxygen saturation

During the study, transcutaneous oxygen saturation (StO_2) was measured with a pulse oxymeter. The electrode was placed around a finger of the left hand of the subject. Measurements were done with a SaO_2 monitor (Fastrac; Sensor medics, Anaheim, California), which is attached to a printer that automatically registers the lowest measured oxygen saturation value every minute.

Submaximal cycle ergometer test

Submaximal exercise testing was performed on an electrically braked cycle ergometer (Examiner 400, Lode, Groningen, The Netherlands). Patients began to exercise at 50% of the maximal cycled load (W_{max}) for 10 minutes. When the patients had performed this exercise, the workload was increased to 70% of W_{max} .¹³ The patient cycled as long as possible but for a maximum of 30 minutes. Mechanical efficiency was calculated by using this submaximal exercise testing protocol. The maximal endurance time was also noted. The mean values of oxygen consumption ($\dot{V}\text{O}_2$) and carbon dioxide production ($\dot{V}\text{CO}_2$) during the last 3 minutes at 50% of W_{max} were taken to calculate the net mechanical efficiency after adjustment for the individual REE.¹⁴

Metabolic and ventilatory parameters and heart rate

Metabolic and ventilatory variables were measured in expired air by using a breathing mask (Oxycon Beta, Jaeger, Wurzburg, Germany). The device was calibrated before each test. Simultaneously heart rate was registered every minute by using a sporttester (PE 3000, Polar electrocy, Kempele, Finland).

Biochemical parameters

A venous blood sample was taken to measure plasma lactate concentration. Blood was collected in a vacuum tube (Vacutainer, Becton Dickinson, New Jersey). The blood samples were stored on ice (4°C) and centrifuged during 5 minutes at 3000 rpm (Sigma 2-15, Lameris, Breukelen, The Netherlands). Plasma lactate concentration was determined by an enzymatic method with use of an automated system (Cobas Mira, Roche, Basel, Switzerland). Plasma lactate was measured at

rest, every 2 minutes during exercise, and once during recovery (2 minutes after completion of the test). In part 2, a venous catheter was placed in the forearm to obtain venous blood samples. These venous blood samples were analyzed for glucose concentration to monitor gastric emptying and lactate concentration indirectly.

Time	9.45	10.00	10.30	10.45	11.15	11.25	11.45	Recovery
Flow-volume	X	supplement	X					
Symptoms	X		X	X				X
StO ₂	every minute							
VO ₂ , VCO ₂ , V _E			every minute					
Heart rate			every minute					
Glucose			X	every 10 minutes			X	
Lactate			X	every 2 minutes			X	
Peak work rate					50% of Wmax	70% of Wmax		

Figure 3.1 Study design

Statistics

The data were analyzed to evaluate the effects of the nutritional supplements on pulmonary function and to examine the endurance and the metabolic, cardiovascular, and subjective responses to exercise. The mean response of $\dot{V}O_2$, $\dot{V}CO_2$, RQ, minute ventilation (V_E) and heart rate was measured 30 minutes after the supplement was consumed and was calculated over 35-40, 40-50, 50-60 minutes, the last 3 minutes while cycling at 50% of Wmax, and the last minute of the exercise test. Oxygen saturation was measured before and after the supplement was consumed and the mean saturation was calculated over 0-5, 5-10, 10-15, 15-30, 30-40, 40-50, 50-60 minutes after the supplement, the last 3 minutes while cycling at 50% of Wmax, and the last minute of the exercise test. The difference in response to the 2 nutritional supplements was assessed at each time interval in every patient. For comparison between the different supplements, analysis of variance (ANOVA) was used with postprandial value as the dependent variable, with treatment and period as fixed factors, and with patient as a random factor. If appropriate, the corresponding baseline value was used as a covariate (analysis of covariance). In part 1, if the results of treatment were significantly different, a post hoc Tukey test was performed. For comparison of the baseline characteristics of the subjects before each test an independent Student's t-test was used. A p-value of <0.05 was considered significant. All measured variables are expressed as mean $\pm$ SD, except when mean $\pm$ SEM are used in the figures.

Results

Part 1

Comparison of lung function before and after supplement ingestion showed no negative effects on pulmonary function (data not shown).

Figure 3.2 Mean ($\pm$ SEM) response of $\dot{V}O_2$, $\dot{V}CO_2$, RQ and heart rate postprandially and during exercise after consumption of placebo (solid line), and a 1046 kJ supplement (dashed line), and a 2092 kJ supplement (dotted line). Last, the last measurement during the exercise test. $n=14$ * $p<0.05$, 1046 kJ versus placebo; ** $p<0.05$, 2092 kJ versus placebo, *** $p<0.05$, 1046 kJ versus 2092 kJ (ANOVA)

The time course of $\dot{V}O_2$ and of $\dot{V}CO_2$ after the different supplements were ingested is shown in figure 3.2. During the measurement period at rest, $\dot{V}O_2$ tended to be higher after the 2092 kJ than after the 1046 kJ supplement or placebo. However, $\dot{V}O_2$ after the 2092 kJ supplement was significantly higher than after the placebo only 50 minutes after the supplement was consumed. During exercise, $\dot{V}O_2$ was not different among the 3 supplements. The value of $\dot{V}CO_2$ was also significantly higher 50 minutes after consumption the 2092 kJ supplement than after the placebo. During exercise, the effects of the supplements on $\dot{V}CO_2$ did not differ significantly.

There was a clear effect of the different energy loads on RQ. At rest at 60 minutes postingestion, RQ was significantly higher after the 1046 kJ and 2092 kJ

supplements than after the placebo (0.87 ± 0.05 , 0.89 ± 0.05 and 0.84 ± 0.04 , respectively). During exercise, RQ remained significantly elevated after the 1046 kJ and 2092 kJ supplements compared with the placebo. At 50% of Wmax, RQ after the 2092 kJ supplement was significantly higher than the RQ after the 1046 kJ supplement, as shown in figure 3.2.

The effect on V_E was less apparent, but after 50 minutes, V_E was significantly elevated after the 2092 kJ supplement compared with the placebo (14.1 ± 2.1 L/min and 12.7 ± 2.4 L/min, respectively; $p=0.01$). During exercise, however, there was no difference in V_E among the 3 supplements. The heart rate after the 2092 kJ supplement was significantly different from that after the placebo at 40 and 50 minutes postingestion, as shown in figure 3.2. There were no significant differences during the exercise test.

The changes in oxygen saturation were small, but significant, at 10 and 30 minutes after ingestion of the 1046 kJ ($93.8 \pm 1.9\%$ and $94.1 \pm 1.6\%$; $p<0.05$) and 2092 kJ ($93.6 \pm 1.6\%$; $p<0.01$; $94.2 \pm 1.4\%$; $p<0.05$) supplements, respectively, compared with placebo. There were no differences in lactate concentrations during the experiment among the 3 supplements. Also, the relative increase in lactate was not significantly different among the placebo, and 1046 kJ and 2092 kJ supplements ($107 \pm 73\%$, $104 \pm 89\%$, and $108 \pm 95\%$, respectively).

From the symptoms assessed by VAS, the change in satiety after the supplements was significantly different for the 2092 kJ supplement than after the placebo, as shown in figure 3.3. The symptoms shortness of breath, fatigue, and pain in the legs did not change during the experiment.

Figure 3.3 Difference between the mean ($\pm$ SEM) post- and preprandial satiety score on a visual analog scale 30 and 60 minutes after consumption of placebo (light grey bar), a 1046 kJ supplement (grey bar); and a 2092 kJ supplement (dark grey bar); * $p<0.05$

The differences in the mean duration of the exercise test after the 3 supplements were small and insignificant. There were insignificant differences in mechanical efficiency after the 3 supplements.

There were 3 patients who were not able to cycle 5 minutes at 50% of W_{max} after the 2092 kJ supplement. The endurance time was dramatically lower in these outliers than in the other 11 patients, as shown in figure 3.4. A low body mass index ($18.9 \pm 1.7 \text{ kg/m}^2$), a low fat-free mass index (fat-free mass divided by height^2 14.7 ± 0.5), low maximal exercise performance ($49 \pm 3 \text{ Watt}$) and low mechanical efficiency characterized these patients.

Figure 3.4 Kaplan-Meier plot of endurance time during submaximal cycle ergometry after consumption of placebo (solid line), a 1046 kJ supplement (dashed line); and a 2092 kJ supplement (dotted line). Left panel: total group – outliers ($n=11$); right panel: outlier ($n=3$)

Part 2

Pulmonary function before and after ingestion of the supplements is shown in table 3.3. Comparable with part 1, there were no negative effects of the supplements on pulmonary function. PEF increased significantly after the carbohydrate-rich supplement compared with baseline and compared with the fat-rich supplement.

Table 3.3 Pulmonary function before and after supplements in part 2 of the study

	Carbohydrate-rich		Fat-rich	
	Before	After	Before	After
FVC, liter	3.1 ± 0.7	3.5 ± 1.3	3.0 ± 0.6	3.0 ± 0.7
FEV ₁ , liter	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.4	1.0 ± 0.4
PEF, liter/sec	3.1 ± 1.0	$3.3 \pm 1.2^*$	3.1 ± 0.9	3.1 ± 0.9

Data are mean $\pm$ SD; * $p < 0.05$ compared to before drink and compared to after fat-rich drink (ANOVA)

The courses of $\dot{V}O_2$ and $\dot{V}CO_2$ are shown in figure 3.5. There were no significant differences in response to the 2 supplements. After the carbohydrate-rich supplement there was a slightly lower $\dot{V}O_2$ during the whole experiment than after the fat-rich supplement. The RQ was significantly higher after the carbohydrate-rich supplement than after the fat-rich supplement during the whole

experiment except at the last minute of the exercise trial. The higher RQ suggests a relatively higher $\dot{V}'\text{CO}_2$ after the carbohydrate-rich supplement. Although $\dot{V}'\text{CO}_2$ and $\dot{V}_E$ are highly correlated (last minute of exercise after the carbohydrate-rich and fat-rich supplement, respectively: $r=0.87$, $p=0.01$, $r=0.96$, $p<0.001$), $\dot{V}_E$ was not significantly different after the ingestion of the fat-rich or carbohydrate-rich supplement.

Figure 3.5 Response of $\dot{V}'\text{O}_2$, $\dot{V}'\text{CO}_2$ and RQ postprandial and during exercise after fat-rich and carbohydrate-rich drink; solid line, fat-rich; dashed line, carbohydrate-rich; * $p<0.05$, ** $p=0.01$, *** $p<0.01$

There were no significant differences in heart rate after carbohydrate-rich and fat-rich supplements. Blood saturation seemed slightly lower after carbohydrate-rich supplement, and was significantly so 10 and 15 minutes after ingestion ($p<0.05$). However, on average, the slightly lower saturation after the carbohydrate-rich supplement was not clinically significant (ie, a drop in $\text{SaO}_2>4\%$).

Lactate concentration was significantly different at the start of the exercise test between patients consuming the carbohydrate-rich and fat-rich supplements: 1.7 ± 0.3 and 1.3 ± 0.2 mmol/L, respectively ($p<0.05$). The relative increase in lactate was not significantly different after the 2 supplements.

Blood glucose concentration was measured during the whole experiment. At rest, blood glucose increased significantly after ingestion of the carbohydrate-rich supplement. The highest value of blood glucose was at 30 minutes after ingestion ($\Delta\text{glucose}$: 2.6 mmol/L, range: -0.2 to 5.5 mmol/L). At the start of the exercise test, blood glucose was not significantly different between subjects who consumed the carbohydrate-rich and the fat-rich supplement (5.7 ± 1.3 and 5.3 ± 0.7 mmol/L, respectively). During the exercise test, blood glucose concentration was not significantly different for the 2 supplements.

There were no significant differences in mean duration of the exercise test after the carbohydrate-rich and fat-rich supplement (12.6 ± 7.2 and 13.1 ± 7.1 minutes,

respectively). Also the mechanical efficiency after the 2 supplements was not significantly different ($20.0 \pm 5.8\%$ and $19.8 \pm 5.9\%$, respectively).

The symptoms satiety, fatigue, and pain in the legs did not change significantly during the experiment after ingestion of the supplement. Only the symptom shortness of breath changed: there was a significantly greater increase in dyspnoea after ingestion of the fat-rich supplement than after the carbohydrate-rich supplement, as shown in figure 3.6.

Figure 3.6 Difference between post- and preprandial of shortness of breath score on a visual analogue scale; grey bar, fat-rich; white bar, carbohydrate-rich; * $p=0.01$, ** $p<0.01$

Discussion

Nutritional supplements are needed in some COPD patients to reverse weight loss or to improve nutritional status. In contrast with a long-held belief, the present investigation did not show significant adverse effects of the studied nutritional supplements on the ventilatory system. Remarkably, there were even positive effects of a carbohydrate-rich supplement relative to those of a fat-rich one at a relatively low energy content, as will be discussed below.

In the first part of the study we evaluated the most optimal energy load to be given as a supplement between regular meals. As expected, relative to the 1046 kJ supplement, the metabolic and ventilatory response at rest was significantly higher after the 2092 kJ supplement. During exercise, this difference was eliminated. For the total group, there were no differences in exercise endurance capacity. Satiety, however, was clearly greater after the 2092 kJ supplement, which might interfere with a normal meal pattern. Another remarkable observation was the strikingly reduced endurance capacity of 3 patients after the 2092 kJ supplement, whereas no difference was seen between the placebo and the 1046 kJ supplement. Although this phenomenon was observed in only a few

patients, these results are important to consider because this subgroup was characterized by a low BMI and FFMI, low maximal exercise capacity, and low mechanical efficiency. One potential cause could be an increased oxygen cost of breathing because Mannix et al¹⁵ recently reported a significant inverse relation between BMI and the oxygen cost of breathing in COPD.¹⁵ Furthermore, we showed in a previous study a significantly elevated ratio of V_E to $V'O_2$ in COPD patients with a decreased mechanical efficiency.⁵

Suggested positive effects of a carbohydrate-rich compared with a fat-rich 1046 kJ supplement are based on the following observations. A significant increase in peak expiratory flow was shown relative to baseline and relative to the fat-rich supplement. In contrast with the forced expiratory flow in 1 second, the peak expiratory flow is dependent of respiratory muscle strength. Blood glucose is a rapidly available substrate, as was indirectly observed in the insignificantly lower increase in lactate during exercise after the carbohydrate-rich supplement. Specifically, for COPD patients, this may be clinically relevant because a reduced oxidative capacity has been observed, as reflected in low muscle concentrations of oxidative enzymes such as citrate (si)-synthase and β -hydroxyacyl dehydrogenase (alone or combined with increased concentrations of the regulating glycolytic enzyme phosphofructokinase).¹⁶ One study even showed a decreased ATP-ADP ratio in resting muscle associated with an increased inosine monophosphate concentration as marker of an imbalance between ATP synthesis and production.¹⁷ Positive effects of a carbohydrate load on muscle have been described and are being used in sports medicine. The amount of carbohydrate given in this study is comparable with the recommended dose.

The RQ was indeed higher after the carbohydrate-rich supplement, but this was not due to an increased $V'CO_2$ but to a lower $V'O_2$. This could reflect more efficient metabolism and could be related to a lower gastric emptying time for the carbohydrate-rich supplement, when given in a fixed period, as was observed previously by Akrabawi et al¹⁸ after a moderate-fat compared with a high-fat supplement. There are clinical ramifications to delayed gastric emptying, especially in patients with COPD. Because of the disease process itself, such patients already have hyperinflation, a flattened diaphragm, and a reduction in abdominal volume, which results in feelings of bloating, abdominal discomfort, and early satiety. A significant delay in gastric emptying may lead to an extended period of abdominal distention, affecting diaphragmatic mobility and thoracic expansion.

The protein content of the supplements was high on the basis of available data showing that, in healthy subjects and in those with stable disease, protein synthesis is optimally stimulated during administration of 1.5 g protein/kg/day.¹⁹ The effects of wasting disease on protein metabolism are characterized by net protein catabolism owing to differences between protein synthesis and breakdown rates. This is seen as a negative nitrogen balance. The pathophysiological mechanisms of this catabolic reaction are related to disease severity. In many chronic wasting disorders, a negative nitrogen balance is associated mainly with a reduced protein synthesis rate, whereas protein breakdown is hardly affected. Morrison et al²⁰ found a reduced protein synthesis rate in

underweight patients with emphysema. In weight-stable COPD patients in a stable clinical condition, we recently found an increased protein turnover rate in the fasting state.²¹ Moreover, voluntary protein intake is important during acute exacerbations of COPD; we previously reported in hospitalized COPD patients a temporarily decreased protein intake that recovered slowly to 1.3 g/kg at discharge from the hospital.⁷

The absence of adverse effects of nutritional supplements was also indirectly confirmed in previous studies that showed positive effects of 2-3 nutritional supplements (~1046 kJ) as an integrated part of pulmonary rehabilitation on weight, fat-free mass, muscle function, and exercise capacity. Future studies using NMR or muscle biopsies might investigate the suggested specific effects of carbohydrates alone or combined with specific bioactive nutrients on oxidative muscle metabolism.

In conclusion, a liquid oral nutritional supplement with an energy content of 1046 kJ is preferable to an energy load of 2092 kJ because after the smaller load there was a better metabolic and ventilatory response and less satiety. Also the carbohydrate-rich supplement was preferable to the fat-rich supplement because lung function increased and there was less shortness of breath.

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Chapter 4

Gastric emptying of different solid meals and postprandial response in patients with chronic obstructive pulmonary disease

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Submitted

Abstract

Introduction

Previously we observed adverse effects of a fat-rich meal on dyspnoea sensation and transcutaneous oxygen saturation in patients with chronic obstructive pulmonary disease (COPD). We hypothesized that this effect could be due to adverse effects of fat-rich food on gastric emptying on top of a disease-related delayed gastric emptying. The aim of the study was to investigate the effect of two isocaloric solid meals, different in fat and carbohydrate content, on gastric emptying and related parameters in 10 depleted COPD patients and 9 healthy age matched control subjects.

Methods

Patients were characterized by severe airflow limitation and lung hyperinflation (FEV₁ 30±8 %predicted, residual volume 230±49 %predicted). The gastric emptying rate was measured using the ¹³C octanoid acid breath test. Other measurements included lung function by spirometry, transcutaneous oxygen saturation, postprandial symptoms by Visual Analogue Scale (VAS) score and dietary intake. The postprandial response of glucose and insulin and the postprandial secretion pattern of gastrointestinal hormones, cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) were measured.

Results

The gastric emptying rate did not differ between COPD patients and control subjects or between the different meals in both groups. No significant changes in lung function and symptoms were found after both meals in COPD patients and in the control group. Postprandial responses in glucose, insulin and CCK also did not differ between the groups. Despite no changes in gastric emptying rate, a significant increase in GLP-1 after the fat-rich meal was observed relative to the carbohydrate-rich meal at 210 minutes in COPD patients ($p=0.025$). Dietary intake at lunch time tended ($p=0.07$) to be lower after a fat-rich test meal versus a carbohydrate-rich meal in COPD patients compared with controls.

Conclusions

In general, gastric emptying and related postprandial response after two different meals did not differ in COPD patients and control subjects. However, unrelated to gastric emptying, a postprandial increase in GLP-1 secretion and decreased dietary intake subsequently were found after a fat-rich meal in COPD patients. Therefore, a potential adverse effect of a fat-rich meal may be more pronounced in perceived satiety sensation and subsequent caloric intake.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disorder characterized by chronic irreversible airflow limitation. Dyspnoea and impaired exercise tolerance, largely related to ventilatory limitations and occurrence of dynamic hyperinflation are important and pronounced symptoms in these patients. Ventilatory limitation is induced by metabolic stress. Diet induced metabolic changes also induce the ventilatory response. This response depends not only on caloric load but also on substrate ingestion since per gram fat intake CO_2 production is reduced in contrast with CO_2 production after carbohydrate intake.¹

Little is known regarding possible differences in gastric emptying between patients with COPD and healthy control subjects regarding its effect on dietary intake. In one study the gastric emptying rate was evaluated in COPD patients after ingesting two different liquid supplements varying in fat content from high (55 energy%) to moderate (41 energy%).² Gastric emptying was significantly delayed after ingesting the high fat supplement compared to the moderate fat supplement.²

Dyspnoea can also adversely affect appetite and dietary intake. Meal-related increase in dyspnoea is reported in hypoxemic patients with COPD, linked to decreased oxygen saturation.^{3,4} Furthermore, eating requires the recruitment of the upper extremities muscles, which may interfere with breathing, since these muscles are often used as accessory muscles for breathing in severe COPD patients with hyperinflation.⁴ Donahoe et al reported a high prevalence of gastrointestinal symptoms like early satiety and bloating, with prevalence of 87% and 80%, respectively in a group of underweight COPD patients.⁵ These symptoms may also limit energy intake resulting in a disturbance of energy balance in patients with COPD.

