Nutritional Depletion in Chronic Obstructive Pulmonary Disease (COPD)

Effect on Morbidity, Mortality and Physical Capacity

RUNA HALLIN
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**Abstract**


The overall aim of this work was to examine the effects of depleted nutritional status on some aspects of Chronic Obstructive Pulmonary Disease (COPD).

**Morbidity.** In paper I, we found that energy intake was lower than the calculated energy demand for all patients. A low body mass index (BMI) at inclusion and weight loss, during the one year follow-up period were independent risk factors for having a new exacerbation (p = 0.003 and 0.006, respectively).

**Mortality.** Nineteen percent of the patients in paper II, where underweight (BMI<20). A significant positive correlation was found between BMI and FEV1, and this correlation remained significant after adjustment for age, sex and pack years (p<0.0001). Being overweight was related to increased overall mortality and respiratory mortality but not to mortality of other causes. 19% of the patients had died within 2 years. The lowest mortality was found among the overweight patients (BMI 25-30 kg/m).

**Physical capacity and effect of training.** In paper III we investigated baseline characteristics of patients that were starting physical training. We found that peak working capacity was positively related to BMI (r=0.35, p=0.02) and fat free mass index (FFMI) (r=0.49, p=0.004) and negatively related to S-Fibrinogen and serum C reactive protein (S-CRP). BMI and FFMI were significantly related to the 12 minutes walking distance when adjusted for body weight. Fifty to 76% of the variation in physical capacity was accounted for when age, gender, FEV1, FFMI and CRP were combined in a multiple regression model.

In paper IV the median change in fat free mass (FFM), after 4 months of physical training was 0.5 kg. Old age, low FEV1 and high level of dyspnoea were independent negative predictors of FFM increase after the training period.

In conclusion nutritional status is an important determinant of morbidity, mortality and physical capacity in COPD. Low FEV1 and high level of dyspnea are negative predictors for increased FFM after physical training.

**Keywords:** chronic obstructive pulmonary disease, nutrition, pulmonary rehabilitation, physical capacity, systemic inflammation

*Runa Hallin, Department of Medical Sciences, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden*

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This book is dedicated to my family and my friends
Preface

When I started to work as a nurse, at a pulmonary ward in 1989, the diagnosis Chronic Obstructive Pulmonary Disease (COPD) did not exist. Patients had asthma, respiratory insufficiency, emphysema or chronic bronchitis. During the many years that I have worked with these chronically ill patients I came to feel more and more both worried about and interested in how to help the very thin COPD patients. At the time when I first started to try to find information on the subject, about 20 or so years ago, I did not find a lot. Nor did the question interest many others, (read doctors) and at the beginning we had no dieticians to help us. Some research had started already then for example in the Nederland’s and that work gave me inspiration to go on trying to help these patients, the best I could. It also made want to learn more.
I am truly grateful to have had this opportunity to enter deeply into this complex subject.
List of papers


Contents

Introduction ................................................................................................... 13
  Chronic obstructive pulmonary disease ................................................. 13
    Definition, symptoms and diagnosis of COPD .................................. 13
    Prevalence, costs and risk factors ............................................... 14
    Treatment .................................................................................. 14
  Pulmonary rehabilitation ................................................................. 15

Nutrition in COPD patients .................................................................... 17
  Causes of weight loss and depletion of fat free mass ....................... 18
    Dietary problems and metabolism .............................................. 18
    Smoking ................................................................................ 18
    Systemic inflammation ............................................................. 19
    Genetic component ................................................................. 19

Two aspects of diet .............................................................................. 20
  Diet as a risk modifying factor for developing COPD ...................... 20
  Diet as a prognostic factor in patients that already have COPD .......... 21
    Morbidity and Mortality .......................................................... 21
    Skeletal muscle dysfunction .................................................. 21
    Quality of life, anxiety and depression .................................... 21
    Methods for detection of patients at risk .................................. 22
    Outcome variables ................................................................. 23

Treatment of poor nutrition ................................................................. 24
  Treating the systemic inflammation .............................................. 24
  Appetite stimulation .................................................................... 24
  Nutritional supplementation ...................................................... 25
  Physical training ........................................................................ 26
  Physical training and systemic inflammation ............................... 26

Aims ..................................................................................................... 27

Ethics ................................................................................................. 28

Paper I and II .................................................................................. 29
  Patients ...................................................................................... 29
  Method ...................................................................................... 30
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>30</td>
</tr>
<tr>
<td>Paper II</td>
<td>31</td>
</tr>
<tr>
<td>Result</td>
<td>31</td>
</tr>
<tr>
<td>Paper I</td>
<td>31</td>
</tr>
<tr>
<td>Paper II</td>
<td>32</td>
</tr>
<tr>
<td>Paper III and IV</td>
<td>34</td>
</tr>
<tr>
<td>Patients</td>
<td>34</td>
</tr>
<tr>
<td>Methods</td>
<td>35</td>
</tr>
<tr>
<td>Paper III and IV</td>
<td>35</td>
</tr>
<tr>
<td>Result</td>
<td>35</td>
</tr>
<tr>
<td>Paper III</td>
<td>35</td>
</tr>
<tr>
<td>Paper IV</td>
<td>36</td>
</tr>
<tr>
<td>Discussion</td>
<td>38</td>
</tr>
<tr>
<td>Conclusions</td>
<td>41</td>
</tr>
<tr>
<td>Clinical importance and what more needs to be done</td>
<td>42</td>
</tr>
<tr>
<td>Sammanfattning</td>
<td>43</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>44</td>
</tr>
<tr>
<td>References</td>
<td>46</td>
</tr>
</tbody>
</table>
Abbreviations