Furthermore, after ingestion of nutrition, a cascade of processes including processes mediating satiety such as the postingestive processes occurs.⁶ Postingestive processes do not only include gastric emptying rate, but also gastric distension, the release of gastrointestinal hormones like cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) and the stimulation of gastrointestinal receptors. CCK has several effects on the gastrointestinal tract, including modulation of gastric emptying and thereby also modulation of satiety. Other hormones are also involved in modulating satiety; GLP-1 has been proposed to play a role in the mediation of gastric emptying and satiety and GLP-1 is released from the intestinal mucosa of the ileum. Currently no data of those postprandial signs in patients with COPD have been described.

The present study was designed to investigate gastric emptying after two different solid meals in patients with COPD compared to healthy controls. We hypothesized that gastric emptying is more delayed in depleted COPD patients with hyperinflation compared with healthy controls. We also hypothesized that a

fat-rich meal compared to an isocaloric carbohydrate-rich meal has more adverse effects on gastric emptying, pulmonary function and symptoms in patients with COPD. Furthermore, we hypothesized that the postprandial response of gastrointestinal hormones is more pronounced in COPD patients compared to healthy controls.

Subjects and methods

Study population

The study group consisted of 10 patients with COPD, with COPD defined according to the GOLD criteria.⁷ All COPD patients were in a clinically stable condition; patients with a history of acute exacerbation in the last month were excluded. COPD patients were recruited from the out-patient population of the University Hospital Maastricht and from the pulmonary rehabilitation center Hornerheide, The Netherlands. Inclusion criteria for depleted patients with COPD were: Body mass index (BMI) ≤ 21 kg/m² or $>5\%$ involuntary weight loss in 1 month or $>10\%$ weight loss in 6 months and BMI ≤ 25 kg/m². Hyperinflation in patients with COPD was defined as residual volume (RV) $>160\%$ of predicted. Exclusion criteria in this study were a history of diabetes mellitus, previous gastrointestinal surgery or use of medication affecting gastric motility.

Ten healthy control subjects were recruited by advertisement and they were matched for age. One healthy subject was excluded because of recurrent illness. All subjects were fully informed of the aim and the procedure of the study and gave written informed consent. The study was approved by the medical ethical committee of the University Hospital Maastricht.

Study design

The two different-test meals were administered in a randomized cross-over fashion. The composition of the isocaloric meals was different in carbohydrate- and in fat content and similar in protein and fibre amounts. Meal A consisted of 55 energy% fat and 31 energy% carbohydrate and meal B consisted of 30 energy% fat and 55 energy% carbohydrate. Caloric load of the both meals was ± 1425 kJ. The measurements were done within 1 week; at least 1 day between the two measurements was applied for a proper washout of the isotope.

Patients with COPD were asked to abstain from medication with theophylline before and during the study, to avoid the possible influence of theophyllines on gastric emptying. Additionally all subjects were asked to register dietary intake the day before the test and to consume exactly the same diet before the other test day, to minimize the influence of the meal content of the previous day on gastric emptying.

The complete design of the study is summarized in table 4.1.

Table 4.1 Study design

	Before meal		Directly after	Until 4 hours after ingestion of the test meal
Gastric emptying	x	Test meal		every 15 minutes
Lung function	x			after 90 minutes
Oxygen saturation	x		x	every 15 minutes
Glucose, insulin	x			every 15 minutes during first 2 hours, than every 30 minutes
GLP-1, CCK	x			every 30 minutes
Symptoms	x		x	every 30 minutes

Gastric emptying

The gastric emptying tests were performed after an overnight fast. The test meals were labeled with a stable isotope, 100 μl ^{13}C -ocatnoic acid (99%; Cambridge Isotope Laboratories, Andover, MA, USA) was mixed with the egg yolk and prepared as a baked egg. The egg was ingested with two slices of bread and margarine, followed immediately by 200 ml of water. All test meals were ingested within 10 minutes. Breath samples for $^{13}\text{CO}_2$ enrichment analysis were drawn from a mixing chamber using Vacutainer tubes at 15-minute intervals for 4 hours after ingestion of the test meals. One breath sample was taken before administration of the meal at $t < 1$ hour to determine background enrichment. The collected breath samples were analyzed for ^{13}C -isotopic enrichment of the expired CO_2 , using Isotope Ratio Mass Spectrometry (Finnigan MAT 252, USA). Mathematical analysis of the $^{13}\text{CO}_2$ data was performed according to Ghooos et al.⁸ Gastric half-emptying time ($t_{1/2}$) and lag phase (t_{lag}) were calculated as outcome parameter.

Pulmonary function

Body weight and height were measured in a standard way before lung function testing. Lung function was assessed by flow volume curves using a portable spirometry (Jaeger, Wurzburg, Germany). Forced expiratory volume in one second (FEV_1), inspiratory vital capacity (IVC), peak expiratory flow (PEF) and inspiratory capacity (IC) were calculated from the curves. The highest value of at least three technical assessments was used for analysis. Lung function was measured before the test meal and 90 minutes after the meal.

To assess hyperinflation, total lung capacity (TLC) and residual volume (RV) were measured only in COPD patients by whole-body plethysmography (Masterlab, Jaeger, Wurzburg, Germany) during one of the study days.

All results of lung function parameters were related to a reference value and expressed as percentage of the predicted value.⁹

Oxygen saturation

Transcutaneous oxygen saturation (StO_2) was measured with a pulse oxymeter (Oxypleth Novamatrix Medical System Inc, Wallingford CT 06492 USA). The

electrode was placed around a finger of the left hand before the test meal was ingested. Measurements were done at baseline, directly after ingestion and at an interval of 15 minutes after ingestion for 4 hours.

Biochemical parameters

Blood was collected from an intravenous catheter in the arm. Blood collection was performed in fasting state and after ingestion of the meal during the experiment, and biochemical parameters were measured in the blood.

Glucose and Insulin

Glucose and insulin were measured in fasting state and after ingestion at 15-minute intervals for 2 hours and thereafter at 30-minute interval till 4 hours after ingestion of the test meal. Blood was collected in a tube containing oxalate and sodium fluoride and centrifuged at 3500 rpm for 15 minutes at 5°C. Quantitative determination of glucose was done using glucose oxidase with oxygen rate detection with an oxygen electrode (Synchron LX® Systems, Beckman Coulter Inc., Fullerton, CA).

To assess insulin, blood was collected in an evacuated coagulation tube and centrifuged for 15 minutes at 3500 rpm at 5°C. Serum was collected and stored until measurement using an immunoassay (AutoDELFIA™ Insulin, Wallac Oy, Turku, Finland).

Cholecystokinin and glucagon-like peptide-1

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An EDTA tube (EDTA Sherwood Medical, St. Louis, MO) was used to collect blood for the measurement of CCK and GLP-1 in fasting state and after ingestion of the test meal at 30-minute intervals. Directly after collection, dipeptidyl peptidase IV (DPP IV) was added as inhibitor. Blood was centrifuged at 3500 rpm for 15 minutes at 5°C within 1 hour after collection. Plasma samples were stored at -70°C until analyzed.

CCK has been assayed using the commercially available EURIA-CCK assay of Euro-Diagnostica AB, Malmö, Sweden. This is a competitive radioimmunoassay in which an antibody is used raised in rabbit against the eight C-terminal amino acids of CCK-33-sulphate (commonly named CCK-8). ¹²⁵Iodinated CCK-8 is equally used as tracer. The separation between the bound and the free fractions is performed by means of an anti-rabbit IgG antiserum coupled to cellulose particles. The assay is calibrated against known solutions of CCK-8. EDTA-Samples with added trasylol have been ethanol extracted. The lowest sensitivity of the assay is 0.3 pmol/l. The inter assay coefficient of variation is between 5 and 10%. Cross reactivity with CCK (26-33), sulphate is 100%, with CCK-33, sulphate is 134% and with gastrin-17 sulphate 0.5%. With all other molecules of interest no cross reactivity has been found. Normal fasting levels of CCK are ≤ 1.12 pmol/l.¹⁰

GLP-1 has been assayed using the commercially available GLP-1 (active) RIA from Linco, StCharles, MO, USA. This is a radioimmunoassay in which the GLP-1 from the samples is in competition with a ¹²⁵J GLP (7-36) amide for the binding sites on

a guinea pig anti GLP (7-36) amide antibody. The separation between the bound and the free fractions is performed using a goat anti-guinea-pig IgG antibody with 3% PEG added. The assay is calibrated against known solutions of GLP-1 (7-36) amide. In order to preserve the active GLP-1 in the samples DPP-IV inhibitor has been added immediately after the withdrawal of the blood. The lowest detectable concentration is 3 pmol/l. The inter assay coefficient of variation is about 6-8% in the concentration range of 40 to 300 pmol/l. Cross reactivity with GLP-1 (7-36) amide, with GLP-1 (7-37) is 100% and with glucagon 16%. Cross reactivity is undetectable with GLP-1 (1-36)amide, GLP-1 (1-37), GLP-1 (9-36) amide and GLP-1 (9-37).¹¹

Subjective symptoms

Symptoms were measured before the test, 5 minutes after ingestion and with an interval of 30 minutes after ingestion of the test meals using a visual analogue scale (VAS-score) of 10 cm length. The following symptoms were assessed: shortness of breath, satiety, hunger, fullness, thirst and appetite and expressed in cm, ranging from 0 to 10 cm.

Dietary intake

Dietary intake was assessed on the two study days of the test, using food records, with the aim to investigate the influence of the test meals on spontaneous dietary intake during the same day. Since dietary intake was recorded on the previous day for standardization of dietary intake, we also compared the energy content of that breakfast with the energy content of the two test meals.

Statistics

It was predicted that the inclusion of 9 participants per group would permit detection of a difference of 25 minutes in gastric emptying rates and a 0.05 difference between the groups at $\alpha=0.05$ and Power=0.90.

Differences in the baseline characteristics between the patients with COPD and the healthy control group were compared using a Student's t-test for independent samples. The data were analyzed to evaluate the effect of the different meals on gastric emptying, pulmonary function, biochemical parameters and symptoms. Differences in the outcome parameters among the two study groups were compared by an analysis of variance (ANOVA) method and period, sequence and treatment were included. All analyzes were performed using the SPSS 11 for Windows statistical package. Values of $p<0.05$ were accepted as statistically significant. Data were expressed as mean ($\pm$ SD) in the text and tables and as mean ($\pm$ SEM) in the graphs.

Results

The baseline characteristics of the study population are shown in table 4.2. All COPD patients were ex-smokers and 2 of 9 healthy subjects had a history of smoking cigarettes. The COPD patients had severe airflow limitation (GOLD stage III-IV, FEV₁ 30±8 %predicted), with severe static hyperinflation under resting conditions (RV: 230±49 %predicted). In the control group, all lung function values were within normal range.

Table 4.2 The baseline characteristics of the study population

	COPD patients n = 10	Control group n = 9
Male / female	8 / 2	6 / 3
Age, years	59 ± 10	60 ± 6
Weight, kg	56.2 ± 9	64.9 ± 14
Height, cm	170 ± 9	169 ± 12
BMI, kg/m ²	19.1 ± 2.1*	22.4 ± 2.1
FEV ₁ , %predicted	30 ± 8*	104 ± 14
IVC, %predicted	82 ± 15*	113 ± 14
RV, %predicted	230 ± 49	-

Data are mean±SD; BMI, Body Mass Index; FEV₁, forced expiratory volume in one second; IVC, inspiratory vital capacity; RV, residual volume; * p<0.05 compared between COPD patients and control group

Figure 4.1 The gastric emptying rate after both meals in COPD patients and control group
Open bars, after fat-rich meal; grey bars, after carbohydrate-rich meal

Gastric emptying

In COPD patients gastric emptying half-time of the fat-rich meal ($t_{1/2}$) was 95±35 minutes and of the carbohydrate-rich meal 89±27 minutes. In the control group

(n=9) $t_{1/2}$ was 96 ± 26 versus 94 ± 28 minutes, respectively. The gastric emptying rate was not different between COPD patients and healthy controls, as shown in figure 4.1. In both COPD patients and controls, there were no significant differences in the gastric emptying rate between the two different meals. The lag phase (t_{lag}) of the fat-rich meal was 52 ± 19 minutes in COPD patients and of the carbohydrate-rich meal it was 50 ± 22 minutes. In the control subjects t_{lag} of the fat-rich meal was 55 ± 20 minutes and of the carbohydrate-rich meal it was 54 ± 21 minutes. Between both groups and within groups no significant differences in t_{lag} after the test meals were observed.

Table 4.3 Pulmonary function before and after supplements of the different meals in COPD patients

	COPD patients			
	Fat-rich		Carbohydrate-rich	
	Before meal	After meal	Before meal	After meal
FVC, liter	3.1 ± 1.0	3.1 ± 1.1	3.1 ± 1.0	3.2 ± 1.0
FEV ₁ , liter	0.9 ± 0.4	0.9 ± 0.5	0.9 ± 0.4	0.9 ± 0.4
PEF, liter/sec	3.3 ± 1.5	3.4 ± 1.7	3.4 ± 1.3	3.3 ± 1.3
IC, liter	2.1 ± 0.7	2.3 ± 0.8	2.4 ± 0.6	2.4 ± 0.7

Data are mean $\pm$ SD; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second, PEF, peak expiratory flow; IC, inspiratory capacity

Lung function and oxygen saturation

Pulmonary function in patients with COPD is shown in table 4.3. No significant changes were found after ingestion of the test meals. Also in the control group there were no differences after both meals, data not shown.

Figure 4.2 shows the slight changes in oxygen saturation in COPD patients after both meals. Directly after ingestion, there was a significant drop in oxygen saturation and this was similar after both meals in COPD patients, $p=0.048$, but not clinically significant, as defined by a drop of $>4\%$ in SaO_2 . In the postprandial pattern of oxygen saturation after the two different meals in COPD patients, there were significant differences, as shown in figure 4.2. After 15 minutes the mean oxygen saturation after the carbohydrate-rich meal was above the level of baseline in COPD patients. From 60 until 195 minutes postprandial, the change in oxygen saturation after the carbohydrate-rich meal was significantly different in patients with COPD, compared to the change in oxygen saturation after the fat-rich meal. There were no changes in oxygen saturation in healthy controls after the two different meals, data not shown.

Figure 4.2 Change in oxygen saturation after both meals in patients with COPD
Open circles, after fat-rich meal; closed circles, after carbohydrate-rich meal
* $p < 0.05$, ** $p = 0.01$, *** $p < 0.01$

Biochemical parameters

The postprandial glucose response in COPD patients was significantly higher after the carbohydrate-rich meal compared to the response after the fat-rich meal for the first 60 minutes ($p < 0.05$). After 60 minutes the postprandial differences were no longer significant between the meals. For insulin, the postprandial response was also significantly higher for the first 60 minutes after the carbohydrate-rich meal compared to the fat-rich meal in patients with COPD ($p < 0.05$). The postprandial patterns of glucose and insulin after both meals in COPD patients are shown in figure 4.3a and 4.3b, respectively.

In the control group, there was also a significant increase in glucose at 30 and 60 minutes postprandial, but there were no significant differences in insulin response between the two meals in this group, shown in figure 4.3e and 4.3f.

The pattern of GLP-1 secretion at baseline and postprandially is shown for both groups in figure 4.4a and 4.4b. There were no significant changes in GLP-1 between both meals in the control group. At 210 minutes postprandially, there was a significant difference in GLP-1 response after the carbohydrate-rich meal compared with the response after the fat-rich meal in patients with COPD, $p = 0.025$.

The postprandial pattern of CCK was not significant different between COPD patients and control subjects and not after both meals in the groups, shown in figure 4.5a and 4.5b.

Symptoms

Changes in symptom score were not different between COPD patients and healthy controls. In COPD patients, the change in satiety was similar after both meals, as shown in figure 4.3c. No significant differences in postprandial change in shortness of breath were observed after both meals in COPD patients, as shown in figure 4.3d. The other symptoms hunger, fullness, thirst and appetite were also not different between the two isocaloric meals in patients with COPD

(data not shown). The pattern of satiety and shortness of breath during the experiment in the control group are presented in figure 4.3g and 4.3h. There were no significant changes in symptoms in the control group between the test meals.

Figure 4.3 Pattern of glucose, insulin, satiety and dyspnoea during both tests in COPD patients, 4.3a, 4.3b, 4.3c, 4.3d; in healthy controls, 4.3e, 4.3f, 4.3g, 4.3h. Open circles, open triangles, open bars, fat-rich meal; closed circles, closed triangles and grey bars, carbohydrate-rich meal; * $p < 0.05$ carbohydrate-rich meal compared with fat-rich meal

Figure 4.4 Pattern of GLP-1 during both meals in patients with COPD, 4.4a and in control subjects, 4.4b. Open circles, after fat-rich meal; closed circles, after carbohydrate-rich meal

Figure 4.5 Pattern of CCK after both meals in COPD patients, 4.5a and in control subject, 4.5b. Open circles, after fat-rich meal, closed circles, after carbohydrate-rich meal

Dietary intake

In 70% of the patients versus 40% in healthy controls, energy content of the test meal was higher than their reported breakfast on the previous day. The energy intake during the test days was 5620 ± 1877 kJ after the fat-rich meal compared to 6619 ± 2465 kJ after the carbohydrate-rich meal in patients with COPD (ns). In the control group, energy intake during the test days was similar after both meals, 5787 ± 1587 kJ after fat-rich meal versus 5665 ± 2074 kJ after carbohydrate-rich meal. In figure 4.6 the energy intake at lunch time after completion of the tests tended to be lower after fat-rich meal compared to carbohydrate-rich meal in COPD patients, $p=0.07$. In healthy control subjects energy intake at lunch time was similar after both meals, shown in figure 4.6.

Figure 4.6 Energy intake at lunch time after completion of the tests in COPD patients and control group. Open bars, after fat-rich meal; grey bars, after carbohydrate-rich meal

Discussion

This is the first study describing the gastric emptying rate in COPD patients compared with healthy control subjects. In contrast to our hypothesis, no differences in the gastric emptying rate in COPD patients and in controls were found and also no differences in the gastric emptying rate between meals in both study groups. Despite no differences in the primary outcome, differences were found in the secondary outcome parameters, namely postprandial GLP-1 secretion and dietary intake at lunch time in COPD patients. A significant higher postprandial increase of GLP-1 secretion was found after the fat-rich meal in COPD patients and this may be related to dietary intake at lunch time in COPD patients which tended to be lower after the fat-rich meal. A potential adverse effect of a fat-rich meal may therefore be more pronounced in perceived satiety sensation and subsequent caloric intake in patients with COPD.

Patients with marked hyperinflation were selected for this study as it can be expected that particularly in this subgroup the possible mechanical disadvantages due to changes in pulmonary mechanics will be more manifested. Hyperinflation in these patients is associated with important alterations in the geometry of the chest wall, particularly at the level of the diaphragm: hyperinflation is associated with a marked flattening of the diaphragm with a dramatic decrease in the zone of apposition height.¹² Furthermore, respiratory cycle-related gastric pressure changes are largely related to the level of lung inflation. In case of resistive and restrictive impediment as in COPD patients with static hyperinflation, positive gastric pressure swings will be more pronounced. Indeed, patients with COPD are able to develop greater maximal inspiratory pressure than normal subjects at a given lung volume possibly due to length adaptation of the diaphragm to the

chronic hyperinflation resulting in a preservation of ventilatory pump capacity.¹³ In addition, studies indicate that in many patients with stable but severe COPD the expiration is a mechanically active process at least in part determined by the active contraction of the transversal abdominal muscle.¹⁴ In the same study a close relationship was found between the rise in gastric pressure during expiration and end-expiratory alveolar pressure, indicating a transmission through the relaxed diaphragm of this rise in abdominal pressure produced by the contraction of the transversus abdominis. Furthermore, dynamic hyperinflation during periods of increased minute ventilation will pronounce these pressure variations. Therefore, despite these more pronounced mechanical effects during in and expiration in this selected group of hyperinflated COPD patients, no differences in gastric emptying could be demonstrated.

In contrast to our study, Akrabawi et al found a significantly lower gastric emptying rate, measured by scintigraphy, after a supplement with high-fat compared with a supplement with moderate-fat content.² Remarkably the difference in fat content between the supplements used in that study was lower compared to the current study (resp. 7.6 g and 9.6 g fat). However, the caloric load of the supplements was higher in the study of Akrabawi (2310 kJ versus 1425 kJ) and that could be the explanation of the conflicting results.²

A significant different response of oxygen saturation after the two meals was observed in COPD patients. However, the change of oxygen saturation after the fat-rich meal was not clinically significant. In line with a previous study³, we found a more distinct decrease in SaO₂ after fat-rich meal compared to carbohydrate-rich meal. The decrease in SaO₂ in our study was less pronounced, probably due to the fact that the COPD patients who participated in the study of Schols were more hypoxemic.³ Furthermore, the higher energy content of the fat-rich warm meal (1870 kJ) and the different meal temperature³ may further explain why we did not detect a difference in meal related dyspnoea in our study.

No correlation between subjective perception of satiety by VAS score and satiety mediating hormones (CCK and GLP-1) are found in the current study. We hypothesized that a fat-rich meal would induce more satiety as result of a delayed gastric emptying and due to a different pattern of gastrointestinal hormone response, compared to the carbohydrate-rich meal. However no differences in satiety perception were reported during the tests, in both COPD patients and controls. In a recently published study of Raben et al¹⁵, no differences in subjectively reported satiety after 4 isocaloric meals with different macronutrient compositions in healthy subjects were observed. In that study the proposed relation between the satiety hierarchy and the oxidation hierarchy of the four macronutrients was not confirmed.¹⁵ The suggestion has been made that satiety is influenced more by protein.¹⁶ In our study we used test meals similar in energy and protein content and that may explain the lack of differences in satiety in our study, in accordance with the study of Raben.¹⁵

Furthermore, the influence of the different meal contents on satiety may be more extended with respect to time. Dietary intake after the test meals showed that energy intake after fat-rich meal was lower at lunch time compared to a previous carbohydrate-rich meal in COPD patients. Spontaneous energy intake at an ad

libitum lunch after intravenously infused GLP-1 has been described in healthy young men.¹⁷ We proposed that decreased dietary intake at lunch time after fat-rich meal in COPD patients was due to the increased GLP-1 secretion. So the role of GLP-1 is more attributed to the inter-meal satiety in patients with COPD.

The secretion pattern of CCK was not different between the meals. Comparing our results with studies describing GLP-1 and CCK secretion patterns is difficult concerning the different used experimental designs.¹⁷⁻²³ For instance, an endogenous load may reveal another secretion pattern of GLP-1 and CCK compared to the response after a pharmacological load. In some of our study population, the postprandial changes in CCK or GLP-1 secretion was less pronounced and we suggested that this may be related to their habitual dietary intake. After ingestion of a higher dietary intake relative to habitual dietary intake, a more pronounced postprandial response in CCK or GLP-1 secretion may occur. Recently an effect of habitual dietary protein intake on appetite and satiety has been described in healthy subjects.²⁴ We hypothesized that besides appetite and satiety, secretion of gastrointestinal hormones varies with habitual dietary intake. Loss of appetite and early satiety may contribute to decreased dietary intake resulting in weight loss. In COPD patients, decreased dietary intake has been described in both stable condition and during acute exacerbation^{25,26} which was associated with loss of appetite and early satiety. Anorexia, defined as loss of appetite and early satiety, was related to higher inflammatory response and nonresponse of nutritional intervention in COPD patients.²⁷ So, inflammation influences appetite negatively and became a predictor for response to nutritional therapy. Still, it is not clear how to interfere in the inflammatory process resulting in improvement of the altered appetite regulation. Recently an appetite stimulant, megestrol acetate, was prescribed in underweight stable COPD patients²⁸ in a randomized double-blind placebo-controlled study. Megestrol acetate induced an improved appetite and weight gain in COPD patients after 8 weeks, mainly fat mass. However despite these improvements, there was no progression in health status or functional performance found.

In summary, gastric emptying and postprandial response in COPD patients was not different compared to healthy controls after two isocaloric solid meals. Subsequent dietary intake was more negatively influenced by the fat-rich meal in COPD patients and satiety sensation may be more extended. Further research concerning the regulation of satiety and appetite likewise by inflammatory markers in COPD patients will be needed to unravel the altered regulation.

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Chapter 5

Energy balance in depleted ambulatory patients with chronic obstructive pulmonary disease; the effect of physical activity and oral nutritional supplementation

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Abstract

Background

Patients with chronic obstructive pulmonary disease (COPD) often suffer from weight loss.

Objective

The aim of the present study was to gain insight into the energy balance of depleted ambulatory COPD patients, in relation to their habitual level of physical activity and consumption of oral nutritional supplements.

Design

Clinically stable and weight-stable patients ($n=20$, body mass index 19.8 ± 2.0 kg/m²) were studied 1 and 3 months after pulmonary rehabilitation or recovery in the clinic and were at random assigned to a control or intervention group with regard to nutritional supplementation. Energy intake was measured with a 7-day food record. Energy expenditure was estimated from a simultaneous 7-day assessment of physical activity with a tri-axial accelerometer for movement registration in combination with measured basal metabolic rate. Body mass was measured at several time points.

Results

The body mass remained stable in both groups after 1 or 3 months and mean energy balances were comparable for both groups. The mean body mass change between month 1 and 3 was negatively related to the mean physical activity level ($r=-0.49$, $p=0.03$).

Conclusions

Weight change over the 3 months was negatively associated with the physical activity level. These results suggest that knowledge about the individual physical activity level is necessary for the estimation of the energy need of the COPD patient.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) often suffer from weight loss, due to an inadequate dietary intake combined with an increased energy expenditure.¹ Nutritional depletion in COPD patients influences functional status and health related quality of life.²⁻⁵ Insight into factors related to the energy balance of depleted COPD patients at home helps to optimize the nutritional status of patients at home.

Nutritional therapy in a rehabilitation setting improves physical condition of depleted COPD patients, especially when it is combined with exercise or another anabolic stimulus such as anabolic steroids.^{2,6} The success of nutritional therapy in ambulatory depleted COPD patients varies and probably depends partly on compliance and appropriate incorporation of the supplements, as there is less control on the food intake of the patients than in a clinical situation.^{7,8}

An increase in energy intake by supplementation does not necessarily imply a positive energy balance. The energy balance of ambulatory depleted COPD patients is also a function of the energy requirement of the patients. Physical activity, as the main determinant of variation in energy requirement, may play an important role. In particular because previous studies by our group have demonstrated an increased energy requirement for physical activity in severe COPD patients.⁹

The aim of the present study was to get insight into the energy balance of ambulatory, depleted COPD patients in relation to their habitual physical activity. A secondary aim of the study was to look at the effect of the consumption of nutritional supplements on the energy balance. Energy expenditure and energy intake were estimated at 1 and 3 months after discharge from the clinic (after recovery of an exacerbation or after rehabilitation in a pulmonary rehabilitation center). Reported food intake was controlled for misreporting or a change in diet while food recording.^{10,11}

Subjects and methods

Protocol

Twenty depleted COPD patients were studied 1 and 3 months after discharge from the university hospital in Maastricht or from the pulmonary rehabilitation center in Horn, The Netherlands. At discharge all patients were in a clinically and weight-stable condition. The patients were then at random assigned (with a randomization table) to the intervention group, who received 3 x 125 ml Respifor® (sip-feed, Nutricia, The Netherlands, nutritional supplement 375 ml=2.38 MJ/day,

composition 20 energy% protein, 20 energy% fat and 60 energy% carbohydrate) or to the control group. Patients were advised to take the supplements in the morning, the afternoon and in the evening respectively. All patients received nutritional advices from a dietician on how to increase the energy intake. Patients from the hospital and rehabilitation center were equally distributed between the intervention group and control group. Food intake, energy expenditure and water loss (to check for misreporting, see also discussion) were measured together over a 1-week period. Measurements of body mass gave insight into whether subjects were in energy balance while food recording. None of the patients participated in an out-patient or home based pulmonary rehabilitation program.

Subjects

Inclusion criteria were a body mass index (BMI) ≤ 22 kg/m² or BMI ≤ 25 kg/m² in combination with recent weight loss ($>5\%$ of usual body mass). Exclusion criteria were severe cardiovascular disease, gastrointestinal abnormalities or endocrine disease, malignancies or dementia. Patients were informed about the aim and procedures of the study and they gave written consent. The medical ethics committee of the university and the hospital approved the protocol. The characteristics of the subjects at discharge are described in table 5.1. Patients had a moderate to severe airflow limitation in combination with normal blood gasses.

Table 5.1 Characteristics of patients with COPD at discharge

	Intervention group n = 11	Control group n = 9	Total group n = 20
Male/female	6 / 5	5 / 4	11 / 9
Age, years	61 $\pm$ 12	62 $\pm$ 10	62 $\pm$ 11
BMI, kg/m ²	19.6 $\pm$ 2.4	20.0 $\pm$ 1.5	19.8 $\pm$ 2.0
FEV ₁ , %predicted	40 $\pm$ 13	41 $\pm$ 19	40 $\pm$ 16
IVC, %predicted	94 $\pm$ 12	83 $\pm$ 18	89 $\pm$ 16
PaO ₂ , kPa	9.4 $\pm$ 1.4	9.5 $\pm$ 1.1	9.5 $\pm$ 1.3
PaCO ₂ , kPa	5.5 $\pm$ 0.9	5.8 $\pm$ 0.7	5.6 $\pm$ 0.8

Data are mean $\pm$ SD; FEV₁, forced expiratory volume in 1 second; IVC, inspiratory vital capacity; PaO₂, arterial O₂ tension; PaCO₂, arterial CO₂ tension. No baseline differences were found between the intervention and control group.

Body mass

Body mass measurements were performed at month 1 and month 3 after discharge and were measured three times, with 7-day intervals, 1 week before the start of the recording week, at the start and at the end of the recording week. Thus, possible weight changes due to a change of diet while food recording can be compared with normal body mass fluctuations. Patients were weighed in indoor clothing and without shoes, in the morning before any drink or beverage consumption and after voiding, on a digital balance accurate to ± 0.1 kg (Seca, Almere, The Netherlands). The balances used in the hospital and in the rehabilitation center were calibrated.

Food and water intake

A 7-day food record was used to measure total food and water intake (at month 1 and month 3 together with the measurement of energy expenditure and water loss). Subjects received instructions from a dietician on how to fill in the food record. The food records were converted into intakes of total energy, macronutrients and water with a computer program based on food tables (Becel Nutrition Program, Nederlandse Unilever Bedrijven B.V., Rotterdam, The Netherlands). The amount of metabolic water was calculated by multiplying energy expenditure by the percentages of energy from protein, fat, and carbohydrate from the 7-day food record. Oxidation of protein yields 0.41 ml water/g, fat yields 1.07 ml water/g and carbohydrate yields 0.60 ml water/g.¹²

Energy expenditure

Energy expenditure was estimated from measured basal metabolic rate (BMR) and physical activity (PA) assessed with a tri-axial accelerometer for movement registration. BMR was measured at the start of the recording week after an overnight fast, while lying for 30 minutes in a supine position, with a ventilated hood system (Oxycon- β ; Mijnhardt, Bunnik, The Netherlands).

PA was estimated with a tri-axial accelerometer for movement registration (Tracmor) during the recording week. The Tracmor is a small device (7 x 2 x 0.8 cm, 30g), which measures accelerations in the anteroposterior, mediolateral and vertical directions of the trunk. Subjects wore the Tracmor during waking hours for 7 days in a belt at the back of the waist. The Tracmor has been validated against doubly labeled water, in a group of men and women between 55 and 74 years, which gave the following formula using Tracmor counts and BMR for the calculation of total energy expenditure (TEE): $TEE \text{ (MJ/d)} = -2.289 + 1.777 \cdot BMR \text{ (MJ/d)} + 0.063 \cdot \text{counts/minute}$ (regression analysis $r^2=0.82$, $p<0.0001$; $n=26$ healthy elderly).¹¹ The physical activity level was calculated by expressing energy expenditure as a multiple of basal metabolic rate ($PAL = TEE/BMR$).

Water loss

Water loss was measured with the deuterium elimination method. The evening before the start of the recording week subjects drank a weighed dose of a deuterium dilution, 70 g water with an enrichment of 5atom% excess 2H , after voiding (background sample). Subjects collected urine samples in the morning and evening of day 1, at the start of the recording week, the evening of day 7 and the morning of day 8. Water loss was calculated from 2H elimination with the equation of Fjeld et al¹², as described before.¹³

Statistics

Mean and standard deviations were calculated. Differences between groups were tested with the Wilcoxon rank-sum test and differences between measurements within groups were tested with paired sign tests. A paired t-test was used to test differences between the two periods within the total group. Correlation coefficients were calculated to describe relations between parameters.

Body mass changes and mean physical activity levels of month 1 and 3 were calculated for 19 subjects, because 1 subject went to rehabilitation center at month 2.

The calculation of the power of the study was not based on expected changes in body mass between the control and the supplemented group, as the main focus of the present study was to elucidate the influence of physical activity on energy balance. Significance was set on $p < 0.05$.

Results

The body mass change between discharge and month 1 was -0.1 ± 1.0 (-1.6 to 2.3) kg and 0.3 ± 2.3 (-2.3 to 5.1) kg for the intervention group and for the control group, respectively (Wilcoxon rank-sum test $p = 0.6$). Between month 1 and month 3 the body mass change was 0.3 ± 1.4 (-1.8 to 2.9) kg and -0.0 ± 2.4 (-4.4 to 3.4) kg for the intervention group and for the control group, respectively (Wilcoxon rank-sum test $p = 0.9$).

Table 5.2 Energy intake, basal metabolic rate, physical activity level and total energy expenditure of the intervention-, control- and total group at 1 and 3 months after discharge

	Intervention group		Control group		Total group	
	Month 1 n = 11	Month 3 n = 11	Month 1 n = 9	Month 3 n = 8	Month 1 n = 20	Month 3 n = 19
BMR, MJ/d	5.9 ± 1.1 (4.5 – 7.7)	5.6 ± 1.3 (3.9 – 8.0)	5.9 ± 0.6 (4.8 – 6.5)	5.5 ± 1.1 (3.8 – 6.9)	5.8 ± 0.1	5.6 ± 1.2
PAL	1.58 ± 0.07 (1.47 – 1.66)	1.60 ± 0.29 (1.40 – 2.44)	1.56 ± 0.07 (1.46 – 1.67)	1.54 ± 0.08 (1.46 – 1.70)	1.56 ± 0.08	1.57 ± 0.22
TEE, MJ/d	8.8 ± 1.6 (5.3 – 11.1)	9.0 ± 2.5 (5.6 – 12.7)	9.4 ± 1.9 (7.2 – 12.4)	8.5 ± 1.7 (6.4 – 10.6)	9.1 ± 1.7	8.8 ± 2.2
EI, MJ/d	9.7 ± 2.0 (6.9 – 12.7)	8.9 ± 1.9 (7.4 – 12.1)	8.7 ± 2.4 (4.9 – 12.6)	9.1 ± 2.4 (6.3 – 13.2)	9.2 ± 2.2	9.0 ± 2.1

Data are mean $\pm$ SD and (range); BMR, basal metabolic rate; PAL, physical activity level; TEE, total energy expenditure; EI, energy intake.

Results on energy intake and expenditure at month 1 and month 3 are presented in table 5.2. Energy intake was not significantly different from energy expenditure, neither for the intervention group, nor for the control group. There was no statistical significant difference in energy balance between the two groups (month 1 Wilcoxon rank-sum test; $p = 0.50$, month 3 Wilcoxon rank-sum test; $p = 0.49$). The intervention group had a positive energy balance of 0.8 ± 2.3 MJ/d and the control group had a negative energy balance of -0.7 ± 2.5 MJ/d in the first month. In the third month the intervention group had a small negative energy balance of -0.1 ± 2.2 MJ/d and the control group had a positive energy balance of 0.6 ± 1.9 MJ/d.

The body mass changes over both recording weeks were not different from the body mass changes over the non-recording weeks (see table 5.3). The patients did not change their diet while food recording, nor did they incorrectly record their food intake; there was also no difference in reported water intake and measured water loss (see table 5.3).

Table 5.3 Total water intake (recorded and metabolic water), water loss and body mass changes over the recording week and a non-recording week for the total group at 1 and 3 months after discharge

	Water intake (l/d)	Water loss (l/d)	BM change over recording week (kg)	BM change over non-recording week (kg)
Month 1	2.7 ± 0.7	$2.8 \pm 0.7^*$	0.08 ± 0.51	$0.09 \pm 0.51^{**}$
Month 3	2.5 ± 0.7	$2.6 \pm 0.7^*$	0.09 ± 0.68	$-0.16 \pm 0.73^{**}$

Data are mean $\pm$ SD; * paired t-test water intake and water loss $p=0.3$, $p=0.1$ for month 1 and 3, respectively; ** paired t-test body mass change recording week and non-recording week $p=0.95$, $p=0.4$ for month 1 and 3, respectively

The differences in body mass (BM) change over time between patients could not be explained by the reported energy intakes ($p=0.32$). The mean body mass change from month 1 to month 3 was negatively correlated with the mean physical activity level (figure 5.1; correlation $r=-0.49$, $p=0.03$). The physical activity level was not related to the body composition (results not shown) of the patients and was not different between months 1 and 3.

Figure 5.1 Body mass change from month one to month three plotted against the mean physical activity level ($n=19$; $r=-0.49$, $p=0.03$)

Discussion

The results show no clear changes in body mass for both groups. At 1 month after discharge, small differences in energy balance between the intervention and control group became visible. The positive energy balance in the intervention group resulted in a weight gain from month 1 to month 3. However, after 3 months the intervention group did not have a higher body mass increase than the control group. Probably, the intervention group compensated for the nutritional supplements by reducing their other food intake. During the recording week the intervention group consumed on average $95 \pm 6\%$ of the prescribed nutritional supplements at month 1 and $89 \pm 14\%$ of the prescribed nutritional supplements at month 3. Not all prescribed supplements were consumed, which might also be a reason for the low weight increase in the intervention group. Furthermore it might be that the sample size was not sufficient to find an effect of supplementation on the energy balance. The power of the current study was calculated to elucidate the influence of physical activity on energy balance, as this was the main focus of this study.

The physical activity level of about 1.56 in this group of out-patients with COPD was lower than measured in COPD patients in a rehabilitation center⁹ and lower than measured in a group of healthy elderly men and women.¹⁴ In the rehabilitation center patients followed a daily program including physical exercises, which might be the reason for the higher physical activity level. Additionally, the physical activity level of the COPD patients in the rehabilitation center, was calculated from energy expenditure measured with the doubly labeled water method and basal metabolic rate measured with the ventilated hood. Thus, the activity-related energy expenditure included also energy needed for the decreased mechanical efficiency in COPD patients.⁹ Here, physical activity was estimated with a triaxial accelerometer for movement registration and an eventually lower mechanical efficiency was not taken into account.

At home physical exercise is probably limited in COPD patients. However, a temporarily lower physical activity level is not per se negative in weight-losing or depleted COPD patients. COPD patients with a lower physical activity level were able to eat sufficient for their energy needs and remained in energy balance or even gained weight (figure 5.1). A high physical activity level must be accompanied with a higher energy intake to maintain at least energy balance. This was probably difficult for the depleted COPD patients with a high physical activity level, because they lost weight. In a controlled setting, a rehabilitation center, patients with a high physical activity level were still able to maintain their body weight or even gained weight.² More research is needed, to target physical activity and food intake to depleted out-patients with COPD. Our results indicate that some of the depleted patients might even temporarily require enteral tube feeding.