12MWD  Distance walked in a 12-minute walk test (m)
12M_work  Distance walked in 12 minutes (m) x body weight (kg)
ATS  American Thoracic Society
BMI  Body mass index; weight (kg)/height (m)^2
BMR  Basal metabolic rate
BODE  Body mass, degree of obstructivity, dyspnoea and exercise capacity index
BTS  British Thoracic Society
COPD  Chronic obstructive pulmonary disease
CRP  C- reactive protein
ERS  European Respiratory Society
FFM  Fat free mass
FFMI  Fat free mass index; fat free mass (kg)/height (m)^2
FVC  Forced vital capacity
GOLD  Global Initiative for Chronic Obstructive Lung Disease
HAD  Hospital anxiety and depression scale
HRQL  Health related Quality of life
IL  Interleukin
ISWT  Incremental shuttle walking test
ISWT_\text{wor}  Distance walked (m) x body weight (kg)
LBMI  Lean body mass index
MA  Megasterol acetate
QOL  Quality of life
REE  Resting energy expenditure
RNS  Reactive nitrogen species
ROS  Reactive oxygen species
SGRQ  St Georges respiratory questionnaire
TDE  Total daily energy expenditure
TNF_α  Tumour necrotic factor alfa
W_peak  Peak exercise capacity (Watt)
WHO  World health organization
Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality world-wide and leads to an economic and social burden that is both substantial and increasing. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until the patients already have had symptoms for some time and the disease is then often already quite advanced [1-3].

Loss of body weight is a common and serious problem for patients with COPD [4, 5]. Low body mass index (BMI) has been found to be an independent predictor of morbidity [6, 7], and mortality [8, 9]. However, there is also evidence to suggest that weight gain can reverse this increased mortality risk [9, 10]. An important aspect of a poor nutritional status is that it is potentially possible to treat. The importance of finding and treating patients with weight loss and depletion of fat free mass (FFM) is stressed in COPD management recommendations [11].

Chronic obstructive pulmonary disease
Definition, symptoms and diagnosis of COPD

The Global Initiative for Chronic Obstructive Disease (GOLD) definition from 2006, states:

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [1].

The characteristic symptoms of COPD are chronic and progressive dyspne, cough, and sputum production [12].

Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD. The spirometric classification of
severity of COPD now includes four stages: stage I, mild; stage II, moderate; stage III, severe; stage IV, very severe [13].

Prevalence, costs and risk factors
COPD prevalence estimation figures vary between one and ten percent worldwide, dependant on the criteria used [14]. COPD is a costly disease and 35-45 % of the total per capita cost for COPD is accounted for by exacerbations [15]. COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries but, in general, are directly related to the prevalence of tobacco smoking, although, in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor [13]. Low socioeconomic background from early in life affect the adult risk of developing COPD independently of smoking in both females and males [16].

As the understanding of the importance of risk factors for COPD has grown, so has the recognition that essentially all risk for COPD results from a gene–environment interaction [17].

Treatment
COPD treatment can reduce symptoms, improve quality of life, reduce exacerbations, and possibly reduce mortality [1].

Smoking cessation
Cigarette smoking is an addiction and a chronic relapsing disorder, and is regarded as a primary disorder by the Department of Health and Human Services Guidelines in the USA [18, 19] and by the World Health Organization (WHO). Treating tobacco use and dependence should therefore be regarded as a primary and specific intervention. Smoking should be routinely evaluated whenever a patient presents to a healthcare facility and all smokers should be offered the best chance to treat this disorder [11].

Pharmacological treatment
Effective medications for COPD are available and all patients who are symptomatic merit a trial of drug treatment [20]. The medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. The inhaled route is preferred [11].
Pulmonary rehabilitation

Pulmonary rehabilitation has become a state of the art intervention in symptomatic patients with COPD. The ATS/ERS in 2006 endorsed a joint statement on pulmonary rehabilitation. The definition adopted, reads as follows [21].

Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease.

Listed below are components that to a varying degree are included in pulmonary rehabilitation. There are different recommendations that emphasize different aspects of the rehabilitation [11].

- Exercise training
- Respiratory muscle training
- Nutrition
- Psychological intervention/cooping strategies
- Education

It is important to individualize rehabilitation to get the best result. Multidisciplinary assessment is crucial to set the track in individual patient [21].

Exercise tolerance is limited by many different factors and anxiety and poor motivation are likely to contribute [22, 23], even though a direct association between emotional status and exercise limitation has not been established [24]. Physiologic factors limiting exercise tolerance include flow limitations [25] leading to dynamic hyperinflation [26-28], peripheral muscle dysfunction, systemic inflammation, oxidative stress, corticoid steroid use and reduction in muscle mass [29]. Respiratory muscle weakness is often present in COPD [30-33], this contributes to hypercapnia [34], dyspnoea [35, 36] and reduced exercise performance [37].
Practice guidelines: [20]

• A minimum of 20 sessions should be given at least three times per week to achieve physiologic benefits; twice weekly supervised plus one unsupervised home session may also be acceptable.
• High-intensity exercise produces greater physiologic benefit and should be encouraged; however, low-intensity training is also effective for those patients who cannot achieve this level of intensity.
• Interval training may be useful in promoting higher levels of exercise training in the more symptomatic patients.
• Both upper and lower extremity training should be utilized.
• The combination of endurance and strength training generally has multiple beneficial effects and is well tolerated; strength training would be particularly indicated for patients with significant muscle atrophy.
There is today a substantial interest in nutritional depletion in COPD, and treatment recommendations for these patients exist. The connection between weight loss and higher mortality risk was described as early as 30 years ago [38]. At the end of 1980s a relation between low weight and higher mortality, independent of lung function was established [39].

Loss of body weight is a common and serious problem for patients with COPD [4, 5, 40]. Weight loss and depletion of fat free mass (FFM) is observed in COPD patients independently of the degree of airflow limitation and being underweight is associated with an increased morbidity and mortality risk [6, 7, 41, 42]. The reason for this weight loss is not known in detail but is thought to be of multi-factorial origin [20, 43].

**Cachexia definition**

There are more than one definition of cachexia, Wagner states that “cachexia in any disease is a state of severely and pathologically low weight, due principally to the loss of mass of tissues other than fat” [43]. Another recent and more detailed definition by Evans *et al* read as follows: “Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity” [44].

**Prevalence**

Prevalence figures for nutritional depletion in COPD patients, vary between 20-40% [45, 46], depending partly on how the limits for depletion are set, and with parameter that are used. Wagner sets the probable prevalence figure to about 25% [43]. Nutritional depletion can occur also in normal weight patients [47].
Causes of weight loss and depletion of fat free mass

Dietary problems and metabolism

Dietary problems can be caused by a wide variety of reasons, such as loss of appetite, dental problems, dyspnoea, fatigue, early satiety and psychosocial reasons [48]. Dietary problems are common in patients with COPD and are related to smoking habits and gender, for example, women are more often worried about gaining weight and smokers more often experience fatigue [48]. Cachexia also leads to anorexia and a vicious circle is started with weight loss leading to less food intake and thereby to continuous weight loss [49].

It has been found that COPD patients have higher metabolic rate [50] and cost of ventilation [51, 52]. Imbalance between this increased energy demand and/or reduced dietary intake, is one reason for weight loss [47]. The oxygen cost of training is higher in patients with COPD than in healthy subjects and Baarends found that the variation in total daily energy expenditure (TDE) for COPD patients did not show differences in resting energy expenditure (REE) but reflected differences in energy cost for activities [53]. To calculate energy requirement for this patient group it is necessary to measure basal metabolic rate (BMR) and assess physical activity [54]. Other factors contributing to weight loss is smoking [55] and exacerbations [55, 56], systemic inflammation [57] and loss of appetite by increased leptin levels [58].

Feeding induces more protein anabolism in normal weight patients with moderate COPD than in healthy control subjects. The reason for this is probably that COPD patients are characterized by adaptive inter organ response to prevent or delay weight loss at this disease stage [59].

Smoking

Cigarette smoking is a determinant of BMI in patients with COPD [60], and smoking men with low BMI are at increased risk for developing COPD [61]. Smoking causes oxidative stress by an imbalance between oxidants and antioxidants, leading to systemic inflammation [62-64]. This inflammation persists even after smoking cessation [65] and is marked by increased levels of CRP [66] fibrinogen [67] and tumor necrotizing factor alpha (TNF-a) [65]. Cigarette smoking elevates leptin levels, and this might be one possible mechanism for why smokers often have a lower body weight than non-smokers [68].
Systemic inflammation

Smoking induced imbalance in oxidants/antioxidants is present in patients with COPD [69] and there is increasing evidence that COPD is a multi organ systemic disease [52, 70-74]. A meta analysis has shown that COPD is characterised by an increased numbers of leucocytes, acute phase proteins as CRP and fibrinogen and cytokines [75]. Similar inflammation has been found in patients with other chronic diseases such as diabetes, chronic heart failure and obesity [76].

Extra pulmonary manifestations of the disease such as skeletal muscle weakness and wasting and impaired exercise performance have been reported as common findings in advanced COPD and are poorly related to air flow limitation [29]. Patients with an increased resting energy expenditure and decreased FFM, have been found to have increased acute phase reactant proteins and inflammatory cytokines and these findings may be causally related [52].

The role of inflammation in cachexia development is not yet fully understood, the markers that are attracting the most interest are TNFα, interleukin (IL) 1β, IL-6 and reactive oxygen species (ROS) and reactive nitrogen species (RNS) [43].

Raised levels of CRP has been found to be a marker of low-grade systemic inflammation [77], impaired energy metabolism, functional capacity and distress due to respiratory symptoms in COPD [66] and have also been associated with lung function decline [72, 73]. Moreover, CRP is significantly higher in COPD patients with a low BMI and thus, like TNF-α, may be considered an indicator of malnutrition in COPD patients [77].

Genetic component

As only about 25% of the COPD patients develop cachexia the production of inflammatory proteins is thought to be partly genetically determined [43, 78]. Search for polymorphisms in genes encoding for pro inflammatory molecules is one target area, correlation with cachexia has been found for polymorphisms in IL-1β gene [79] and in the bradykinin receptor [80] and tumor necrosis factor gene [81]. Other studies has found no polymorphisms for TNF α or IL-6 [79].

However, it is still early in the research for genetic polymorphisms and more studies are needed to find the genetic background in the systemic component of COPD [43, 78].
Two aspects of diet

Diet as a risk modifying factor for developing COPD

As described earlier COPD is a disease caused by smoking, but there is a discrepancy between the number of people smoking and the number of COPD patient, i.e. only about 50% of the smokers develop COPD. It is possible that the smoking induced imbalance between oxidants and antioxidants can be affected by diet, so that diets with high contents of antioxidants should be beneficial to COPD patients.

The amount of circulating antioxidants is partly determined by diet and there are some epidemiological evidence that food containing high concentrations of antioxidants such (fruit, vegetables and fish), might have a protective effect against developing COPD. One study found that high intake of fruit and vitamin C is associated with higher FEV$_1$ and can reduce the decline rate in lung function [82]. A diet rich in fruit and vegetables have been found to have an inverse association with the development of COPD in smokers [83, 84]. Also intake of whole grain products and a moderate intake of alcohol can have that kind of effect [85]. A survey on the intake of omega-3 fatty acids was carried out by measuring the amount of fish consumed. Almost 9000 ex smokers and current smokers were included. An inverse relation between amount of fish in the diet and COPD cases developed was found [86]. However McKeever et al found that high intake of n-3 fatty acids did not protect against COPD and that high intake of n-6 fatty acids seems to be associated with FEV$_1$ reduction. [87] Carotenoids and vitamin A and E, don’t seem to have any protective effects [88-90]. Denny et al concluded in a state of the art paper that the results from several paper on this topic suggests that people with diet rich in fruit and vegetables, i.e. rich in antioxidants, have lower risk of poor respiratory health. They therefore found it justified to recommend a diet rich in these food items [91].