The food intake was reported accurately and the patients did not change their diet while food recording. The patients were motivated to report their food intake accurately and had probably sufficient time to record everything, because they were mostly at home. Results on reported food intake could therefore be used to compare the energy balance between the intervention and control group.

The water balance technique can give an indication whether subjects recorded their food intake accurately. A good recording of water intake does not necessarily imply that the same holds for the recording of food intake. Most foodstuffs contain a certain amount of water and therefore if a individual records his/her water intake accurately it is expected that they record their whole food intake accurately. Also a good recording does not say anything about a change in diet while food recording and body mass changes over the recording period must be measured. Earlier studies showed that the water-balance method was able to measure misreporting of food intake on the group level. The sum of a change in diet and misreporting as assessed with the water balance method was equal to the total amount of misreporting as measured with the doubly labeled water method.^{10,11} A good reporting of food intake in free-living subjects is not very common as most subjects tend to misreport their food intake or change their diet while food recording.¹⁰

In summary, the weight change from month 1 to month 3 was negatively associated with the energy requirement for physical activity. These preliminary results suggests, that knowledge about the individual physical activity level is necessary for the estimation of the energy need of the patient and to give an appropriate advise about food intake and the use of supplements. However, more research is needed to find out which combination of oral or enteral supplementation and physical activity results in the highest weight gain and functional improvement in depleted COPD patients at home.

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Chapter 6

Effects of an acute exacerbation on nutritional and metabolic profile of patients with chronic obstructive pulmonary disease

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Abstract

Introduction

In this study, we investigated the influence of an acute disease exacerbation on the nutritional and metabolic status of patients with chronic obstructive pulmonary disease (COPD).

Methods

The study group consisted of 23 patients acutely admitted to the hospital for standardized medical treatment. Dietary intake (dietary records and diet history), resting energy expenditure (ventilated hood), body composition (bio-electrical impedance spectroscopy) and disease symptoms (visual analogue scale) were assessed on admission, daily throughout the hospitalization period, at discharge and 3 months thereafter in stable clinical condition.

Results

Dietary intake, since aggravation of disease symptoms, prior to admission, (5.64 ± 2.67 MJ) was significantly lower than habitual intake (7.86 ± 2.00 MJ). The balance between dietary intake with measured resting energy expenditure and estimated diet-induced thermogenesis was severely impaired during the first 3 days of hospitalization, stabilizing thereafter to 145 ± 24 at discharge. Resting energy expenditure decreased from 6.81 ± 0.90 MJ ($123 \pm 11\%$) on admission to 6.19 ± 0.79 MJ ($113 \pm 14\%$) on discharge ($p < 0.001$). During treatment, no significant shift in water compartments, fat-free mass and body weight was seen. Follow-up data were obtained from 10 out of 23 patients. Three months after admission, dietary intake was not significantly different from usual dietary intake (8.51 ± 2.29 and 8.41 ± 2.60 MJ, respectively), resting energy expenditure was similar to the value at discharge, and a significant body weight gain was seen.

Conclusions

We conclude that an acute exacerbation of chronic obstructive pulmonary disease is accompanied by an impaired energy balance due to a decreased dietary intake and an increased resting energy expenditure.

Introduction

Tissue depletion frequently occurs in patients with chronic obstructive pulmonary disease (COPD). Reported (prevalence) rates range from 20% in clinically stable out-patients¹ up to 50% in patients with acute respiratory failure.² Weight loss and, in particular, loss of fat-free mass (FFM) have been shown to adversely influence functional performance and survival, independently of the compromised lung function.³⁻⁵ Wasting of FFM is related to weakening of respiratory and peripheral skeletal muscles and to an impaired exercise performance.^{1,3,4} Dysfunction of the respiratory muscles is furthermore related to the patient's sensation of dyspnoea⁶.

Weight loss results from an imbalance between dietary intake and energy expenditure. In the majority of COPD patients, weight loss appears to develop gradually, while they are in an otherwise stable clinical condition. Previous studies using diet histories found a normal to elevated dietary intake in COPD patients when compared to normal values.^{7,8} A within-group comparison, however, showed a significantly lower dietary intake in weight-losing than in weight-stable patients, both in absolute terms and when expressed as percentage of measured resting energy expenditure (REE).⁸ Several studies have shown an increased REE, in addition to a relatively decreased dietary intake, in clinically stable COPD patients, the cause of which is unclear.^{9,10}

Retrospective data suggest that, in a subgroup of patients, weight loss follows a stepwise pattern related to acute disease exacerbations. However, limited data are available on dietary intake and energy metabolism in COPD during an acute disease exacerbation. The aim of the present study was, therefore, to investigate the effect of an acute exacerbation on the nutritional and metabolic profile of patients with COPD.

Subjects and methods

Patients

Patients admitted to the respiratory unit of the University Hospital Maastricht with an acute exacerbation of COPD were considered for inclusion in the study. COPD was defined according to the criteria of the American Thoracic Society.¹¹ All patients were current or ex-smokers. None had evidence of significant reversibility (>15% of predicted baseline) of airflow limitation after 500 µg of terbutaline inhalation. An acute exacerbation was defined as a recent increase in dyspnoea, cough and sputum production of sufficient severity to warrant hospital admission. Patients suffering from concomitant diseases such as diabetes mellitus, lung

carcinoma, thyroid and cardiovascular disease were excluded from the study. In-hospital treatment consisted of parenteral corticosteroids and theophylline in addition to nebulized beta-agonists and ipratropium bromide and broad spectrum antibiotic therapy, in case of bacterial infection confirmed by clinical data and sputum culture. The daily 500 mL infusion solution contained 5% glucose, which is equivalent to 0.42 MJ/day. This value is incorporated in the calculations of the energy balance during hospitalization, but not in the calculations of "spontaneous" dietary intake.

Measurements were performed during hospitalization period, and all patients were invited for a follow-up consultation 3 months after discharge when they were in stable clinical condition. The study was approved by the medical Ethics Committee of the University Hospital Maastricht. Informed consent was obtained from all subjects.

Dietary intake

Habitual dietary intake, dietary intake prior to admission since aggravation of dyspnoea and other disease symptoms, as well as dietary intake during the follow-up consultation were evaluated using the diet history method with cross-check.¹² All interviews were performed by the same trained dietician. During hospitalization, dietary intake was registered daily using dietary records and an automated food distribution system. Patients were not receiving nutritional support during their hospitalization, but they had the opportunity to choose their menus. Food composition data were coded for computer energy and nutrient analysis. The database was derived from the Dutch food composition tables.¹³

Resting energy expenditure

REE was measured the day after admission, at discharge and during the out-patient follow-up by indirect calorimetry using a ventilated hood system (Oxycon- β , Mijnhardt, Bunnik, The Netherlands).¹⁴ Standardized measurements of volume of oxygen utilization ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were performed in the early morning in the fasting state (between 08.30 and 09.30 h) approximately 3 h after the patients had received their regular medication. If patients were on oxygen therapy, the oxygen was withdrawn temporarily 30 min prior to the measurement and, in these patients, oxygen saturation was measured continuously during the measurement. The patients did not experience a worsening of dyspnoea after withdrawal of the oxygen. In a subgroup of nine patients, REE was measured daily to assess the variability and course of REE during hospitalization.

Diet-induced thermogenesis

Diet-induced thermogenesis (DIT) was estimated as 10% of dietary intake.

Body composition

During hospitalization, fasting body weight was assessed daily using a digital weighing chair. Body composition was measured the day after admission, at

discharge and during the out-patient follow-up by bio-electrical impedance spectroscopy (Xitron 4000B; Xitron Technologies Inc., San Diego, CA. USA).¹⁵ The principle of this method is based on the conductivity of an electrical sinusoidal alternating current through body fluids. Conductivity is higher in FFM, which contains all body fluids and electrolytes, than in fat mass. The resistance of the body can be measured at a spectrum of frequencies (ranging 5-500 kHz). At low frequency (<50 kHz), the conductivity is mainly through the extracellular part, while at higher frequency conductivity takes place through total body water. Resistance of intracellular and extracellular water was measured by extrapolation of the measured resistance and reactance according to the Cole-Cole model.¹⁶

Disease symptoms

Disease symptoms were scored using a visual analogue scale (VAS) on admission, on day 5 of hospitalization, at discharge and during the follow-up consultation. The following symptoms were evaluated: loss of appetite; dyspnoea at rest and while eating; early satiety; nausea; obstipation; dry mouth; problems with chewing and swallowing; diarrhoea; flatulence; nervousness; fatigue; and disturbed sleeping.

Statistics

Groups were compared by analysis of variance or by the Mann-Whitney U-test, where appropriate. The Chi-squared test was used to compare categorical variables. Changes within the patient were compared using a paired t-test. Results are presented as mean $\pm$ SD unless stated otherwise. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the Statistical Products and Service Solutions (SPSS; Chicago, IL, USA) for Windows package¹⁷.

Results

Twenty three consecutive patients were studied. Characteristics of the total group, as well as the subgroup of 10 patients that participated in the follow-up consultation, are given in table 6.1.

Mean forced expiratory volume in one second (FEV₁) amounted to 37 $\pm$ 12 %predicted. Mean body mass index (BMI) was 23 kg/m², ranging from 16-29 kg/m². Based on BMI $\leq$ 21 kg/m², eight patients were underweight. Five patients were admitted with acute respiratory failure (arterial oxygen tension (PaO₂)<7.3 kPa and/or arterial carbon dioxide tension (PaCO₂)>6.0 kPa). Fifteen patients were treated with antibiotics.

Table 6.1 Baseline characteristics of the total study group and the subgroup that participated in the follow-up

	Total group n = 23	Follow-up n = 10
Male/female	12 / 11	7 / 2
Age, years	63 ± 8	65 ± 9
IVC, %predicted	70 ± 22	81 ± 23
FEV ₁ , %predicted	37 ± 12	41 ± 9
PaO ₂ , kPa	8.8 ± 2.3	9.9 ± 2.9
PaCO ₂ , kPa	5.0 ± 0.9	4.6 ± 0.7
Habitual weight, kg	63.5 ± 12.0	67.2 ± 12.2
Weight on admission, kg	63.4 ± 11.9	67.5 ± 12.2
BMI, kg/m ²	23.0 ± 3.2	24.4 ± 2.5

Values are mean±SD, or absolute number for sex. None of the differences between the total group and the follow-up group were significant. IVC, inspiratory vital capacity; FEV₁, forced expiratory volume in one second; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; BMI, body mass index.

Dietary intake

Dietary intake in the period prior to admission amounted to 5.64±2.67 MJ/day and was significantly ($p<0.001$) than habitual dietary intake (7.86±2.00 MJ/day). Dietary intake increased substantially during hospitalization from 4.46±2.29 MJ/day at day 1 to 9.04±2.49 MJ/day at day 4, after which it remained stable. Dietary intake at discharge was significantly higher than habitual dietary intake (9.54±2.68 MJ/day and 7.86±2.00 MJ/day, respectively, $p<0.01$). Protein, fat and carbohydrate intake in absolute terms and expressed as a percentage of total energy intake is shown in table 6.2a and 6.2b. Protein intake was low prior to hospitalization, gradually increasing thereafter. Fat intake was low prior to and on admission, but increased thereafter by a greater proportion than carbohydrate intake. Figure 6.1a shows the daily dietary intake pattern of the subgroup of nine patients in which resting energy expenditure was also measured daily. This figure showed a similar pattern as described for the total group.

Table 6.2a Macronutrient intake (habitual and pre-admission intake)

	Dietary history	
	Habitual	Pre-admission
Protein, g	64.3 ± 19.4	49.2 ± 23*
Protein, g/kg	1.03 ± 0.32	0.78 ± 0.33*
Protein, en%	14.9 ± 3.1	14.1 ± 12.2
Fat, g	80.6 ± 23.5	58.2 ± 27.7*
Fat, en%	40.5 ± 10.0	38.9 ± 7.7
CHO, g	217.3 ± 74.8	155.7 ± 91.7*
CHO, en%	44.1 ± 12.1	46 ± 9.6

Data are mean±SD; CHO, carbohydrates, * $p<0.005$ comparison between habitual and pre-admission.

Table 6.2b Macronutrient intake during hospitalization

	Day 1	Day 2	Dietary records		Day 5	Discharge
			Day 3	Day 4		
Protein, g	37.4 ± 20.6	61 ± 25.4	69.7 ± 27.9	74.4 ± 24.2	73.7 ± 24**	81 ± 27.1****
Protein, g/kg	0.59 ± 0.33	0.6 ± 0.33	0.96 ± 0.4	1.12 ± 0.53	1.22 ± 0.42**	1.32 ± 0.5****
Protein, en%	14.1 ± 2.5	14.9 ± 3.7	14.1 ± 3.2	13.7 ± 3.0	14.2 ± 2.9	14.1 ± 2.7
Fat, g	40.2 ± 23.7	67.9 ± 38.5	90.4 ± 33.2	94.7 ± 33.8	89.2 ± 27.9**	103.5 ± 32.5****
Fat, en%	32.9 ± 10.1	35.7 ± 9.2	41.7 ± 6.8	38.8 ± 6.9	38.2 ± 5.2*	40.5 ± 6.7****
CHO, g	140 ± 74.4	204.7 ± 83.6	217.8 ± 77.6	253.9 ± 71.6	251 ± 84.3**	258 ± 83****
CHO, en%	53.1 ± 15.0	49.4 ± 10.5	44.2 ± 8.1	47.5 ± 7.0	47.7 ± 6.6	45.4 ± 7.5****

Values are mean±SD; CHO, carbohydrates, * p<0.05, **p<0.01, day 5 compared to day 1; **** p<0.05, **** p<0.01, discharge compared to day 1.

Resting energy expenditure

REE amounted to 6.81 ± 0.90 MJ/day on admission and decreased significantly ($p < 0.001$) to 6.19 ± 0.79 MJ/day at discharge. In the patients in whom resting energy expenditure was measured daily, REE remained elevated during the first 4 days after which it decreased until discharge (figure 6.1b).

Figure 6.1 Daily course of dietary intake, 6.1a; daily course of measured resting energy expenditure (REE), 6.1b during hospitalization in nine COPD patients; closed circles, REE; open circles, REE and diet-induced thermogenesis (DIT). * $p = 0.002$, ** $p = 0.001$, *** $p = 0.0004$

Changes in REE were not related to changes in body temperature. Respiratory quotient increased significantly ($p < 0.001$) from 0.77 ± 0.05 on admission to 0.85 ± 0.01 at discharge. Measured REE was also compared to the commonly used prediction formulas by Harris and Benedict.¹⁸ REE was $123 \pm 11\%$ the day after admission and $113 \pm 14\%$ at discharge ($p < 0.001$). On basis of a REE $> 110\%$ predicted at discharge, 10 patients were still hypermetabolic at discharge. The day after admission, REE in the hypermetabolic patients at discharge was also significantly higher than in the normometabolic patients at discharge ($130 \pm 12\%$ versus $124 \pm 12\%$, respectively, $p < 0.05$), but did not decrease significantly during hospitalization. The hypermetabolic group at discharge was furthermore characterized by a significantly lower BMI (20.9 ± 2.8 versus 24.7 ± 2.5 kg/m², respectively, $p < 0.05$). Prevalence of bronchial infection between the subgroups of

hyper- (7 out of 10) and (8 out of 13) normometabolic patients at discharge was not different.

Energy intake compared to REE (and estimated DIT)

During the first days after admission, a negative energy balance was seen. Energy intake (including intravenous glucose) the day after admission, expressed as percentage of REE and DIT, amounted to $68 \pm 28\%$. In the subgroup of patients in whom a daily REE measurement was performed, it was shown that the negative balance quickly improved from $69 \pm 32\%$ on day 1, and $109 \pm 24\%$ on day 2, to $136 \pm 18\%$ on day 4, further increasing to $145 \pm 24\%$ at discharge.

Body composition

No significant weight change was seen during the hospitalization period. Mean body weight was 63.4 ± 12 kg on admission and 62.9 ± 11 kg at discharge. FFM did not change either in this period (42.9 ± 7.8 and 43.2 ± 7.5 kg, respectively). Furthermore, no significant change in the ratio between the resistance of intracellular and extracellular water was detected (2.1 ± 0.4 and 2.2 ± 0.5 , respectively).

Disease symptoms

Figure 6.2 displays the VAS score of those disease symptoms that changed significantly during hospitalization. Symptoms that did not change were "bloating", "nausea", "vomiting", "difficulties with chewing and swallowing", "obstipation" and "diarrhoea". On day 5, most symptoms had improved significantly compared to admission, except for symptoms "dyspnoea while eating", "loss of appetite" and "early satiety". At discharge, the score of these three symptoms was also significantly improved.

Figure 6.2 Disease symptoms (VAS scores) on admission (dark grey bars), at day 5 (open bars) and at discharge from the hospital (grey bars). Symptoms: 1, dyspnoea; 2, loss of appetite; 3, disturbed sleeping; 4, fatigue; 5, dry mouth; 6, nervousness; 7, early satiety; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

A significant relationship ($r=0.52$, $p=0.004$) between the changes in REE and the changes in dyspnoea at rest was observed (figure 6.3).

Figure 6.3 Significant relationship between the changes in REE and dyspnoea sensation during the total hospitalization period ($r=0.52$, $p=0.004$)

Follow-up consultation

All patients were asked for a voluntary follow-up consultation 3 months after discharge from the hospital. A minority of the group (43%) responded. Although the follow-up group tended to have a better lung function and weighed more than the patients that were not followed after 3 months, no significant difference in baseline characteristics was found between these subgroups (table 6.1). Figure 6.4 shows the course of dietary intake, using the diet history method, of the follow-up patients. The pattern during hospitalization was comparable with the total group. Three months after discharge, dietary intake was similar to habitual dietary intake (8.51 ± 2.29 and 8.41 ± 2.60 MJ/day, respectively). REE also showed a similar decrease during hospitalization, as was seen in the total group, from 6.93 ± 1.24 ($121 \pm 8\%$) to 6.28 ± 0.96 MJ/day ($110 \pm 9\%$), $p=0.01$. REE amounted to 6.48 ± 1.63 MJ/day ($112 \pm 11\%$) at follow-up and was not significantly different from the value at discharge. Subsequently energy balance changed from $75 \pm 35\%$ on admission to $133 \pm 43\%$ at discharge, decreasing to $118 \pm 34\%$ at follow-up. Although body weight did not change either during hospitalization, a significant ($p < 0.05$) mean increase in body weight of 1.6 ± 2.1 kg was seen at follow-up. No significant changes were detected in the ratio between intracellular and extracellular water. Furthermore, no clear changes were observed in symptomatology since discharge from the hospital.

Figure 6.4 Course of dietary intake in 10 patients prior to and during hospitalization for an acute exacerbation and 3 months afterwards in stable clinical condition; 1, habitual dietary intake; 2, pre-admission dietary intake; 3, dietary intake on admission; 4, dietary intake at discharge; 5, dietary intake at follow-up; * $p < 0.01$, ** $p < 0.001$

Discussion

Nutritional depletion is a common but possibly reversible problem in patients with COPD. From a therapeutic perspective, it is important to know the course of and contributing factors to weight loss. It is still unclear whether weight loss progresses gradually in patients who are otherwise in a stable clinical condition, or if it follows a stepwise pattern related to acute disease exacerbations. At present, only anecdotal reports have addressed this issue. In the present study, therefore, we assessed the nutritional and metabolic profile of a group of COPD patients suffering from an acute disease exacerbation, on admission to, during the treatment period in, and at discharge from the hospital. In a subgroup of patients, this profile was additionally studied 3 months afterwards in a stable clinical condition.

Several studies of clinically stable patients showed that dietary intake was equivalent to, or exceeded, estimated daily requirements.^{7,8} In the present study the majority of patients, however, reported a decreased appetite prior to, and a very low dietary intake during the first 3 days of hospitalization for an acute exacerbation. Thereafter, dietary intake improved quickly during the remaining hospital period. Based on the course of the symptoms VAS scores, multiple factors appear to be related to changes in dietary intake. Taking also the baseline values into consideration, it is hypothesized that it was not so much a decreased appetite, but more the “inability” to eat more due to dyspnoea and fatigue that was related to the very low intake in the first days after admission. In qualitative terms, protein intake was low prior to and during the first days of hospitalization, restored thereafter but remained rather low in order to optimize protein synthesis. Furthermore, it is of interest to note that a low appetite and a decreased dietary intake were reflected in a very low fat intake, which could be related to the early

feeling of satiety during these days. This spontaneous response in macronutrient intake is in contrast to a long-held but not yet scientifically confirmed belief that COPD patients would benefit from a high fat, low carbohydrate meal, particularly during acute metabolic stress. When comparing the diet histories prior to admission, at discharge and at the follow-up consultation, the data clearly indicate that at discharge, dietary intake was significantly higher than habitual intake. This could be a compensation related to improvement of symptoms such as dyspnoea, appetite and fatigue, possibly related to reduced resting oxygen consumption and related ventilation and/or inflammation. Another suggested explanation could be an appetite-stimulating effect of high-dosage corticosteroid treatment. Remarkably, energy intake was highest during the tapering-off phase of parenteral corticosteroid treatment.

Several studies measured REE in clinically stable COPD patients with standard methods of indirect calorimetry and found an average increase in REE of 10-20% higher than predicted from age, weight, height and gender using the Harris and Benedict equations.^{9,10} Limited data are available on the course of REE during an exacerbation. Expressed as percentage of predicted values, REE was enhanced in all patients on admission to the hospital and decreased gradually towards the end of the hospitalization period.

Several factors could contribute to a temporary (further) increase in metabolic rate during an exacerbation. An increased oxygen cost of ventilation related to an increase in elastic and resistive work of breathing, metabolic effects of theophyllines and β_2 -agonists, or a systemic inflammatory response.¹⁹⁻²¹ The oxygen cost of ventilation was not measured in the present study. The significant relationship between changes in REE and changes in the VAS score for dyspnoea at rest, however, provides indirect evidence for a contribution of the oxygen cost of ventilation to REE during an acute exacerbation. Recently, Vanderhoven-Augustin et al²² investigated, in a group of patients hospitalized for an acute exacerbation, the influence of theophylline on REE and found no relationship between (changes in) REE and (changes in) theophylline dose or plasma theophylline levels. Since β_2 -agonists are commonly given as part of the pharmacological therapy during an acute exacerbation, Creutzberg et al²³ studied, as part of the present study, the acute effects of 5 mg salbutamol hemisulphate 0.5% and 1 mL sodium chloride 0.9% on REE in COPD patients recovering from an acute exacerbation. Mean REE was raised by 4.2% up to 45 min after salbutamol administration, but was not significantly different from a healthy age-matched control group. Using the same dose, Burdet et al²⁴ even found a slightly greater thermogenic effect of salbutamol in clinically stable COPD patients, which lasted for several hours. Since patients received both salbutamol by nebulizer and by inhalation during their hospitalization period, we were not able to calculate an average daily dose for subsequent comparison with REE. Two studies have recently reported a significantly enhanced level of tumor necrosis factor α (TNF α) in plasma of weight-losing COPD patients.^{25,26} Acute administration of TNF α in men causes an increase in acute-phase proteins, provokes an elevation of REE, promotes proteolysis and lipolysis and causes anorexia.²⁷ In clinically stable COPD patients with elevated REE and depletion of FFM, Schols et al²¹ reported increased

serum levels of acute phase reactant proteins and soluble tumor necrosis factor (sTNF) receptors suggestive of a relationship between metabolic derangements factor and a systemic inflammatory response in a subset of COPD patients. Further research is needed to investigate if the relationship between metabolic derangements and inflammation involves a sustained systemic effect of acute inflammatory exacerbations or merely reflects a chronic inflammatory state.

In this group of mostly bed-rested or sedentary patients, it is conceivable to assume that the energy expenditure of activities is not very high and that the other components (REE and DIT) are a good estimate of total daily energy expenditure. Several studies have shown that DIT is normal in patients with COPD, amounting to approximately 10% of dietary intake. Analysis of the balance between REE and dietary intake revealed a negative balance on admission, which soon restored to normal. Further evidence for a temporary state of negative energy balance was seen in changes in respiratory quotient from close to 0.7 to 0.8. In view of the sensibility of the bio-electrical impedance spectroscopy measurement and duration of hospitalization, the energy imbalance was probably too short to be reflected in body weight and body composition data. The improvement in energy balance was accompanied by a significant improvement in symptoms such as dyspnoea and fatigue. These results imply that an (acute) disease exacerbation can indeed temporarily affect both dietary intake and REE in patients with COPD, but that if a patient responds adequately to the medical treatment, aggressive nutritional support is not indicated in a temporarily unstable clinical condition.

In qualitative terms, our data indicate that protein intake should be increased (1.5 g/kg/day) in order to provide optimal conditions from a nutritional point of view, for protein synthesis in the recovery period. Despite insignificant changes in body weight during hospitalization, improved body weight in the subgroup of patients that were studied 3 months afterwards suggests the presence of a pre-existing period of energy imbalance in association with the acute exacerbation. To provide more insight in this period, dietary consultation and metabolic evaluation of patients with chronic obstructive pulmonary disease, suffering from an acute exacerbation should include a (retrospective) evaluation of the period prior to hospitalization and be expanded from the in-hospital period to the out-patient recovery period immediately afterwards. The conclusions of this study apply only to patients with acute exacerbation of moderate severity and further studies are needed in patients with severe respiratory failure, especially those requiring mechanical ventilation.

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Chapter 7

Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial

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Clinical Nutrition in press

Abstract

Background & aims

Previous studies reported a severely impaired energy balance in COPD patients during the first days of an acute exacerbation, mainly due to a decreased energy and protein intake. The aim of the study was to investigate the feasibility and effectiveness of energy- and protein-rich nutritional supplements during hospitalization for an acute exacerbation in nutritionally depleted COPD patients.

Methods

In a randomized double-blind, placebo-controlled two-center trial, 56 COPD patients were randomized and 47 patients completed the study. Nutritional intervention consisted of 3 x 125 ml (2.38 MJ/day) and the placebo group received similar amounts of a non-caloric fluid. Medical therapy and dietetic consultation were standardized and dietary intake was measured daily. Body composition, respiratory and skeletal muscle strength, lung function and symptoms were measured on admission and on days 4 and 8 of hospitalization.

Results

Forty-seven percent of the patients had experienced recent involuntary weight loss prior to admission. The degree of weight loss was inversely related to resting arterial oxygen tension ($r=0.31$; $p<0.05$). Nutritional intervention resulted in a significant increase in energy (16% versus placebo) and protein intake (38% versus placebo). Mean duration of hospitalization was 9 ± 2 days. Relative to usual care, no additional improvements in lung function or muscle strength were seen after nutritional intervention.

Conclusions

Oral nutritional supplementation during hospitalization for an acute exacerbation is feasible in nutritionally depleted COPD patients and does not interfere with normal dietary intake.

Introduction

Weight loss frequently occurs in patients with moderate to severe chronic obstructive pulmonary disease (COPD), and is associated with increased morbidity and mortality.¹⁻³ It has been suggested that in a subgroup of COPD patients weight loss follows a stepwise pattern, related to acute exacerbations of the lung disease.⁴ Connors and associates found that besides disease severity and age, also body mass index (BMI) was independently related to survival time after an acute exacerbation of COPD.⁵ Low BMI and weight loss during hospitalization were furthermore indicators for early re-admission in patients with COPD.² In two earlier studies we described a disturbed energy balance during the first days of hospitalization due to an acute exacerbation.^{6,7} Both a decreased dietary intake and an increased resting energy expenditure (REE) were shown during this period. A low ratio between dietary intake and REE was related to increased symptoms and to elevated levels of systemic inflammatory markers.^{6,7} Besides a disturbed energy balance, COPD patients may be at increased risk for a negative nitrogen balance during an acute exacerbation, due to an enhanced systemic inflammatory response, high dose of systemic glucocorticoids, immobility and low protein intake. Only two studies have yet measured nitrogen balance in hospitalized COPD patients with an acute exacerbation.^{8,9} Both studies reported a negative nitrogen balance. In addition, Saudny and coworkers⁸ showed a negative correlation between high dose of methylprednisolone and nitrogen balance ($r=-0.73$, $p=0.0048$). The efficacy of nutritional support during a period of negative nitrogen balance in terms of functional improvement depends on whether predominantly protein synthesis is decreased or whether there is accelerated protein breakdown. Protein supplementation will theoretically increase protein synthesis but not affect protein breakdown. During periods of acute protein breakdown this type of nutritional intervention will therefore not be able to induce a positive protein balance, but could limit the catabolic state. To our knowledge only one study has described in a controlled design the effectiveness of nutritional intervention during an acute exacerbation of COPD until now. No significant improvement was found in body weight, inspiratory and peripheral muscle strength, but a trend was observed in improvement in well-being score.⁸ Although nutritional status was not an inclusion criterion in this study, one could speculate that particularly underweight or weight-losing patients might benefit from nutritional intervention.

The aim of our study was therefore to investigate the feasibility and the effectiveness of oral nutritional supplementation to improve protein and energy intake during hospitalization for an acute exacerbation in nutritionally depleted patients with COPD.

Subjects and methods

Study group

The study group consisted of patients acutely admitted to the hospital for an exacerbation of COPD. The diagnosis COPD was based on the GOLD criteria.^{10,11} Criteria for hospitalization were a recent increase in breathlessness, cough and sputum production of sufficient severity to warrant hospital admission, judged by an independent chest physician. Inclusion criteria for nutritional intervention were a BMI ≤ 22 kg/m² or a BMI ≤ 25 kg/m² and $>5\%$ weight loss in one month, or $>10\%$ weight loss in 6 months prior admission to the hospital. Patients with diabetes mellitus type 1, patients with thyroid or intestinal diseases and patients with carcinoma were excluded from the study.

Study design

A randomized double-blind, placebo-controlled two-center trial was performed in the University Hospital Maastricht, and the regional hospital 'Maxima Medical Center' in Veldhoven, the Netherlands. Randomization took place on the first day of hospitalization.

Nutritional intervention was implemented in the standardized usual care management of these patients. Medical therapy (bronchodilator therapy and systemic glucocorticoids) was standardized, but slightly different between the two centers. In the University Hospital Maastricht, methylprednisolone was given during the first seven days in dosage of 0.4 mg/kg body weight, from day 8 on as 0.2 mg/kg body weight. Theophylline was given in doses of 7–10 mg/kg body weight during the study period. In Maxima Medical Center the medical therapy was 40 mg methylprednisolone/day for the first three days, then 30 mg methylprednisolone/day for day 4/5/6 and 20 mg methylprednisolone/day from day 7 onwards. The dose of theophylline was 400 mg theophylline/day in underweight patients and 600 mg theophylline/day in normal weight COPD patients. Mean methylprednisolone intake was similar between both hospitals. Oxygen therapy was given if indicated based on resting arterial blood gas measurements.

The study was approved by the medical ethical committee of the University Hospital Maastricht and of Maxima Medical Center. All subjects gave written informed consent.

Nutritional intervention

The intervention (I) consisted of 3 x 125 ml Respifor®/day (Nutricia, Zoetermeer, The Netherlands); 2.38 MJ/day, 20 energy% protein, 20 energy% fat and 60 energy% carbohydrate. The control group received placebo (P), 3 x 125 ml vanilla flavored water with 0 MJ/day. All supplements were given in white packages and

were offered from the first day of hospitalization. Supplementation was given three times daily during daytime between main meals. Besides the supplementation, all the patients had the opportunity to select their own menus from a standardized hospital form. Dietetic consultation was standardized during the study period.

Measurements

During hospitalization, dietary intake and body weight were assessed daily. Muscle function, lung function and symptoms were measured on the day after admission, on day 4 and day 8. Day 4 was chosen because previous studies showed that generally the acute phase of an exacerbation lasted 3 days and day 8 was chosen because mean hospital duration was 9 days in both hospitals. Measurement of all these outcome variable was standardized in the morning.

Energy balance

Habitual dietary intake, dietary intake prior to admission since aggravation of dyspnoea and other disease symptoms were assessed using the dietary history method with cross check.¹² All interviews were performed by two trained dietitians. During hospitalization dietary intake was recorded daily with dietary records and using an automated food distribution system. Dietary records were reported by the patients with support of the nursing staff. The dietary records were verified within one day by the two trained dietitians. The obtained food composition data from the dietary history and records were coded for computer nutrient analysis. The nutrient database was derived from the Dutch food composition tables.¹³ Energy intake was expressed as total energy intake (kJ/day), as cumulative energy intake during total study period and as kJ/kg body weight/day. Total protein intake was also expressed as gram/kg body weight/day. Carbohydrate and fat intake were presented as proportions of total energy intake (energy%).

The daily 500-ml infusion solution contained 5% glucose, which is equivalent to 420 kJ/day. This amount of energy was incorporated in the calculations of the daily dietary intake during hospitalization.

Body composition

Body height was determined to the nearest 0.5 cm (WM 715®, Lameris, Breukelen, The Netherlands) with subjects standing barefoot. Body weight was assessed with a beam scale to the nearest 0.1 kg (SECA®, Hamburg, Germany) with subjects standing barefoot and in light clothing. Body composition was estimated using single frequency (50 kHz) bio-electrical impedance analysis (Xitron technologies Inc., San Diego, CA, USA) while subjects were in supine position. Fat-free mass (FFM) was calculated from COPD- and gender specific regression equations.¹⁴ FFM depletion was defined as FFM index (FFMI: FFM in kg/height in m²) ≤15 (females) or ≤16 (males) kg/m².

Lung function

Forced expiratory volume in one second (FEV_1), inspiratory vital capacity (IVC) were calculated from the flow volume curve using a portable spirometer (Jaeger, Würzburg, Germany). Results of lung function parameters were expressed as percentage of the predicted normal values.¹⁵ Respiratory muscle function was assessed by measuring maximal inspiratory mouth pressure (Pi-max) according to the method of Black and Hyatt.¹⁶ The best of three attempts was taken for analysis. Pi-max values were noted as positive values.

Disease severity

Disease severity was defined according to the GOLD guidelines.^{10,11} The classification of severity of COPD is stage 0, at risk: normal spirometry, chronic symptoms; stage 1, mild COPD: $FEV_1 \geq 80\%$ predicted and with or without chronic symptoms; stage 2, moderate COPD: $50\% \leq FEV_1 < 80\%$ predicted and with or without symptoms; stage 3, severe COPD: $30\% \leq FEV_1 < 50\%$ predicted and with or without symptoms and stage 4, very severe COPD: $FEV_1 \leq 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure. This classification is based on post bronchodilator FEV_1 .

Arterial blood gases

Blood was drawn on admission from the brachial artery while the patients were breathing room air. Arterial oxygen tension (PaO_2) and carbon dioxide tension ($PaCO_2$) were analyzed on a blood gas analyzer (Radiometer, ABL 330, Copenhagen, Denmark).

Quadriceps strength

Isometric quadriceps strength was measured using a Cybex II+ dynamometer (Lumex, New York). Peak torque in newton-meters (Nm) was measured at the dominant side, during a maximal isometric knee extension maneuver with the hip in 90° flexion and the knee in 60° flexion. At least three attempts were performed. The highest value of three measurements was taken.

Handgrip strength

Handgrip strength was assessed with use of a handgrip dynamometer (Yamar®, Preston, Jackson, MI, U.S.A.). The isometric grasp was determined by measuring the maximally developed strength of the flexors of the right and left hand respectively. The highest value of three maneuvers was used. The average of the maximal left and right handgrip strength was taken for analysis.

Disease symptoms

Disease symptoms, including dyspnoea at rest and while eating, loss of appetite, early satiety, bloating and fatigue were scored using a visual analogue scale (VAS), ranging from 0 to 100 mm and evaluated during hospitalization.

Statistics

The differences in the baseline characteristics between the groups of the two hospitals were compared using a Student's t-test for independent samples.

For evaluating the feasibility and effectiveness of the intervention only the data of COPD patients who completed the study period were analyzed.

For comparison between the intervention group and control group, analysis of variance (ANOVA) was used with the day 8 value of the outcome parameter as the dependent variable, with intervention as a fixed factor, with institution and disease severity (GOLD stages) as random factor and the corresponding baseline value was used as a covariate.

A p-value of less than 0.05 was considered statistically significant. Data were expressed as mean $\pm$ SD in the text and tables and as mean $\pm$ SEM in the graphs.

The statistical analyses were performed using the Statistical Product and Service Solutions (SPSS, version 10.0 for Windows, SPSS Inc., Chicago, IL).

Results

Fifty-six COPD patients were randomized in the study (29I, 27P). Forty-seven patients completed the study (23I, 24P). The dropouts were caused by medical problems (n=4), alcohol withdrawal delirium (n=1) and 4 patients experienced nausea after supplementation (3I, 1P). The baseline characteristics of the total study population are summarized in table 7.1.

There were no differences in BMI and FFMI between the hospital populations. Also between the intervention and control group there were no significantly differences in BMI and FFMI at baseline. Thirty-three of 56 patients received antibiotic therapy in case of a bacterial infection confirmed by positive sputum cultures, and there were no differences in response on the nutritional intervention. Mean duration of hospitalization was equal between the two centers: 9 $\pm$ 2 days. Mean intake of methylprednisolone during hospitalization was also similar in both groups, namely 25 $\pm$ 5 mg/day.

The COPD patients, who experienced involuntary weight loss prior to admission, were characterized by a significant lower arterial oxygen tension (7.8 $\pm$ 1.4 versus 8.7 $\pm$ 1.1 kPa, p=0.035) but a comparable FEV₁, (35 $\pm$ 11 versus 34 $\pm$ 15 %predicted). In figure 7.1 a significant correlation is shown between the change in body weight prior to admission and arterial oxygen tension on admission (r=0.31; p<0.05).

Table 7.1 The baseline characteristics of the total study population

	University Hospital n = 28	Regional Hospital n = 28	Study population		
			I-group n = 23	P-group n = 24	Drop-outs n = 9
Male / female	18 / 10	19 / 9	14 / 9	18 / 6	5 / 4
Age, years	65 ± 9	68 ± 7	66 ± 8	65 ± 10	72 ± 3
Weight, kg	58.6 ± 12.5	59.2 ± 8	57.1 ± 12.5	59.6 ± 8.5	58 ± 9.9
Height, cm	167 ± 10	164 ± 11	167 ± 12	166 ± 10	163 ± 11
BMI, kg/m ²	21.0 ± 2.7	21.9 ± 2.0	20.4 ± 2.7	21.4 ± 2.3	21.9 ± 2.3
FFMI, kg/m ²	15.4 ± 2.0	16.1 ± 1.9	15.6 ± 2.2	15.8 ± 1.9	15.7 ± 1.7
PaO ₂ , kPa	7.8 ± 1.1*	9.0 ± 1.4	8.0 ± 1.2	8.5 ± 1.4	8.9 ± 1.4
PaCO ₂ , kPa	6.3 ± 1.3*	5.5 ± 0.9	6.0 ± 1.2	5.7 ± 0.7	6.3 ± 2.1
Disease severity, stages II/III/IV	0 / 12 / 16*	5 / 21 / 2	2 / 11 / 10	1 / 16 / 7	2 / 6 / 1
FEV ₁ , %predicted	29 ± 8*	42 ± 13	32 ± 12	34 ± 12	43 ± 12
IVC, %predicted	66 ± 19	77 ± 21	67 ± 13	73 ± 23	64 ± 19
FEV ₁ /IVC, %predicted	43 ± 12	56 ± 16	48 ± 17	47 ± 11	54 ± 18
PEF, %predicted	34 ± 9*	45 ± 16	38 ± 16	41 ± 13	38 ± 8
Pi-max, cm H ₂ O	48 ± 13	60 ± 24	54 ± 16	53 ± 22	58 ± 22
Mean handgrip strength, kg	27 ± 9	29 ± 10	28 ± 10	28 ± 9	25 ± 8
Weight loss/weight stable	16 / 12*	7 / 21	10 / 13	12 / 12	1 / 8**

* p<0.05, baseline characteristics are compared between the study group of the university hospital and the regional hospital; ** p<0.05, baseline characteristics are compared between the intervention group, placebo group and the dropouts.