It is also known that starvation by itself can cause emphysema-like changes in the lungs [92]
Diet as a prognostic factor in patients that already have COPD

Morbidity and Mortality

COPD patients with impaired nutritional status have a higher morbidity [7, 39], an increased risk of having new exacerbations after admission to hospital [6, 93]. Low BMI and or weight loss have also been found to be an independent predictor of mortality [6, 8-10, 94-96] independent of the degree of airflow obstruction [9].

One aspect of low weight is loss of muscle mass and Marquis et al. found that mid thigh cross sectional area, was a better indicator of mortality than BMI [97]. Patient that is normal weight but depleted in FFM, can have the same mortality risk as underweight and FFM depleted patients [20].

Skeletal muscle dysfunction

In COPD outpatients 30% of subjects suffer from weight loss and peripheral muscle wasting [47]. Peripheral muscle dysfunction, can be caused by, inactivity induced de-conditioning, systemic inflammation, oxidative stress, blood gas abnormalities, corticoid use and reduced muscle mass [98]. Upper limp skeletal muscle strength is thought to be less affected than lower limbs [99-101].

A fiber type shift in skeletal muscle often occur in COPD patients with less type 1 fiber and more type II fibers, and a decreased oxidative enzyme capacity [37, 98, 102-105]. This increases fatigability and reduces muscular endurance as type II fibers are fast, anaerobic and easily fatigued muscle fibers. This shift in fiber types have also been associated with impaired health status [106].

Quality of life, anxiety and depression

Anxiety and depression are common in patients with COPD, and correlates with poor quality of life (QOL) [107]. COPD patients also experience significantly more psychological distress than the general population [108] and lower QOL predicts morbidity and mortality in COPD [109-111].

Patients with nutritional depletion have worse QOL than normal weight COPD patients, and this is thought to be mediated by dyspnoea [112, 113]. Tissue depletion is an important determinant of health related quality of life (HRQL) independent of exercise capacity and dyspnoea [114]. There are
also indications that nutritional interventions may be important for improving dyspnea and HRQL in COPD patients [113, 115].

Methods for detection of patients at risk

**Eating difficulties and involuntarily weight loss**

Patients that complain about eating difficulties of any kind, and patients with involuntary weight loss, need assessment by health professionals [48].

Weight loss (> 10 % in the past 6 months or > 5 % in the past month) is sign of patient at risk and also a important predictor of morbidity and mortality [20].

**Anthropometric measurements**

Weight measurement should be carried out on COPD patients regularly, preferably at every visit to hospital or other care giver.

**BMI and FFMI**

One common and simple way to evaluate nutritional status is to measure BMI. That is body weight corrected for body height, calculated as kg/m². The BMI limits used vary but BMI < 21 is considered to be underweight, BMI 21-25 normal, BMI 25-30 over weight and BMI >30 obese [20].

Another way is to use FFM. FFM is measured by skin-fold anthropometry, bio-impedance analysis [116], or dual- energy X-ray absorptiometry (DEXA scan) [117]. Bioelectrical impedance analysis (BIA) is a easy method to measure, the body composition of fat mass and fat free mass compartments[118]. FFM can be expressed as (kg) as (% of body mass) or as FFMI kg/body height m². Limits for normal FFMI or lean body mass index (LBMI) is 16 kg/m² for men and 15kg/m² for women [42, 119]. Using these criteria 35 % of COPD patients admitted for pulmonary rehabilitation and 15 % of the out patients with COPD were depleted [20].

Recently, several studies have suggested that FFM is the best parameter to assess nutritional status because it is an independent predictor of mortality, regardless of BMI [120] or fat mass [42]. Furthermore FFMI has been suggested in the assessment of body composition as a systemic marker of disease severity in COPD staging [42], and FFMI has been found to be superior to BMI when used to assess disease severity and severity staging [121].
**Recommendation**

In a summary of the American Thoracic Society (ATS) and European Respiratory Society (ERS), i.e. the ATS/ERS position paper it is stated that nutritional screening is recommended in the assessment of COPD patients. Simple screening can be based on measurements of BMI and involuntary weight loss [12].

**Outcome variables**

Lung function has been the most used measure for assessing prognosis in COPD [122].

BODE is a multidimensional grading system that take into account both functional impairment and systemic consequences of COPD when determining outcome [123].

BODE stands for: B = body mass index (BMI), O = degree of airflow obstruction (FEV₁), D = functional dyspnoea, measured by the modified Medical Research Council scale and E = exercise capacity, measured as 6-minutes walk distance, all variables correlated to mortality. Combining these variables the BODE index was better at predicting death than FEV₁ alone [123]. BODE index has also been shown to be improved by pulmonary rehabilitation and is associated with better outcome [124].
Treatment of poor nutrition

**Significance**

Weight gain seems to reverse the increased mortality risk [9, 96] and have positive effects on QOL and dyspnoea [113].

A combination of oral nutritional supplements and exercise or anabolic stimulus appears to be the best treatment approach to obtaining significant functional improvement. Patients responding to this treatment even demonstrated a decreased mortality. Poor response was related to the effects of systemic inflammation on dietary intake and catabolism. The effectiveness of anti catabolic modulation requires further investigation [125].

**Treating the systemic inflammation**

Statins have been associated with a lower decline in lung function [126] and to lower CRP levels [127] in elderly patients. Use of Statins has also been found to have a relation to reduced exacerbation frequency and requirement of intubation [128] and mortality after exacerbations [129]. However, data from randomized clinical trials with statins in COPD are still lacking. Diet rich in antioxidants, might be used to reduce chronic metabolic stress and thereby may be beneficial in COPD [130]. Inhaled and oral corticosteroids are effective in reducing CRP levels [131] and have been associated with reduced incidence of ischemic heart disease in COPD patients [132].