BMI, body mass index; FFMI, fat-free mass index; FEV₁, forced expiratory volume in one second; IVC, inspiratory vital capacity; PEF, peak expiratory flow; Pi-max, maximal inspiratory mouth pressure.

Figure 7.1 The correlation between change in body weight prior to admission and arterial oxygen tension on admission, $r=0.31$, $p<0.05$

Nine patients with COPD (4I, 5P) were readmitted at the pulmonary ward within 3 months. These patients were characterized by a lower FEV₁ compared with those patients, who were not readmitted, 27 ± 10 %predicted FEV₁ and 36 ± 13

%predicted FEV₁ ($p=0.08$) respectively. 5 of those patients (2I, 3P) experienced involuntary weight loss on readmission, of which 4 (2I, 2P) had also lost weight prior to the first admission.

Dietary intake prior to admission

Twenty-four COPD patients (51%) reported a decrease in habitual dietary intake prior to admission from 9.53 ± 2.64 MJ/day to 6.07 ± 2.25 MJ/day ($p < 0.01$). Also protein intake per kg body weight was decreased in this group from 1.3 ± 0.3 g/kg body weight to 0.7 ± 0.2 g/kg body weight, $p < 0.01$. The mean period of decreased dietary intake was 3 ± 1 months.

Dietary intake during hospitalization

Over the period of hospitalization the mean energy intake in the intervention group (I) was significantly higher compared to the placebo group (P), 10.89 ± 2.01 MJ/day versus 9.40 ± 2.54 MJ/day, $p < 0.05$. Cumulative energy intake during hospitalization was significantly higher in the intervention group relative to the control group (89.9 ± 17.9 versus 77.1 ± 18.3 MJ, $p < 0.05$). Expressed in kJ/kg body weight, the mean energy intake was 194 ± 50 kJ/kg body weight (I) compared to 159 ± 42 kJ/kg body weight (P) ($p = 0.022$). Mean protein intake was 38% higher in the intervention group, 1.8 ± 0.4 g/kg body weight (I) versus 1.3 ± 0.3 g/kg body weight (P) ($p < 0.01$). See figure 7.2a and 7.2b for the pattern of daily energy intake and protein intake during hospitalization. The mean carbohydrate intake during hospitalization was 54 ± 4 energy% (I) versus 47 ± 5 energy% carbohydrate (P) ($p < 0.01$). Mean fat intake was 27 ± 3 energy% (I) versus 33 ± 4 energy% fat (P) ($p < 0.01$).

The proportion of oral supplementation that was ingested during hospitalization was carefully monitored by the nurses and amounted to $98 \pm 2\%$. The dotted line in figure 7.2a and 7.2b shows that dietary intake without supplements was comparable between the treatment and the placebo group.

Figure 7.2 Pattern of energy intake during hospitalization, 7.2a, pattern of protein intake during hospitalization, 7.2b. Closed circles and solid line, the intervention group; closed circles with dashed line, the spontaneously intake of the intervention group without the supplementation; open circles and solid line, the placebo group. * $p = 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Body weight and body composition

In both groups body weight improved significantly and comparably during hospitalization (table 7.2). The change in body weight during hospitalization, expressed as percentage weight change was not significantly different between the groups, $2.6 \pm 2.5\%$ (I) and $2.0 \pm 2.2\%$ (P). Twenty-two patients (47%) experienced involuntary weight loss prior to admission. Their usual body weight was similar to that of weight-stable COPD patients ($n=25$), namely 61.4 ± 11 kg and 61.5 ± 10 kg. The weight-losing patients lost on average 5.9 ± 2.4 kg ($10 \pm 4\%$ weight loss) in 3 ± 1 months before hospital admission. Weight gain during hospitalization in the weight-losing patients tended to be higher than in the weight-stable patients, 1.5 ± 1.3 kg and 0.9 ± 1.1 kg ($p=0.08$), respectively or $3.1 \pm 2.4\%$ compared to $1.6 \pm 2.1\%$ in the weight stable patients ($p=0.05$). There were no significant changes in FFM in both groups. FM increased significantly in both groups during hospitalization (see also table 7.2).

Lung function, muscle function and symptoms

In table 7.2 the changes in lung function, inspiratory muscle strength, handgrip strength and symptoms are shown. FEV₁ and IVC improved slightly but significantly in the total group. All symptoms improved significantly in the total group during hospitalization, but no differences were observed between the treatment and control group.

The majority of patients were unable to perform a valid quadriceps strength test on day 1. Therefore quadriceps strength measurements were compared only between days 4 and 8. There was no significant change in muscle strength between these days and also no difference between the intervention and control group.

Table 7.2 Changes in outcome parameters from admission to discharge

	Intervention		Placebo	
	n		n	
Weight, kg	23	$1.37 \pm 1.3^*$	24	$1.12 \pm 1.2^*$
Fat-free mass, kg	21	-0.5 ± 2.6	22	-0.4 ± 2.7
Fat mass, kg	21	$1.7 \pm 2.5^*$	22	$1.5 \pm 2.5^*$
FEV ₁ , %predicted	23	$5 \pm 6^*$	23	$5 \pm 9^*$
IVC, %predicted	23	$7 \pm 12^*$	23	$10 \pm 17^*$
Pi-max, cm H ₂ O	20	3 ± 10	23	3 ± 13
Mean handgrip strength, kg	20	0 ± 3	22	0 ± 3
Quadriceps strength, Nm ^a	20	3 ± 8	23	2 ± 9
Score of dyspnoea at rest	23	$-3.8 \pm 2.5^*$	24	$-4.3 \pm 3.2^*$
Score of dyspnoea while eating	23	$-4.2 \pm 2.5^*$	24	$-4.7 \pm 3.3^*$
Score of loss of appetite	23	$-2.7 \pm 3.2^*$	24	$-2.6 \pm 2.9^*$
Score of early satiety	23	$-3.2 \pm 3.3^*$	24	$-2.5 \pm 3.3^*$
Score of bloating	23	$-2.4 \pm 3.4^*$	24	$-3.0 \pm 2.8^*$
Score of fatigue	23	$-4.2 \pm 3.7^*$	24	$-3.9 \pm 3.5^*$

^a change in quadriceps strength is compared between day 4 and day 8

* $p < 0.05$; FEV₁, forced expiratory volume in one second; IVC, inspiratory vital capacity.

Discussion

This study shows that nutritional supplementation is feasible and able to increase energy intake and particularly protein intake in nutritionally depleted COPD patients during hospitalization for an acute exacerbation. There were however no significant differences in body weight gain and functional improvement between the treated and control group.

The following considerations were made in the nutritional support strategy. In contrast to the earlier study by Saudny et al⁸ who did not use nutritional status as inclusion criterium, we focused on COPD patients at risk of malnutrition and normal weight patients with recent involuntary weight loss. Indeed 47% of the patients had experienced weight loss prior to hospitalization, during a period of 2-4 months. The caloric support was moderate (2.38 MJ/day) and primarily aimed at maintaining body weight during the average 9 days hospitalization, because we previously reported that a low BMI and weight loss during hospitalization was an independent predictor of early hospital readmission.² The group with recent weight loss tended to increase weight during hospitalization while this was not observed in the weight-stable patients. Based on the observation, we speculate that these results indicate that recent weight loss may be a more appropriate criterion for nutritional intervention during hospitalization for an acute exacerbation than BMI.

During hospitalization COPD patients are at risk for protein catabolism due to several factors including systemic glucocorticoid treatment, a flare up of the systemic inflammatory response, inactivity and hypoxia. Optimizing protein intake may reduce this catabolic response, even when anabolism will not be reached. A protein intake of 1.5 g/kg body weight has been identified to optimize protein synthesis in several acute and chronic conditions.¹⁷ No specific protein requirements are available for COPD, but already in clinical stable condition whole body protein turnover is increased.¹⁸ This study clearly shows that the normal hospital diet alone was unable to reach the requirement of 1.5 g/kg body weight but that the supplements increased daily protein intake to 1.8 g/kg body weight. The protein-rich supplementation however was not reflected in an improvement in FFM. Since both treatment and control group showed an increase in FM, it is likely that body compositional response occur independently from the nutritional intervention. Theoretically, the maintenance of FFM does not exclude actual loss of muscle mass and FFM could be masked by water retention. Previous studies showed that systemic glucocorticoid treatment is associated with a negative nitrogen balance in a dose dependent way.⁸ In addition Spruit et al recently reported peripheral skeletal muscle weakness in COPD patients during hospitalization for an acute exacerbation.¹⁹ Interestingly our muscle function measurements were not dramatically low compared to the clinical stable condition²⁰ and patients did not show any further decline in muscle function

during hospitalization. This may be related to the relatively low mean daily dose of glucocorticosteroids that patients received in this study (25 mg/kg body weight) compared to previous studies.^{6-8,19} To assess more specifically protein requirements in COPD patients during an acute exacerbation, further research is indicated.

Some nutritional intervention studies have shown that nutritional supplements may cause a drop in normal dietary intake so that the effectiveness of the treatment is limited.²¹ This could particularly be a problem during acute exacerbations because we previously reported severe dyspnoea and a low spontaneous dietary intake during the first day of hospitalization.⁶ In an earlier study we analyzed the acute effect of different portion sizes and macronutrient composition on symptoms and functional capacity in clinically stable COPD patients. We noticed that although on average patients could tolerate supplements up to 2092 kJ, severely underweight patients experienced a dramatic drop in postprandial exercise capacity after 2092 kJ relative to 1046 kJ. In the same study we also reported that a fat-rich supplement caused a postprandial increase in dyspnoea sensation while no effect was seen after a carbohydrate-rich supplement.²² The current protein-rich and carbohydrate-rich supplement was well tolerated, even in patients with acute respiratory failure. Portion size was limited to 125 ml instead of the commonly used 200 ml and was indeed well tolerated and taken additionally instead of replacing normal dietary intake. In a subgroup of patients (12I, 10P) PaCO₂ was routinely measured not only on admission, but also on day 4 of hospitalization. There were no significant differences in PaCO₂ between the intervention group and the placebo group. So the increase of carbohydrate consumption over the day during the acute phase of the exacerbations had no adverse effects.

Remarkably in contrast to our two earlier studies, spontaneous energy intake, particularly during the first days of hospitalization was higher both in the treatment and in the placebo group. Perhaps participation to a clinical trial per se including more regular and standardized dietetic consultation as well as the placebo drink may have increased patient's awareness to eat well.

We confirmed that a high proportion of patients reported recent involuntary weight loss prior to hospitalization which was inversely related to resting arterial oxygen tension. In general acute hypoxia leads to weight loss and loss of appetite²²⁻²⁵, irrespective of hypobaric hypoxia. At high altitude, a rapid increase in satiety reduces meal size and obviously dietary intake²⁵, which might be similar during an acute exacerbation of COPD. Furthermore it is known that the systemic inflammatory response in depleted patients with COPD which in itself may affect appetite and dietary intake^{7,26} can also be triggered by hypoxia.²⁷ Nevertheless, this study clearly shows that after normalization of the arterial blood gases by oxygen therapy, this subgroup of patients shows a comparable response to nutritional support than normoxemic patients.

We recognize that a mean hospital stay of 9 days is very short to show effectiveness of nutritional intervention on functional outcome measures which

was indeed not observed. A more appropriate outcome measure would have been for instance hospital readmission rate. Nine patients were readmitted within 3 months after discharge of whom again 56% had suffered involuntary weight loss. Besides optimizing nutritional screening and support during hospitalization, these figures indicate that more attention should also be paid to home care during the first weeks immediately after hospitalization.

In summary nutritional supplementation is feasible and recommended protein intake could only be reached in the treatment group.

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Chapter 8

General discussion

General discussion

The studies in this thesis aimed to gain more insight into the nutritional profile of patients with COPD under acute and stable conditions in order to improve the efficacy of nutritional support.

The rationale for nutritional support in COPD is based on the concept that COPD is a systemic disorder¹; besides lung impairment, progressive impairment in respiratory and skeletal muscle function and exercise capacity occurs.²⁻⁴ Recently a multidimensional grading system with four independent predictors of outcome in COPD patients was developed and validated.⁵ This so called BODE-index includes body mass index (B), the degree of airway obstruction (O), dyspnoea (D) and exercise capacity (E). COPD-patients with a higher score of the BODE-index were at higher risk of death.⁵ The score of each predictor alone did not predict outcome better, which supports the concept of COPD as a multicomponent systemic disease that requires an integrated management approach.

Impaired nutritional status is an important determinant of decreased physical capacity and prognosis in COPD patients. In nutritionally depleted patients physical impairment is partly reversible when weight gain is achieved by nutritional support.^{6,7} Unfortunately not all studies were able to reach weight gain after dietetic intervention or nutritional supplementation. Therefore the research as outlined in this thesis aimed to improve not only outcome but also proper implementation of dietetic intervention.

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Nutritional assessment

In order to identify patients who will benefit from nutritional intervention, nutritional status should be incorporated in the diagnostic work-up.

Measurement of body weight (changes) or body mass index (BMI) alone has its limitations, since it provides no qualitative information on specific body tissues. In clinical practice, there is no standard method for assessment of body composition. Generally a two compartment model is applied distinguishing fat mass (FM) and fat-free mass (FFM). Bio-electrical impedance analysis (BIA) performed at a frequency of 50 kHz is a valid and reproducible method to assess FM and FFM in clinical stable COPD patients.⁸⁻¹¹ In general, loss of FFM is the critical component related to increased disability risk in chronic disease.¹² In chapter 2 we assessed the prevalence and pattern of nutritional depletion (defined on the basis of both BMI and FFMI) in a large COPD out-patient population. 27% of the patients were considered depleted (low BMI and/or low FFMI). Most remarkable was a high prevalence of hidden loss of FFM, with preservation of body weight (15%). Furthermore this proportion was substantially higher in normal weight women than in normal weight men with COPD, 25% versus 11% respectively. Hidden loss

of FFM is only detectable by assessment of body composition. FFM depletion is related to decreased peripheral skeletal muscle function and affects respiratory muscle function as well as exercise performance.^{13,14} This study clearly indicates that it is essential during out-patient screening of COPD patients to assess body composition, even in normal weight COPD patients.

When fluid shifts occur, for instance during acute disease, assessment of body composition requires measurement or estimation of the distribution of intracellular water (ICW) and extracellular water (ECW) compartments. Bio-electrical impedance spectroscopy (BIS) performed at frequencies from 5 to 500 kHz not only measures total body water (TBW) but also extracellular water (ECW). During an acute exacerbation it is thought that fluid shifts may occur in hospitalized COPD patients. Therefore, in chapter 6 we applied BIS to measure body compositional changes during an inventarisation of the nutritional and metabolic profile of COPD patients hospitalized for an acute exacerbation and at three months after discharge in clinically stable condition. No significant changes in the ratio between the volume of ICW and ECW were found during hospitalization in the total study group and after discharge. This suggests that no major fluid shifts were present during the acute phase of COPD in our study population. However in another study, when acute exacerbation resulted in acute respiratory failure requiring mechanical ventilation, indeed a higher ECW/ICW volume ratio was found.¹⁵ This suggests that fluid shifts may be more pronounced related to the severity of COPD exacerbation.

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As described earlier, a remarkably high prevalence of hidden loss of FFM was found in an out-patient population (chapter 2). Also many hospitalized COPD patients appeared to be characterized by hidden loss of FFM (chapter 6), as was confirmed in another group of hospitalized COPD patients.¹⁶ These observations suggest an association between loss of FFM and exacerbation frequency. Hidden loss of FFM may be indicative of specific alterations in protein metabolism in COPD patients which may be particularly pronounced during acute COPD exacerbations. Besides, an increased whole-body protein synthesis and breakdown were found in weight-stable COPD patients.¹⁷ Protein turnover refers to a dynamic flux in protein metabolism whereby proteins are degraded and synthesized simultaneously. Protein rates may differ considerably depending on function and specific needs. A potential explanation for this elevated protein turnover¹⁷ is thought to be enhanced acute phase protein synthesis, associated with acute or low-grade inflammation. This is balanced by an increased amino acid release from the skeletal muscle compartment resulting in net muscle protein breakdown. Previously Pouw et al indeed observed an inverse relationship between the acute phase protein LPS binding protein and the total sum of plasma amino acid levels in COPD patients.¹⁸ In another study COPD patients with an acute phase response and elevated resting metabolic rate, were characterized by selective depletion of FFM.¹⁹ More studies are needed, however, to confirm this hypothesis using advanced techniques to measure (acute phase) protein synthesis and breakdown at the whole body level and across skeletal muscle. These studies

are important because they highlight that maintenance of homeostatic regulation of metabolic processes in COPD under certain circumstances is an unstable equilibrium. Evoked in inflammatory conditions the acute phase response includes the hepatic synthesis of large quantities of proteins with a wide variety of functions to clear tissue debris. This is an energy-intensive process with high rates of hepatic protein synthesis requiring large quantities of essential amino acids. The need for essential amino acids drives the loss of skeletal muscle. The trade off may be viewed as a shift in the body's priorities from offensive to defensive.²⁰ This adaptation is effective over the short term because skeletal muscle is replaced rapidly as recovery is completed. Because skeletal muscle depletion significantly contributes to morbidity and mortality, problems ensue when the process is chronic, related to continuous low grade inflammation or frequent acute (infectious) exacerbations.

Treatment of weight loss

Weight loss will occur if energy demands exceeds dietary intake over a period of time. Not only decreased dietary intake, but also increased energy expenditure can be present in COPD. These impairments of energy balance can simultaneously be present, but can also act alone.

Clinical stable condition

In some of the clinically stable COPD patients an increased REE was found²¹⁻²³, which was related to markers of systemic inflammation such as C-reactive protein, LPS-binding protein and TNF-alpha.^{19,24} This association has also been observed in many other chronic wasting conditions^{25,26} and REE can therefore be considered as a metabolic marker of systemic inflammation. However unrelated to (increased) REE²⁷, total energy expenditure (TEE) can be increased in stable patients with severe COPD. Potential factors involved in an elevated TEE are a decreased efficiency of skeletal muscle energy metabolism and an increased oxygen cost of breathing.²⁸⁻³⁰

The most variable component of TEE is energy requirement for physical activity. In chapter 5, measurement of physical activity was done by a tri-axial accelerometer for movement registration in stable COPD patients at home; the range of physical activity level (PAL) was wide, varying from 1.40 to 2.44. In COPD patients with a high PAL, it was difficult to reach a positive energy balance (chapter 5). Recently a study was published, using doubly labeled water technique for measuring TEE in COPD patients in the community.³¹ Here also a great range in PAL (1.15 to 1.80) was found and TEE varied between 5.2 MJ and 11.1 MJ. These studies confirm that physical activity is very variable in COPD patients in the community and that it is important to measure PAL. While accelerometers are not (yet) readily

available for clinical practice, a validated method for physical activity assessment in COPD patients in the community is advisable. A more accurate establishment of physical activity will certainly improve indication and efficacy of nutritional intervention. Furthermore, measurement of physical activity additional to measured or estimated REE, can also be used for validity of reported energy intake.³² More research is certainly needed in this area to provide dietitians with more objective tools to guide and evaluate treatment.

At the other part of the energy balance, dietary intake can be disturbed in COPD patients. Dietary intake can be influenced by several symptoms likewise dyspnoea and fatigue; these symptoms are particularly pronounced during acute exacerbations as outlined in chapter 6. Also anxiety or severe psychiatric disorders such as depression or depressive symptoms can adversely influence dietary intake.³³ The presence of these psychiatric symptoms is high in COPD patients³⁴ especially in severely oxygen dependent COPD patients.³⁵ Furthermore, patients with severe COPD are at increased risk of developing depression.³⁶ It can be hypothesized that adequate treatment of depressive symptoms in depleted COPD patients will also improve dietary intake in quantitative and qualitative terms and thereby improve the efficacy of nutritional support. Attention must be paid to these depressive disorders by care givers in a multidisciplinary setting and perhaps questionnaires could be used under certain circumstances (for instance in difficult to treat patients) by the dietitian.