**Appetite stimulation**

Megestrol acetate (MA), a progestational appetite stimulant commonly used in patients with AIDS and cancer, was tested for its effect on under weight COPD patients. It was concluded that MA increased appetite and body weight, stimulated ventilation, and improved body image in underweight COPD patients, but did not improve respiratory muscle function or exercise tolerance [133].
Nutritional supplementation

Research on nutritional supplementation is difficult to perform, as patients might not be compliant to the treatment. It is difficult to get correct reports on diet and it is also expensive to make large studies with a long enough follow up time.

Different review articles also come to varying conclusion about the effect of nutritional supplementation. In a review article on treatment of protein-energy malnutrition in chronic nonmalignant disorders, Akner och Cederholm concluded that treatment of protein energy malnutrition in COPD, may have positive effects on body composition, respiratory function and muscle strength [134]. While a Cochrane report by Ferreira et al in 2005, did not find that nutritional support had any significant effect on anthropometric measures, lung function or exercise capacity in patients with stable COPD [135].

Recommendations

Caloric supplementation is indicated to meet elevated energy requirements; with often is the case in patients with COPD. It is also important to meet the need of proteins for stimulation of protein synthesis to maintain or restore FFM. This is important, not only for under weight patients but for all COPD patients. The increased exercised induced energy requirements must also be met for all COPD patients [20].

The joint statement of ATS/ERS from 2005 (update at 2006), states: [20]

Caloric supplementation intervention should be considered for the following conditions: a BMI less than 21 kg/m², involuntary weight loss of more than 10% during the last 6 months or more than 5% in the past month, or depletion in FFM or lean body mass. Nutritional supplementation should initially consist of adaptation in the patient’s dietary habits and the administration of energy-dense supplements.
Physical training

Effect of physical training

Physical training of patients with COPD has been proven to have positive effects on exercise tolerance, quality of life and to induce an anabolic stimuli [136]. It is therefore recommended that physical training should be included in COPD rehabilitation programs [137, 138].

Physical training of nutritionally depleted patients is especially challenging as some of these COPD patients have an elevated energy metabolism, but still need to be more physically active. Therefore, COPD patients that loose weight or even weight stable patients should be encouraged to increase their energy intake especially when starting exercise training programmes [139, 140].

Depletion of fat free mass can be treated by the addition of strength training to aerobic training. This is associated with significantly greater increases in muscle strength and muscle mass, but does not provide additional improvement in exercise capacity or quality of life [141].

A short-term course of anabolic steroids had an overall positive effect relative to placebo on FFM in one study of patients with COPD [142]. Replacement testosterone doses increased lean body mass and leg muscle strength in men with moderate to severe COPD and low testosterone levels. Resistance training of the legs yielded similar benefits and the combination tended to be additive [143].

Physical training and systemic inflammation

Oxidative stress is higher in COPD patients than in normal subjects and muscle glutathione is depleted by training [144, 145] Exercise training can increase oxidative stress in COPD patients [146, 147]. However cachectic patients seems to increase their exercise capacity after training to the same degree as non cachectic patients and controls [146].
Aims

The aim of this work was:

• To examine the relationship between nutritional intake, change in body weight and the risk of exacerbation in patients with COPD.

• To investigate the association between nutritional status and long-term mortality in COPD patients in a multicentre study conducted at four university hospitals (Reykjavik, Uppsala, Tampere and Copenhagen).

• To examine relations between, nutritional status, systemic inflammation and physical capacity, in COPD patients.

• To evaluate the effect of physical training on FFM and investigate factors related to change in FFM during a physical training program.
Ethics

IRB and/or ethic committee for each institution or country approved the study and an informed consent was obtained from all the patients.
Patients

The study population was recruited from a prospective multi centre, readmission study, [107, 148, 149]. Consecutive patients with acute exacerbations of COPD, that were admitted to hospital were included [150].

![Location of study centres.](image)

Figure 1. Location of study centres.

The study aimed to include 100 patients each from five University Hospitals (Bergen, Reykjavik, Uppsala, Tampere and Copenhagen) in the Nordic countries (Fig. 1). The departments included were: The Department of Respiratory Medicine and Allergology, Akademiska sjukhuset, Uppsala, Sweden; The Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; The Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland; The Department of Respiratory Medicine, Vifilstadir University Hospital, Gardabaer, Iceland and The Department of Respiratory Medicine, Hvidovre Hospital, Copenhagen Denmark.
An acute exacerbation was defined as a change in condition from baseline that was of such a magnitude that the COPD patient needed an acute hospital admission. Only patients that were admitted more than 24 hours were included. All the patients had COPD stage 1 or higher, according to the global initiative for chronic obstructive lung disease (GOLD) criteria [17].

Figuge 2. Patient flow study one and two.

Paper I comprised 41 patients from Uppsala that completed a food diary at the 12 month follow up. Paper II, included patients from the 4 countries (Sweden, Finland, Denmark and Iceland) that had weight and height included in their protocol (Fig2).

Method

Paper I

Weight, height were measured within 48 hours of admission and lung function were measured at discharge. A structured interview protocol was used and patients were asked about smoking habits and social situation. Health status (quality of life) was assessed using the disease-specific St.George’s
Respiratory Questionnaire (SGRQ). Psychological status was assessed with the Hospital Anxiety and Depression Questionnaire (HAD).

At the 12-month follow-up, weight change and current weight were assessed by a telephone interview and nutritional intake was recorded in a food diary for 7 days. An acute exacerbation was defined as having been admitted to hospital and/or made an emergency visit to hospital, due to COPD during the follow-up period.

Paper II

In four of the five hospitals the protocol also included measurement of body weight and height. The present analysis includes 261 of the total 316 patients (83%), from Reykjavik, Copenhagen, Uppsala and Tampere. A structured interview protocol was used and patients were asked about smoking habits and social situation. Health status (quality of life) was assessed using the disease-specific St.George’s Respiratory Questionnaire (SGRQ). Psychological status was assessed with the Hospital Anxiety and Depression Questionnaire (HAD). Information on co-morbidity (diabetes and cardiovascular disease) was obtained from patient records. Spirometry was performed at discharge.

After 2 years, mortality data was obtained from the national registers in each country.

Result

Paper I

Of the 87 patients included, 13 (15%), had died within the first year. The remaining 74 were followed up by a phone interview. 42 completed a food diary for 1 week and were included in the present study. One of the 42 patients that completed the food diary was excluded, as weight was not recorded. We found no differences in terms of gender, age, pack years, FEV, or BMI between dose who filled or did not fill in the food diary.

Patients with low BMI had significantly fewer pack years than the normal weight group and significantly lower FEV than the overweight group. All patients had a lower energy intake than energy demand; the level of energy deficiency was significantly lower in the underweight group compared with the other groups. Underweight patients used diet supplementation more often and were more likely to have had dietary advice then normal and over weight groups.
We found that a low BMI at inclusion or weight loss during the follow-up period were independent risk factors for having an exacerbation (P = 0.003 and 0.006, respectively).

Figure 3. Kaplan–Meier cumulative survival plot for days until next COPD exacerbation in COPD patients divided into BMI categories.

Paper II

Of the 261 patients included, 19% were underweight (BMI < 20), 41% were of normal weight (BMI 20–25), 26% were overweight (BMI 25–30) and 14% were obese (BMI > 30). FEV₁ was lowest in the underweight group and the prevalence of cardio-vascular disease and diabetes were higher in the overweight group.

We found an independently significant negative correlation between FEV₁ and BMI (p = 0.0001). Nineteen % of the patients died within the 2 year follow up period. Patient that died had a lower BMI (p = 0.0007), higher age (p = 0.0005), and lower FEV₁ (p = 0.0005) they were also more likely to be men (p = 0.03).

The lowest mortality was found among the overweight patients, (BMI 25-30) (RR = 7.7, p = 0.03), whereas underweight, (BMI < 20 kg/m²) (RR = 12.9, p = 0.001) was related to an increased respiratory and overall mortality.
Figure 4. Risk of mortality in under-weight patients (BMI < 20 kg/m2) compared to patients with a BMI > 20 kg/m2 in relation to cause of death (HRR = hazard risk ratio). The HRR is adjusted for hospital, age, sex, FEV₁, health status and diabetes.
Patients

The study population was recruited from patients included in a physiotherapy exercise study comparing different training methods [151, 152]. All patients included in the training study from the autumn 2002, were asked if they wanted to participate in the current study.

Patient flow study 3 and 4.

Inclusion to the physiotherapy study: patients with moderate to severe COPD according to the BTS guidelines, was consecutively invited to participate in the study. Inclusion criteria was COPD with a FEV1/FVC-ratio < 0.7 and a FEV₁ > 60% of the predicted [151, 152].
Methods

Paper III and IV

Information on smoking history was obtained by a structured interview. A symptom-limited ramp ergometer test, incremental shuttle walking test (ISWT), 12-minute walk distance (12MWD) and hand grip strength test were performed. In addition, because body weight is a substantial contributor to the workload (W) during walking, each walking distance (m) was multiplied by body weight (kg). The body weight corrected distances are ISWT x weight = ISWT<sub>work</sub> and 12MWD x weight=12M<sub>work</sub> [153, 154].

Weight, height, sagittal diameter and skinfold thickness were measured and bioelectrical impedance was performed. Blood were taken for analyses of CRP and fibrinogen.

Forty nine patients were examined before training, of these the 27 patients that completed training, were also examined at the end of the training period.

Physical training sessions were performed two times a week, every session started with cycling. Once weekly training continued with calisthenics and relaxation and once a week with resistance training. Patients who desaturated during training were given supplemental oxygen during training sessions and all patients with BMI below 21 kg/m<sup>2</sup> was given nutritional support ad lib [155].

Result

Paper III

The study included 33 woman and 16 men (mean age 66 years and mean FEV<sub>1</sub> 31% of predicted). A statistically significant correlation was found between BMI and FFMI (r=0.69, p<0.0001) though nine of the patients with normal weight and two of the overweight patients had depleted FFMI.

W<sub>peak</sub> was positively related to both BMI (R=0.35, P=0.02) and FFMI (R=0.49, r=0.0004). Age was negatively and male gender positively correlated with all measures of physical capacity. FEV<sub>1</sub> was positively correlated with W<sub>peak</sub>, ISWT, ISWT<sub>work</sub>, 12MWD and 12M<sub>work</sub> but not to hand grip strength.

W<sub>peak</sub>, ISWT<sub>work</sub> and 12M<sub>work</sub> were positively associated with BMI, FFMI and arm and leg circumference. Hand grip strength was significantly related to FFMI and arm and leg circumference but not to BMI. Sagittal diameter
was only significantly associated with 12M\textsubscript{work}. A negative association was found between CRP and W\textsubscript{peak} and ISWT. Fibrinogen was negatively associated with W\textsubscript{peak}.

Between 50 and 76% of the variation in physical capacity was accounted for when age, gender, FEV\textsubscript{1}, FFMI and CRP were combined in multiple regression models (Table 1)

<table>
<thead>
<tr>
<th></th>
<th>W\textsubscript{peak}</th>
<th>ISWT</th>
<th>ISWT x w</th>
<th>12MWT</th>
<th>12MWT x w</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.76</td>
<td>0.52</td>
<td>0.61</td>
<td>0.50</td>
<td>0.72</td>
</tr>
<tr>
<td>Ccoeff</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>25</td>
<td>0.0003</td>
<td>46</td>
<td>0.23</td>
<td>4510</td>
</tr>
<tr>
<td>Age</td>
<td>-1.2</td>
<td>0.0024</td>
<td>-5.9</td>
<td>0.004</td>
<td>-417</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>1.8</td>
<td>&lt;0.0001</td>
<td>7.1</td>
<td>&lt;0.0001</td>
<td>443</td>
</tr>
<tr>
<td>FFMI</td>
<td>3.0</td>
<td>0.02</td>
<td>7.8</td>
<td>0.27</td>
<td>1788</td>
</tr>
<tr>
<td>CRP</td>
<td>-16</td>
<td>0.005</td>
<td>-68</td>
<td>0.03</td>
<td>-4226</td>
</tr>
</tbody>
</table>

Table 1. Association between physical capacity and gender, age, FEV\textsubscript{1}, FFMI and CRP. The estimates (Beta coefficients) are adjusted for all the variables in the table.