Altered appetite regulation results in a decreased dietary intake and this process was related to higher levels of inflammatory markers including TNF receptors and leptin.³⁷⁻³⁹ Recently, ghrelin, a novel peptide, has been developed and there is growing evidence that indicates that ghrelin is involved in appetite regulation. Ghrelin stimulates growth hormone secretion and influences appetite and hunger, resulting in improved dietary intake. Furthermore the action of leptin can be antagonized by ghrelin, as it has been shown in rats that leptin-induced inhibition of food intake was reversed by ghrelin injections.⁴⁰ Ghrelin has been demonstrated to stimulate food intake⁴¹ and acts as a meal initiator in humans.⁴² In weight-losing persons and in cachectic patients with chronic heart failure increased circulating levels of ghrelin were reported.^{43,44} Future studies are required to establish the role of ghrelin in the pathogenesis of a dysregulation of energy balance in COPD patients.

Pharmacologic modulation of appetite-regulation, by use of substances such as megestrol acetate (MA) or ghrelin, may develop as a supplemental method to promote appetite and anabolism in depleted COPD patients. Recently the progestational appetite stimulant megestrol acetate, was investigated in underweight stable COPD patients⁴⁵ in a randomized double-blind placebo-controlled study. Megestrol acetate induced an improved appetite and weight gain. However, mainly an increase in FM was found with no progression in health status or functional performance.⁴⁵ MA treatment was initiated as a single intervention, while the results of the study clearly indicate that pharmacological modulation of appetite must be accompanied by an anabolic stimulus. These studies indicate the need for a multidisciplinary approach to wasting in severe COPD.

Nutritional intervention in clinically stable condition

The efficacy of nutritional support in COPD patients was recently reviewed in a meta-analysis.⁴⁶ It was concluded that nutritional supplementation had no effect on improving anthropometry or functional exercise capacity in COPD patients. However in this review, no distinction between failure to intervene and failure of intervention was made. Nutritional therapy in studies often corresponds to an energy supplement of 0.84-2.1 MJ/day, which does not automatically mean that total energy intake increases accordingly, since individual differences exist in total daily energy and protein requirements. In some studies the prescribed dietary supplementation was used to replace regular meals and was not additional to habitual intake^{47,48}, and so nutritional intervention fails to achieve an increase in energy intake. Furthermore, in some studies nutritional supplementation was given in addition to habitual intake. When total energy requirement is not (accurately) established, it is possible that even with additional supplements, a positive energy balance is not reached, because of a (very) low habitual dietary intake at baseline. In the studies, where a positive energy balance was reached, weight gain and functional improvements were found.^{49,50} In chapter 5 energy balance was studied in COPD patients at 1 and 3 months after discharge from the hospital or rehabilitation center. All COPD patients received dietary counseling aimed to improve dietary intake according to estimated total energy requirements. The supplemented group used additional nutritional supplementation and they had a positive energy balance already at 1 month after discharge. The control group however reached a positive energy balance later on, namely at 3 months, which indicates that nutritional supplementation can improve energy balance sooner than by changes in habitual dietary intake alone.

The efficacy of nutritional supplementation was found to improve when nutritional support was incorporated in a multidisciplinary rehabilitation program.^{51,52} Improvements in body weight, body composition, muscle strength and exercise performance were found, but also health status improved in COPD patients.⁵² If nutritional support results in weight gain during a rehabilitation program, even an improved survival was reported.⁶

Even in a controlled environment such as an in-patient pulmonary rehabilitation center, some COPD patients do not respond to nutritional intervention. In addition to non-compliance to therapy, an inadequate energy intake relative to energy requirements and the inability of the patients to ingest the extra energy, inadequate metabolic handling may contribute to poor treatment response. The interaction between nutritional depletion and systemic inflammation as well as an inverse association between systemic inflammation and response to nutritional supplementation³⁷ have drawn attention to the potential beneficial effects of anti-catabolic agents in specific modulation of the systemic inflammatory response.

The efficacy of anti-catabolic nutritional modulation like n-3 polyunsaturated fatty acids requires further investigation.

Acute exacerbation of COPD

An impaired energy balance was found in COPD patients during the first days of hospitalization for an acute exacerbation (chapter 6), mainly due to an increased REE and a temporarily decreased dietary intake. The change in REE was significantly correlated with the change in dyspnoea score during the period of hospitalization. Besides a low dietary intake during hospitalization, also a decreased dietary intake prior to admission was reported in a substantial part of nutritionally depleted patients who were studied in chapter 7.

Little is known on the pattern of body weight decline in COPD patients. It is possible that weight loss occurs steadily or it may be related to acute phases of the disease like exacerbations. In chapter 6 we found in well nourished COPD patients that during the hospitalization period weight could be maintained and that at 3 months after discharge the patients on average gained weight. This latter may suggest that there was some weight loss prior to admission. In the depleted COPD study population (chapter 7), the prevalence of involuntary weight loss prior to admission was high (47%). Involuntary weight loss was reported over a period of 1-4 months and negatively correlated with resting arterial oxygen tension. It has indeed been described that hypoxemic conditions, such as during high altitude climbing, lead to weight loss.^{38,53-56} Besides, alterations in intermediary metabolism can further aggravate weight loss and muscle wasting during acute exacerbation, as described earlier. These data indicate that nutritional deterioration is aggravated during exacerbations of the disease and is caused by several metabolic and inflammatory changes, which influence dietary intake negatively during the exacerbation or even before the exacerbation is manifested.

Efficacy of nutritional intervention in acute conditions

Until now only one study has described the efficacy of nutritional intervention during an acute exacerbation of COPD in a controlled design. No significant improvement was found in body weight, inspiratory and peripheral muscle strength, but a trend was observed in improvement in well-being score.⁵⁷ Although nutritional status was not an inclusion criterion in this study, one could speculate that particularly underweight or weight-losing patients might benefit from nutritional intervention. Therefore in chapter 7 we investigated the feasibility and the efficacy of oral nutritional supplementation to improve protein and energy intake during hospitalization for an acute exacerbation in nutritionally depleted patients with COPD. Surprisingly, nutritional supplementation was feasible and

well tolerated. Furthermore, it was able to increase energy intake and particularly protein intake in nutritionally depleted COPD patients during hospitalization for an acute exacerbation. However, the mean hospital stay of 9 days was very short to show efficacy of nutritional intervention on functional outcome measures, which was indeed not observed.

Possible adverse effects of nutritional intervention

As described earlier, dietary intervention with sip feeding could lead to reduced habitual dietary intake as a result of (acute) adverse postprandial effects on appetite, satiety or metabolism. To gain more insight into these possible adverse effects of nutritional supplementation, different nutritional experiments were conducted in stable COPD patients (chapter 3). Besides symptoms like appetite, satiety and dyspnoea, the acute effect of food ingestion was studied on energy metabolism, lung function and exercise performance. Food ingestion leads to an increase in oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) secondary to nutrient processing. As $\dot{V}CO_2$ will raise, ventilation will be stimulated. Especially in COPD patients with limited ventilatory reserves, it can be hypothesized that the composition of nutrition may play a prominent role, as it is known that carbohydrate ingestion results in higher $\dot{V}CO_2$. Indeed, adverse effects of carbohydrate-rich drinks have been reported in COPD patients.^{58,59} These effects were however reported after a very high energy load, namely 3.86 MJ. In chapter 3, we could not confirm these findings even in severe COPD patients after a more physiological energy load. No differences in metabolic response and exercise performance were found after a fat-rich supplement and an isocaloric carbohydrate-rich supplement (1.04 MJ in 200 ml). These findings indicate that the energy load influences the metabolic response more than the food composition and this was confirmed by a more pronounced metabolic response after a higher energy load, namely 2.09 MJ versus 1.04 MJ (chapter 3). In chapter 7, we studied the efficacy of nutritional support in hospitalized patients for an acute exacerbation of COPD. The nutritional supplements that were used were not only protein and energy-rich, but also carbohydrate-rich. Especially during acute exacerbations of COPD, it could be suggested that more carbohydrates would influence outcome negatively, since ventilation will be more limited and $\dot{V}CO_2$ excretion more difficult. However, no differences in arterial blood gases (PaO_2 and $PaCO_2$) were found between the intervention and placebo group during admission and day 4 of hospitalization (chapter 7). Probably the small size of carbohydrates per portions (28 gram) given at three times during the day, will have little impact on ventilatory load. Furthermore, the compliance was high during hospitalization indicating good feasibility of the used nutritional supplementation (chapter 7). The nutritional supplementation consisted of 3 packages of a small portion size (2.38 MJ/day), namely 125 ml instead of the commonly used 200 ml. A recent study by our group surprisingly showed that

nutritional support with a smaller portion size and lower energy content (3x125 ml; 2.38MJ/day) can result in more weight gain than nutritional support with a larger portion size and even higher energy content (3x200ml; 3.36MJ/day).⁶⁰ The macronutrient composition of both nutritional regimens was similar in the study, namely 60 energy% carbohydrates, 20 energy% protein and 20 energy% fat. Besides smaller portion size, also a better timing of nutritional supplementation can improve the efficacy of nutritional support in COPD patients. Differences in macronutrient composition of meals or supplements may also have differential effects on gastric emptying and on (the release of biomarkers of) satiety.⁶¹ Previously it was reported that nutritional supplementation with a higher fat content resulted in a delayed gastric emptying in COPD patients.⁶² In chapter 4 we investigated gastric emptying rate and postprandial changes after two solid meals with different macronutrient composition, namely fat-rich versus carbohydrate-rich. The protein content was similar in both meals, because it has been suggested that satiety is influenced by protein.⁶³ Besides gastric emptying rate, physiologic and subjective measures of satiety were incorporated in this study. Remarkably gastric emptying rate after both meals was not different in COPD patients as well as in healthy control subjects and this was similar for satiety perception during the experiment. Unrelated to gastric emptying rate, the actual food intake at the next eating episode tended to be lower after the fat-rich meal in COPD patients. This suggests that the effect of different food ingredients enhances satiety on longer term and thereby reduces appetite at the subsequent eating moment, which was supported by postprandial increased level of glucagon-like peptide-1 after the fat-rich meal in COPD patients (chapter 4).

To a more behavioral approach of dietary management

Nutritional intervention studies in COPD patients were mainly pointed to additional oral supplementation to improve habitual dietary intake. Efficacy of dietary management might be improved by combining medically prescribed nutritional supplementation with a more behavioral approach aimed at long term changes in eating behavior and dietary intake.

Health promotion programs can be useful in COPD patients in every stage of the disease as recently reviewed by Brug et al.⁶⁴ In the development of such a health promotion program including planned dietary change interventions, three phases can be identified: problem analysis, behavior analysis, and behavioral determinants analysis.⁶⁴ So the first step is an analysis of health or quality of life problems, to identify whether a health issue is important enough to spend time, money and other resources on attempts to reduce it. The following step is to identify important and potentially changeable causes of the health problem. The last step is the identification of the determinants of the risk behavior. Three categories of important as well as changeable determinants of dietary behavior have been identified: attitudes (weighing expected or perceived pros and cons),

social influences and perceived control. These factors are assumed to influence eating behavior mostly by behavioral intentions.⁶⁵

Education programs of healthy life style and self-management in COPD patients may improve the benefits of nutritional intervention, especially if it is initiated at less advanced stage of the disease. Weight loss is easily detectable, so COPD management should be aimed at early detection and treatment of weight loss. However prevention of involuntary weight loss will be even better.

Suggestions have been made that diet, besides a role in disease progression, also is implicated in the early onset of COPD. Not only dietary habits, but also a low BMI may be related to the risk of COPD.⁶⁶ Thereby nutrition may play a role in the primary prevention of COPD. Recently, associations of the intake of n-3 fatty acids, antioxidants, fruit and vegetables and the risk of COPD have been suggested.⁶⁷ However, the available evidence is not substantial enough to specify dietary advice aimed at preventing COPD. In general, the preventive dietary habits like consumption of fatty fish and fruit are in line with the guidelines of healthy nutrition. More studies are needed to address the benefits of healthy nutrition and improvements in eating behavior in patients with COPD.

Nevertheless the currently available evidence suggests that nutrition plays a pivotal role in the total disease management of COPD, from early onset until end-stage disease.

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Chapter 9

Summary

Introduction

The studies presented in this thesis aimed to gain more insight into dietary factors that adversely affect nutritional status in patients with chronic obstructive pulmonary disease. The following topics were addressed: 1) nutritional status characterized by body composition in an out-patient COPD population in the Netherlands, 2) potential acute postprandial adverse effects of supplemental nutrition in depleted COPD patients that may limit effectiveness and compliance of nutritional support and 3) the influence of hospitalization for an acute exacerbation on the nutritional profile as well as the feasibility of nutritional supplementation.

Nutritional status

Nutritional depletion and muscle dysfunction commonly occur in patients with COPD. Nutritional depletion is associated with adverse effects on respiratory and peripheral muscle function, exercise capacity and health status. In chapter 2, the prevalence of nutritional depletion in relation to functional performance, airflow limitation, dyspnoea and health status is reported in a large multi-center out-patient population with moderate and severe COPD. Body composition was measured by bioelectrical impedance analysis in 389 COPD patients in the Netherlands. Nutritional depletion was defined as body mass index (BMI) $\leq 21 \text{ kg/m}^2$ and/or fat-free mass index (FFMI) ≤ 15 (females) or ≤ 16 (males) kg/m^2 .

Nutritional depletion was present in 27% of the patients. The prevalence of nutritional depletion was not different between patients with moderate and severe COPD. Surprisingly, the prevalence of nutritional depletion was higher in female compared to male COPD patients. Furthermore, a high prevalence of (hidden) loss of FFM was found in 15% of the total COPD population. In 25% of the female COPD-patients FFM depletion with body weight preservation occurred, which was significantly higher than in males (11%). Furthermore, comparison between depleted and non-depleted COPD patients revealed no differences in FEV₁, %predicted, dyspnoea score and health status. Besides FFM depletion, age and especially gender were found as independent predictors of muscle weakness in COPD measured by handgrip strength.

These data indicate that for diagnostic purpose, assessment of body composition is useful to assess systemic disease severity, not only in patients with severe COPD, but also in those with mild to moderate disease.

Adverse effects

When optimal adaptation of dietary habits fails to improve dietary intake to reverse weight loss, nutritional supplementation is commonly indicated. Implementation of nutritional supplements in COPD patients requires careful balancing between positive effects on outcome and possible acute adverse effects on metabolism and exercise performance. Therefore, in chapter 3 the acute effects of different liquid oral nutritional supplements on lung function, symptoms and exercise capacity were investigated. In part 1 of the study, the effects of supplements with a different energy load (placebo: 209 kJ, 1046 kJ, 2092 kJ) and a normal macronutrient distribution were measured in 14 COPD patients. In the second part of the study, the effects of a fat-rich versus a carbohydrate-rich supplement (1046 kJ) were studied in 11 COPD patients.

In general this study did not show significant adverse effects of the studied nutritional supplements on the ventilatory system. A higher energy load (2092 kJ) resulted in a significantly higher metabolic and ventilatory response and in a higher satiety sensation, but was not reflected in a decreased exercise capacity for the total study group. A remarkable observation in part 1 of the study was the dramatically decreased endurance capacity after 2092 kJ in 3 COPD patients compared to 1046 kJ and placebo. These patients were exactly the ones in great need for nutritional support, since they were characterized as being severely cachectic with a low BMI, low FFMI and a low maximal exercise capacity.

The suggestion that carbohydrate-rich supplements would induce a higher ventilation due to a higher respiratory quotient was not confirmed in the second part of this study. Differences in fat versus carbohydrate content of supplements were not reflected in differences in endurance capacity in COPD patients. In contrast, shortness of breath increased postprandial more after ingestion of the fat-rich supplement than after the carbohydrate-rich supplement. These combined findings indicate that in clinically stable COPD patients, when given in moderate size amounts, a carbohydrate-rich drink is preferable to a fat-rich drink.

We hypothesized that delayed gastric emptying might be present in depleted COPD patients with lung hyperinflation relative to healthy control subjects due to different macronutrient content. Furthermore a more pronounced effect of different macronutrient content on gastric emptying might be seen in these patients that might need to be accounted for during dietary management. In Chapter 4 the effect of two isocaloric solid meals, different in macronutrient content, on gastric emptying and related parameters were investigated in 10 depleted COPD patients and 9 healthy control subjects. The meals were provided as breakfast. Gastric emptying rate was measured by ^{13}C octanoic acid breath test. Other measurements included lung function, oxygen saturation, symptoms and dietary intake. In addition, the biochemical markers, glucose, insulin,

cholecystokinin and glucagon-like peptide-1 (GLP-1) were measured. The two different test meals were served in a randomized cross-over fashion.

No differences in gastric emptying rate after the two different meals were found in COPD patients and in control subjects and between both groups. Reported symptoms, like dyspnoea and satiety, were not different between both meals. Postprandial glucose and insulin response after the two meals were comparable in COPD patients and in healthy controls. A postprandial increase in GLP-1, a marker of satiety, after a fat-rich meal was found only in COPD patients. Furthermore, spontaneous dietary intake at lunch-time tended to be lower after a fat-rich meal in comparison with a carbohydrate-rich meal in depleted COPD patients. Therefore a potential adverse effect of a fat-rich meal seems more pronounced in perceived satiety sensation and subsequent caloric intake in depleted COPD patients with severe hyperinflation.

More insight into the energy balance of depleted ambulatory COPD patients was achieved in chapter 5. Besides body weight and energy intake, energy expenditure was established in 20 clinically stable COPD patients. Besides measurement of resting energy expenditure (REE), a 7-day assessment of physical activity with a tri-axial accelerometer for movement registration was performed. Assessments were done at one month and at three months after discharge from the hospital or from the pulmonary rehabilitation center. All patients were randomly assigned to an intervention or control group with regard to nutritional supplementation. In both groups body weight remained stable after 1 or 3 months. The supplemented patients achieved a positive energy balance at month 1 in contrast to the control group which achieved balance at month 3. The range of physical activity level (PAL) found in this population was wide, varying from 1.40 to 2.44 and mean PAL was 1.56. Weight change over the study period was negatively associated with PAL. In COPD patients with a higher PAL it appeared very difficult to reach a positive energy balance compared to COPD patients with a lower PAL as reflected in weight change during the study period. These results indicate that more insight about the individual level of physical activity is necessary for a more appropriate estimation of energy requirement and dietary advice in ambulatory COPD patients.

Acute disease exacerbations

In 23 COPD patients acutely admitted to the hospital, dietary intake, resting energy expenditure, body composition and disease symptoms were measured to investigate the influence of an acute disease exacerbation on the nutritional and metabolic profile (chapter 6). These assessments were done on admission, daily throughout the hospitalization period and at discharge. In a subgroup of 10 COPD patients these assessments were also done at 3 months after discharge from the hospital. Patients received no nutritional support during hospitalization, but had the opportunity to choose their own menus.

Prior to admission, since aggravation of symptoms, dietary intake was decreased and amounted on average 72% of habitual dietary intake. The majority of the patients also reported a very low dietary intake during the first three days of hospitalization. During hospitalization protein intake improved but remained rather low given the low activity level of the patients and the high risk for increased protein requirements. Resting energy expenditure decreased during hospitalization, but a subgroup of patients remained hypermetabolic at discharge. Interestingly, these patients were characterized by a lower BMI. Changes in dyspnoea score during hospitalization were significantly related to changes in REE. Furthermore, at discharge dietary intake was significantly higher than habitual intake, which could be related to improvement of symptoms adversely affecting appetite and dietary intake, or induced by an appetite-stimulating effect of the high dose systemic glucocorticosteroid treatment. At three months after admission, a significant body weight gain was seen. Dietary intake at three months was comparable with habitual dietary intake and REE was similar to the value of REE at discharge.

In chapter 7 the feasibility and effectiveness of an energy- and protein-rich nutritional supplement during hospitalization for an acute exacerbation was investigated in depleted COPD patients. The study design was a randomized double blind, placebo controlled two-center trial. Besides dietary intake, body composition, respiratory and skeletal muscle strength, lung function and symptoms were measured during hospitalization.