**Paper IV**

The study included 27 patients that completed a four month physical exercise training period. No differences in age, sex, FEV\textsubscript{1}, BMI, FFMI, CRP, W\textsubscript{peak}, ISWT, 12M\textsubscript{WD}, handgrip strength or weight change the year before inclusion were found between participants that completed the training and those that did not. The median change in FFM was 0.5 kg
A significant positive correlation between change in fat free mass and FEV (p=0.03), dyspnoea (p=0.03) and fibrinogen (p=0.03) was found in bivariate analyses.

In the multivariate analyses between 68 and 70 % of the variation in fat-free-mass change was accounted for when age, gender, FEV1, dyspnoea, FFMI and fibrinogen were combined in multiple regression models (Table 2). Δ FFM were negatively correlated with age while both Δ FFM and Δ FFMI in % of baseline were positively correlated with FEV1 and the CRDQ dyspnoea score. In the model higher FEV1 and lower level of dyspnoea remained significantly correlated with higher increase in FFM, while the association between change in FFM and fibrinogen and FFMI at baseline became statically non significant.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Δ FFM</th>
<th>Δ FFM % of baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>0.697</td>
<td>0.682</td>
</tr>
<tr>
<td>Coeff</td>
<td>p</td>
<td>Coeff</td>
</tr>
<tr>
<td>Age</td>
<td>-0.120</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.519</td>
<td>0.58</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.104</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyspnoea CRDQ</td>
<td>0.336</td>
<td>0.01</td>
</tr>
<tr>
<td>FFMI</td>
<td>-0.086</td>
<td>0.64</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.588</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 2. Association between change in fat-free mass, and dyspnoea, FEV1, fibrinogen, FFMI, age and sex. The estimates (Beta coefficients) are adjusted for all the variables in the table.
Discussion

Patients with COPD often have problems with weight loss and depletion of FFM. Our findings from paper I and II show that COPD patients with under weight have a higher exacerbation frequency, and a mortality risk that is almost three times higher than normal and over weight patients.

This is consistent with other reports that have found an increased need of medical care and a higher mortality in underweight COPD patients [7, 8, 10, 93-95]. Pouw and co-workers reported that patients, who lost weight during an exacerbation related hospitalisation, had a higher risk of early non-elective re-admission [6].

In hypoxemic COPD patients a low BMI [41] or even a BMI < 25, leads to an increased mortality risk [9]. The increased mortality risk in low weight COPD patients is thought to be caused by loss of muscle mass [97]. In paper III we found that although there is good correlation between BMI and FFMI, still there were many patients with normal BMI that had a depleted FFM. This might be the reason to why there was no significant difference between underweight and normal weight patient in the exacerbation frequency. The loss of FFM in weight stable patients, is often caused by a selective atrophy of type II muscle fibres [156, 157]. In paper II patients with over weight had the lowest overall mortality. This has also been found in other COPD studies [9, 10, 96]. Our results are also in accordance with a Korean cohort study of the general population where a decreasing risk of death by pulmonary causes with increasing BMI was present [158]. The reason for why, being overweight may be a positive prognostic factor in COPD is to our knowledge unknown.

Physical training of patients with COPD has been proven to have positive effects on exercise tolerance, quality of life and to induce an anabolic stimuli [136]. It is therefore recommended that physical training should be included in COPD rehabilitation programs [137, 138].

In Paper III we reported baseline data on COPD patients that were to start physical training. We found that physical exercise capacity was related to three different aspects of COPD, namely, lung function decline, nutritional status and systemic inflammation. Nutritional status affects physical capac-
ity, as depletion of muscle mass, measurable by assessment of FFM, significantly affects peak oxygen consumption, ventilatory response, oxygen pulse and anaerobic energy metabolism in patients with COPD [159]. In the paper III, we found a significant correlation between $W_{\text{peak}}$ and BMI, and an even stronger correlation between $W_{\text{peak}}$ and FFMI. These findings are in accordance with other studies showing that nutritional status is related to exercise capacity [121, 160]. We also found a correlation between FFMI and 12M$_{\text{work}}$, ISWT$_{\text{work}}$ and hand strength but not to 12MWD or ISWT.

The physical training of nutritionally depleted patients is especially challenging as some of these COPD patients have an elevated energy metabolism, but still need to be more physically active. Therefore, COPD patients that lose weight or even weight stable patients should be encouraged to increase their energy intake especially when starting exercise training programmes [139, 140].

Our food diary results from paper I, suggest that an insufficient dietary intake is very common in COPD patients. We found no significant association between energy deficiency and weight loss, and energy deficiency was lowest in the group of patients with a BMI of $>20 \text{ kg/m}^2$. This is probably explained by the more intensive information and use of food supplementation that were also found in this group of patients. Another reason for the somewhat paradoxical relationship between body mass and energy deficiency may be that over weight patients tend to under-report their food intake. The finding from paper IV, that patients with depleted FFMI before the start of physical training seems to have increased more in FFM, than the patients with normal FFMI are a bit unexpected. Also this result might be explained by the fact that, all patients with a BMI less than 21 kg/m$^2$ were given nutritional supplementation during the exercise training period. In a study by Schols et al a combination of physical training and nutritional support led to the best result not only on weight but also increased FFM and respiratory muscle strength, and even survival rates were increased.