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126 A substantial part of the COPD patients reported recent involuntary weight loss prior to admission. Weight loss was inversely related to resting arterial oxygen tension on admission. A significant higher increase in energy and protein intake was seen in the treatment group and the supplementation did not interfere with normal dietary intake. Only the treatment group achieved the required protein intake of 1.5 g/kg body weight. No significant differences in body weight were found. Furthermore, no adverse effects of carbohydrate-rich supplementation during acute exacerbation of COPD were reported in this study. The oral nutritional supplements were well tolerated and compliance was high with only a small compensatory decrease in spontaneous dietary intake, even in patients with acute respiratory failure. In contrast to earlier reports by other groups, during hospitalization no decline in muscle function consequent to the acute exacerbation was found in all patients. Probably due to the short length of stay in the hospitalization, no additional improvements in muscle strength were seen in the treatment group.

Chapter 8 comprises the general discussion of the thesis and gives implication for further investigations.

Conclusion

The studies described in this thesis demonstrate that assessment of nutritional status (body composition additional to body weight and height) is necessary in all COPD patients, not only in weight losing or severe COPD patients. Furthermore, previously suggested adverse effects of nutrition and nutritional supplements in COPD patients were not reported in the studies.

Nutritional support is indicated not only to treat clinically stable COPD patients, but also prevent weight loss and limit an impaired protein balance in COPD patients. Nutritional intervention during hospitalization for an acute exacerbation is feasible even in patients suffering from acute respiratory failure and able to increase energy intake, in particular protein intake. These results provide further argumentation to include dietary assessment and management in an integrated approach of COPD, from prevention to end of life care.

Chapter 10

Samenvatting

Inleiding

COPD is de engelse afkorting voor chronisch obstructieve longziekten en omvat de ziektebeelden longemfyseem en chronische bronchitis. De ziekte wordt gekenmerkt door een onomkeerbare vernauwing van de luchtwegen, die over een langere periode verergert. COPD is een invaliderende aandoening en treedt met name op bij personen van 50 jaar en ouder. Deze ziekte komt vooral voor bij mannen, maar vanwege veranderingen in het rookgedrag gedurende de afgelopen decennia neemt het aantal vrouwen met COPD sterk toe. De verwachting is dat in 2020 COPD de vierde plaats als oorzaak van sterfte zal innemen.

De prognose van de aandoening wordt bepaald door de ernst van de longfunctiestoornis op het moment dat de aandoening wordt vastgesteld en door de jaarlijkse afname van de longfunctie, maar ook door de body mass index.

De laatste jaren wordt COPD niet meer gezien als alleen een lokale orgaanstoornis, maar meer als een systeemaandoening waarbij lokale en systemische ontsteking, ontregelingen in het metabolisme, gewichtsverlies en spierzwakte een belangrijke rol spelen. De belangrijkste beperkingen die COPD-patiënten ondervinden zijn de kortademigheid en de beperkingen in het dagelijks functioneren. Het voorliggende proefschrift is met name gericht op de gewichtsproblematiek bij COPD.

Doel van het onderzoek

Het doel van het onderzoek is om de huidige tekortkomingen in de diëtistische kennis van COPD-patiënten na te gaan. De onderzoeken van het proefschrift zijn onder te verdelen in drie thema's:

1. bestudering van de omvang van een verstoorde voedingstoestand bij poliklinische COPD-patiënten.
2. bestudering van mogelijk nadelige effecten van voedingssupplementen en hieraan gerelateerde factoren op het klachtenpatroon van de patiënt die kunnen leiden tot een beperkte effectiviteit van voedingsinterventie.
3. onderzoek naar de invloed van acute opflakkingen van de ziekte waarvoor patiënten moeten worden opgenomen in het ziekenhuis, op de voedingstoestand en daarmee samenhangend de toepasbaarheid en effectiviteit van voedingssuppletie gedurende deze periode.

Voedingstoestand

Bij patiënten met COPD is aangetoond dat een verstoorde voedingstoestand nadelige gevolgen heeft voor het dagelijks functioneren, zoals een verminderde kracht van de ademhalingsspieren en skeletspieren, een verminderd inspanningsvermogen, verminderde kwaliteit van leven en zelfs een kortere overleving. Het is van belang om de voedingstoestand tijdig in kaart te brengen, om (verdere) verstoring van de voedingstoestand en daarmee samenhangende consequenties te voorkomen. In hoofdstuk 2 wordt de prevalentie van een verstoorde voedingstoestand, in relatie tot perifere spierkracht, luchtwegvernauwing, kortademigheid en kwaliteit van leven weergegeven. In 389 COPD-patiënten is de voedingstoestand bepaald met behulp van lengte, gewicht en lichaamssamenstelling. Het onderzoek heeft poliklinisch plaatsgevonden in 39 verschillende centra in Nederland. Een verstoorde voedingstoestand was gedefinieerd als een body mass index (BMI) ≤ 21 kg/m² en/of vetvrije massa index (VVMi) ≤ 15 (vrouwen) of ≤ 16 (mannen) kg/m². In 73% van de totale groep van COPD-patiënten was er sprake van een goede voedingstoestand. In de resterende 27% was de voedingstoestand verstoord. Er werden geen verschillen gevonden tussen patiënten met matig COPD en patiënten met ernstig COPD. Verborgen verlies van vetvrije massa (VVM), met behoud van lichaamsgewicht, kwam voor bij 15% van de totale populatie en bij vrouwen was deze prevalentie hoger (25%) dan bij mannen (11%). Er werden geen significante verschillen in longfunctie, kortademigheidsscore en kwaliteit van leven tussen COPD-patiënten met een verstoorde voedingstoestand in vergelijking tot COPD-patiënten met een goede voedingstoestand gevonden. Niet alleen depletie van VVM was een onafhankelijke voorspeller van spierzwakte, maar ook leeftijd en geslacht. Met behulp van eenvoudig te bepalen klinische meetmethodieken, werd in deze studie dus de relatie tussen voedingstoestand en verminderde spierkracht bevestigd en deze correlatie was onafhankelijk van de ernst van de ziekte.

Aangezien depletie van VVM een belangrijke determinant is voor functionele capaciteit, is bepaling van de lichaamssamenstelling gewenst in de diagnosestelling en follow-up bij alle poliklinische COPD-patiënten.

Nadelige effecten

Voedingssuppletie is geïndiceerd, indien na optimalisatie van de voedselinname door aanpassing van de voedingsgewoonten gewichtsbehoud of gewichtstoename uitblijft. Implementatie van de voedingssupplementen in patiënten met COPD vraagt zorgvuldige afstemming van beoogde positieve effecten op functionele capaciteit en mogelijk nadelige effecten op ventilatie en metabolisme. In hoofdstuk 3 zijn de acute effecten van verschillende vloeibare

voedingssupplementen op longfunctie, symptomen en inspanning beschreven. In het eerste deel van de studie, zijn de effecten van drie supplementen met een verschillende energiehoeveelheid (placebo: 209 kJ, 1046 kJ, 2092 kJ) nagegaan bij 14 COPD-patiënten. In het tweede deel van de studie, is bij 11 COPD-patiënten gekeken naar de effecten van twee voedingssupplementen met een verschillende samenstelling van macronutriënten, namelijk vetrijk of koolhydraatrijk, maar met een gelijke hoeveelheid aan energie (1046 kJ).

Over het algemeen, zijn er geen nadelige effecten van de bestudeerde voedingssupplementen gevonden op de ventilatie. Een hogere energiehoeveelheid resulteerde wel in een hogere metabole en ventilatoire respons en een hoger verzadigingsgevoel, maar niet in een verminderde inspanningscapaciteit in de totale groep. Een opmerkelijke bevinding in het eerste deel van de studie was dat bij 3 COPD-patiënten de inspanningscapaciteit sterk verminderde na inname van het voedingssupplement van 2092 kJ terwijl deze verschillen niet gevonden waren na inname van placebo en 1046 kJ. Deze drie patiënten hadden een lage BMI, VVMI en een lage maximale inspanningscapaciteit.

De suggestie dat een koolhydraatrijk supplement de ventilatie negatief beïnvloedt ten gevolge van een hoger respiratoir quotiënt, werd in deze studie niet bevestigd. De verschillende samenstelling van macronutriënten had geen invloed op de inspanningscapaciteit. Verder bleek de kortademigheid na inname van het vetrijke supplement significant meer toe te nemen dan na inname van het koolhydraatrijke supplement.

Een vertraagde maaglediging kan optreden bij deplete COPD-patiënten met hyperinflatie en mogelijk speelt de macronutriënten samenstelling van de voeding hierbij ook nog een rol. Hoofdstuk 4 beschrijft de maaglediging na twee vaste maaltijden met een gelijke energiehoeveelheid maar verschillend in macronutriënt samenstelling, vetrijk versus koolhydraatrijk. Deze studie is verricht bij 10 COPD patiënten met hyperinflatie en ondergewicht en bij 9 gezonde controle personen. De maaglediging was niet verschillend na beide maaltijden bij zowel COPD-patiënten als bij gezonde controle personen en tussen beide groepen. De klachten, kortademigheid en verzadiging waren vergelijkbaar na de verschillende maaltijden. Ten aanzien van de bloedparameters, werd alleen een significante toename van glucagon-like peptide-1 (een marker voor verzadiging) na de vetrijke maaltijd gevonden bij COPD-patiënten. Na voltooiing van het onderzoek, was de spontane voedselinname tijdens lunch na inname van de vetrijke maaltijd lager dan na inname van de koolhydraatrijke maaltijd. Hoewel dit verschil niet statisch significant was, duidt het resultaat mogelijk op een nadelig effect van een vetrijke maaltijd, in de perceptie van verzadiging voor of tijdens het volgende eetmoment.

Er zijn weinig gegevens beschikbaar over de energiebalans van COPD-patiënten in de thuissituatie (hoofdstuk 5). Bij 20 klinisch stabiele COPD-patiënten werd daarom lichaamsgewicht, energie-inname en het dagelijkse energiegebruik in de thuissituatie in kaart gebracht. Lichamelijke activiteit werd gemeten met behulp van een activiteitenmonitor, gedurende 7 dagen, 1 maand en 3 maanden na ontslag uit het ziekenhuis of het longrevalidatiecentrum. Door loting werd bepaald

of een patiënt tot de interventiegroep of controlegroep behoorde. In beide groepen bleef het gewicht gelijk gedurende de studieperiode. Vergelijking tussen deze twee tijdstippen toonde echter dat de interventiegroep eerder in een positieve energiebalans kwam dan de controlegroep. Het niveau van lichamelijke activiteit varieerde van 1.40 tot 2.44 in deze onderzoekspopulatie. Gewichtsverandering gedurende de studieperiode was negatief gecorreleerd met het niveau van lichamelijke inspanning. Voor COPD-patiënten met een hoger niveau van lichamelijke activiteiten was het moeilijker om in gewicht aan te komen. Daarentegen namen patiënten met een lager niveau van activiteiten wel in gewicht toe tijdens de studie. Dit onderzoek toont de noodzaak voor diëtisten om het dieetadvies niet alleen af te stemmen op de voedingsanamnese of voedingsdagboekjes, maar op een objectieve meting van de lichamelijke activiteiten.

Acute exacerbatie

Om de invloed van een acute exacerbatie (opflakking) van COPD op de voedingsstatus en het metabole profiel te onderzoeken werd in 23 COPD-patiënten, acuut opgenomen in het ziekenhuis, voedselinname, ruststofwisseling en lichaamssamenstelling gemeten (hoofdstuk 6). Deze metingen werden verricht bij opname, dagelijks tijdens het ziekenhuisverblijf en bij ontslag. In een subgroep van 10 COPD-patiënten zijn deze metingen 3 maanden na ontslag herhaald. Patiënten hebben tijdens opname geen voedingsinterventie gekregen, maar zij hadden de mogelijkheid om hun eigen maaltijden samen te stellen.

De voedselinname voorafgaand aan de ziekenhuisopname was verminderd samenhangend met een toename van ziektesymptomen en bedroeg gemiddeld 72% van de gebruikelijke voedselinname. Het merendeel van de patiënten rapporteerde daarbovenop een erg lage voedselinname gedurende de eerste drie dagen van opname. Gedurende de ziekenhuisperiode verbeterde de energie- en eiwitinname, maar de eiwitinname bleef lager dan de aanbevolen hoeveelheid.

De ruststofwisseling was verhoogd gedurende de eerste dagen in het ziekenhuis, maar daalde tijdens het resterende ziekenhuisverblijf. In een subgroep van patiënten bleef het rustmetabolisme verhoogd bij ontslag. Opvallenderwijs waren deze patiënten gekarakteriseerd door een lage BMI. Veranderingen in de kortademigheidsscore tijdens ziekenhuisopname waren significant gerelateerd aan veranderingen in de ruststofwisseling. Bij ontslag was de voedselinname significant hoger dan de gebruikelijke inname. Mogelijk ten gevolge van de negatieve balans was er sprake van een compensatie die samengaat met de verbetering van klachten of geïnduceerd kan zijn door het eetluststimulerende effect van de hoge dosis glucocorticosteroïden als medicamenteuze therapie. Drie maanden na ontslag vertoonde de subgroep van 10 COPD-patiënten een significante gewichtstoename. De voedselinname was drie maanden na ontslag vergelijkbaar met de gebruikelijke voedselinname en het rustmetabolisme was hetzelfde als bij ontslag.

In hoofdstuk 7 zijn de toepasbaarheid en de effectiviteit van een energie- en eiwitrijk supplement tijdens de ziekenhuisopname voor een acute exacerbatie onderzocht in 56 deplete COPD-patiënten. De gerandomiseerde, dubbel-blinde, placebo-gecontroleerde studie werd verricht in twee ziekenhuizen, namelijk azM en MMC, locatie Veldhoven.

Een aanzienlijk deel van de COPD-patiënten rapporteerde recentelijk ongewenst gewichtsverlies voorafgaande aan de ziekenhuisopname. Gewichtsverlies was gerelateerd aan de zuurstofspanning in het bloed bij opname in het ziekenhuis; hoe lager de arteriële zuurstofspanning, hoe hoger het gewichtsverlies bij COPD-patiënten. De toename van de energie- en eiwitinname was significant groter in de groep met voedingssupplementen en de supplementen interfereerden niet met de normale voedselinname. Alleen de gesuppleerde groep patiënten bereikte de aanbevolen eiwitbehoefte van 1.5 g/kg lichaamsgewicht. Geen significante verschillen in het verloop van het lichaamsgewicht traden op tussen de interventie groep en de controle groep. De voedingssupplementen werden goed getolereerd, een goede compliance met een kleine afname in de spontane voedselinname, ook in die patiëntengroep met acuut respiratoir falen. In tegenstelling met eerdere bevindingen door andere onderzoeksgroepen, werd er tijdens opname geen vermindering van de spierfunctie gevonden in alle patiënten. Waarschijnlijk ten gevolge van de korte duur van de ziekenhuisopname, werden er geen aanvullende verbeteringen in spierkracht gevonden in de interventiegroep.

Hoofdstuk 8 omvat de algemene discussie en een aanzet voor verder onderzoek.

Conclusie

De studies, beschreven in dit proefschrift, tonen het belang aan van het meten van de lichaamssamenstelling aanvullend op lichaamsgewicht en lengte tijdens diagnostiek en follow-up van alle poliklinische COPD-patiënten, en niet alleen bij patiënten die gewichtsverlies vertonen of met ernstig COPD. In tegenstelling tot suggesties uit de literatuur werden er geen acute nadelige effecten van voeding en voedingssupplementen gevonden op het klachtenpatroon, de ventilatie en de stofwisseling van COPD-patiënten.

Voedingsinterventie is geïndiceerd niet alleen om klinisch stabiele COPD-patiënten te behandelen, maar ook om gewichtsverlies te voorkomen en om de verstoorde eiwitbalans te beperken bij patiënten met COPD. Voedingsinterventie tijdens ziekenhuisopname voor een acute exacerbatie is toepasbaar, ook bij COPD-patiënten met acuut respiratoir falen, en resulteert in een verbetering van de energie-inname en in het bijzonder van de eiwitinname.

Deze resultaten bieden een verdere onderbouwing van de toepassing van nutritional assessment en management in een geïntegreerde benadering van COPD, van preventie tot palliatieve zorg.

Abbreviations

Abbreviations

%FM	fat mass as percentage of body weight
%predicted	percentage of predicted
ANOVA	analysis of variance
ATP/ADP ratio	adenosine triphosphate/adenosine diphosphate ratio
BIA	bioelectrical impedance analysis
BIS	bioelectrical impedance spectroscopy
BM	body mass
BMI	body mass index
BMR	basal metabolic rate
CCK	cholecystokinin
CHO	carbohydrates
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DIT	diet-induced thermogenesis
Dlco	diffusing capacity for CO
DEXA	dual-energy x-ray absorptiometry
ECW	extracellular water
ECW/ICW ratio	extracellular/intracellular water ratio
EDTA	ethylene-diamine-tetraacetic acid
EE	energy expenditure
EI	energy intake
ELISA	enzyme-linked immunosorbent assay
en%	energy%
FEV ₁	forced expiratory volume in one second
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
FVC	forced vital capacity
g	gram
GLP-1	glucagon-like peptide-1
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
h	hour
HB	Harris and Benedict
ICW	intracellular water
IGF	insulin-like growth factor
IL	interleukin
ITGV	intrathoracic gas volume
IVC	inspiratory vital capacity
kg	kilogram
kJ	kilojoules
LPS	lipopolysaccharide

m	meter
MA	megesterol acetate
MEF	mean expiratory flow
MJ	megajoules
min	minutes
MRC	the Medical Research Council
mRNA	messenger ribonucleic acid
n	number
Nm	Newton meters
NMR	nuclear magnetic resonance
ns	not significant
OCB	oxygen cost of breathing
p (-value)	statistical significance
PaCO ₂	arterial carbon dioxide tension
PA	physical activity
PAL	physical activity level
PaO ₂	arterial oxygen tension
Pe-max	maximal expiratory mouth pressure
PEF	peak expiratory flow
Pi-max	maximal inspiratory mouth pressure
r	correlation coefficient
Raw	airway resistance
REE	resting energy expenditure
RQ	respiratory quotient
RV	residual volume
SaO ₂	arterial oxygen saturation
StO ₂	transcutaneous oxygen saturation
SD	standard deviation
SEM	standard error of the mean
SGRQ	St. George's Respiratory Questionnaire
SPSS	statistical product and service solutions
t _{1/2}	gastric emptying half-time
t _{lag}	lag phase
TBW	total body water
TEE	total energy expenditure
TLC	total lung capacity
TNF α	tumor necrosis factor α
VAS	visual analogue scale
V'CO ₂	carbon dioxide production
V'E	minute ventilation
V'O ₂	oxygen consumption
Wmax	maximal exercise performance

Dankwoord

Dankwoord

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De twee personen, weergegeven in mijn proefschrift, zijn voor mij een weergave van een interactie of samenspel die kan plaatsvinden tussen personen. Het samenspel waarvoor meerdere personen nodig zijn, zo ook bij het tot stand komen van een proefschrift. Maar ook de interactie die plaats vindt tussen de diëtist en de patiënt om de dieetbehandeling tot een goed resultaat te brengen. Deze interactie tussen de verschillende personen kan heel divers plaatsvinden, kan zeer intrigerend zijn en maakt het geheel vaak interessant en boeiend. En hoe beter de interactie of het samenspel, hoe beter of mooier het resultaat.

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Curriculum vitae

Curriculum vitae

Marja Vermeeren was born on August 30th, 1964 in Rijsbergen, The Netherlands. After she finished secondary school (Katholieke Scholengemeenschap Etten-Leur, The Netherlands) in 1982, she started education for Dietetics (Hogeschool Wachtendonck, Heerlen, The Netherlands) and she graduated in July 1986. From December 1986 until May 1990 she worked as dietitian in Sophia Hospital in Zwolle, The Netherlands. From 1989 – 1990 she attended a post-graduate course 'Research by Dietitians' (Hogeschool Voeding en Diëtetiek, Nijmegen, The Netherlands). The research conducted as an assignment of this course was her first experience with scientific research. Since July 1990 she has been working as a dietitian in the Department of Dietetics at the University Hospital Maastricht. In 1992 she started working with patients with pulmonary disease, such as COPD. Since January 1998, she started with research activities concerning this thesis at the Department of Respiratory Medicine of the University Hospital of Maastricht. Firstly for one day in the week and after one year, for two days per week till now. The other days of the week she continued her dietetic activities. The research is especially directed towards optimal implementation of nutritional therapy in patients with COPD.