Even if weight loss is of multifactorial origin, energy intake is probably of importance. One cause of low intake is a variety of eating difficulties [48] observed in many malnourished COPD patients. Loss of appetite has also been suggested to be explained by, a cytokine leptin link leading to increased levels of leptin. These increased leptin levels leads to reduced food intake and higher energy demand and therefore poor response to nutritional support [161].
In paper IV we found that high age, a high level of dyspnoea and a low FEV\textsubscript{1} were independent risk factors for not increasing FFM during physical training. Some studies have found that muscle strength and FEV\textsubscript{1} are factors limiting exercise capacity [101]. Others have found only weak correlation between FEV\textsubscript{1} and impaired exercise tolerance [162]. There are multiple possibilities for the correlation between FEV\textsubscript{1} and exercise limitation, for example, dynamic hyperinflation [27] resulting in increased work of breathing, increased load on the respiratory muscles [28, 163] and the intensified perception of respiratory discomfort. Another possible reason is that a low FEV\textsubscript{1} is related to hypoxic muscles due to insufficient oxygen caused by insufficient blood supply or hypoxemia [164].

Although dyspnoea can cause difficulties in physical performance, and was found to be one of the independent risk factors to not increase FFM, patients that did complete training did not have significantly less dyspnoea that the ones that failed to do so. Dyspnoea during daily activities is considered to be a better measurement than peak dyspnoea during exercise for evaluating disease severity [165]. Fear of worsening dyspnea by exercise can result in inactivity and thereby worsen the exercise intolerance and social isolation of COPD patients [166-168]. Dyspnoea can of course have many different explanations and some of them are probably possible to treat at least to some extent [166-168].

Low body weight is related to worsening of both dyspnoea and quality of life [113]. There are indications that nutritional interventions can improve dyspnoea and quality of life [113] and also may be beneficial in COPD rehabilitation [130].

In paper II patients had lower FEV\textsubscript{1} but despite this they had a similar level of smoke exposure in terms of pack years as the patients that were normal or overweight. The cause–effect relationship explaining the negative correlation between FEV\textsubscript{1} and BMI is unclear. The low BMI may be caused by the more severe lung impairment, but it may also reflect the findings of Harik-Khan et al [61], that low-weight smokers are at a higher risk of developing COPD than normal and overweight smokers. The underweight group had a lower prevalence of co-morbidity, which may partly explain why no difference was found in health status despite the relatively large difference in FEV\textsubscript{1}. 
Conclusions

Underweight and weight loss at admission to hospital for an exacerbation was related to a higher risk of exacerbations the following year in patients with COPD. This study underlines the importance of examining nutritional status and monitoring weight changes in patients with severe COPD.

COPD patients that are underweight at admission to hospital for an exacerbation have a higher risk of dying within the next 2 years. COPD patients with overweight have the significantly lowest mortality risk.

In COPD peak working capacity is related to lung function, nutritional status and systemic inflammation. A characterisation of all these three aspects of the disease is therefore important when directing intervention strategies such as physical training in COPD.

The most important factor limiting increase in fat free mass during physical training in COPD patients seems to be FEV₁ and dyspnoea.
Clinical importance and what more needs to be done

There are indications that the mortality, low QOL and high level of dyspnoea that is caused by low weight in COPD is possible to reverse. It is, therefore, important to examine nutritional status and monitor weight changes in patients with severe COPD. It is also important to continue with research concerning causative mechanisms for depletion of nutritional status in COPD patients.

As COPD is a disease that is not possible to cure it is important to try to treat the factors that can improve any aspect of life for COPD patients. Factors limiting physical performance, such as depleted FFM and elevated levels of CRP are possible to treat and this may improve quality of life, for many COPD patients.
Sammanfattning

Syftet med detta arbete var att undersöka effekterna av nutritionsstatus på några aspekter av kroniskt obstruktiv lungsjukdom (KOL).

Sjuklighet
I arbete I fann vi att energiintaget var lägre än kaloribehovet för alla KOL patienter. Ett lågt body mass index (BMI) vid inklusionen i studien och viktförlust året efter var oberoende riskfaktorer för att åter få en exacerbation, dvs. en försämrings period av sjukdomen (p = 0.003 respektive 0.006).

Dödlighet
Nitton procent av patienterna i arbete II var underviktiga (BMI< 20). BMI var signifikant positivt korrelerat till lungfunktionen (FEV₁), även efter att vi justerat för ålder, kön och antal rökår (p = 0.0001). Undervikt var relaterat till en ökad dödlighet och en ökad lungdödlighet men inte till dödlighet av andra orsaker. Nitton procent av patienterna hade avlidit under den 2 år långa uppföljningsperioden. Den lägsta dödligheten fann vi för överviktiga patienter (BMI 25-30).

Fysisk kapacitet och träningseffekt
I arbete III undersökte vi utgångsdata karakteristiska för patienter som skulle påbörja fysisk träning. Vi fann att arbetsförmågan var positivt korrelerad med BMI (r 0 0.35, p = 0.02) och fett masse index (FFM) (r 0 0.49, p = 0.004) och negativt korrelerad med S-Fibrinogen och serum C reaktivt protein (CRP). BMI och FFMI var signifikant korrelerade till 12 minuters gångsträcka, justerad för vikt. Femtio till 76 % av variationen i fysisk kapacitet förklarades när ålder, gender, FEV₁, FFMI och CRP kombinerades i en multipel regression modell.

I arbete IV är median förändringen i FFM efter 4 månaders fysisk träning 0.5 kilo. Lågt FEV₁ och mer dyspne var oberoende faktorer för sämre ökning av FFM av träningen.

Vår slutsats blir att nutritions status är en viktig prediktor för sjuklighet, dödlighet och fysisk förmåga hos KOL patienter. Sämre lungfunktion och mer dyspne är negativa prediktorer för ökning av muskelmassan efter fysisk träning.
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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)