Cost-effectiveness issues related to malnutrition and nutritional intervention in COPD
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Because nutritional counseling and oral nutritional supplements are competing with other treatments for a part of the publicly funded healthcare budget it is important to assess its cost-effectiveness. However, there is virtually no evidence on the economic implications of these interventions in COPD. Therefore we start this section with a paragraph describing the association between nutritional status and healthcare utilization/costs in COPD. This is followed by reviewing the evidence on the impact of nutritional counseling and supplements on healthcare utilization/costs. The third part concentrates on cost-effectiveness and the fourth part gives suggestions for future research.

1. Association between nutritional status and utilization/costs of healthcare

Many studies report on the association between nutritional status and healthcare utilization. Most of these studies focused on predictors for hospitalization for a COPD exacerbation or included patients hospitalized for a COPD exacerbation. In a prospective, observational study in about 3,300 patients with moderate to very severe COPD a low body mass index (BMI<18.5 kg/m²) was identified as a risk factor for respiratory hospitalization or death [1]. In stable patients with moderate and severe COPD BMI was found to be a significant predictor of hospitalization for an exacerbation in the univariate analysis, but not in multivariate analysis [2]. Two studies in patients hospitalized for a COPD exacerbation found that the duration of hospital stay was negatively correlated with BMI [3,4] and fat free mass (FFM) [3], suggesting that patients with lower BMI or FFM had significantly longer hospital stays. A study in patients with end-stage emphysema undergoing lung volume reduction surgery showed that patients with a low BMI (20.9 ±2.1) had a higher probability to require prolonged ventilatory support and a longer hospital length of stay than patients with a normal BMI (26.1±2.0) [5]. In COPD patients receiving long-term oxygen therapy (LTOT), a BMI below 20 kg/m2 at the start of LTOT was an independent predictor of annual number of days spent in hospital as well as annual number of admissions [6]. However, Soler et al. found no significant differences in weight, BMI or other nutritional parameters between COPD patients with at least one hospital admission or emergency room visit in the year before the start of the study and controls without any inpatient hospital care but otherwise similar in terms of age, PaO₂ and FEV₁ [7].

The impact of malnutrition in patients hospitalized for a COPD exacerbation on the probability to be readmitted was investigated in at least four studies [3,8-10]. A study by Giron et al reported that patients who were readmitted in the three months after the initial hospitalization had a significantly lower FFM than patients who were not readmitted [3].
Pouw et al and Hallin et al found that weight loss during the initial hospitalization and BMI on admission were significant independent risk factors for unplanned emergency room (ER) visit and/or readmission [9,10]. Malnourished patients defined as patients with a score of less than 17 points on the Mini Nutritional Assessment (MNA) questionnaire were reported to have a higher risk for readmission within 6 months (HR 2.9, 95%CI: 1.05-7.32) in comparison with well-nourished patients [8]. Another study using the same definition for malnutrition found that malnourished patients also had a higher probability not to live in their own homes or to require daily community service and meals-on-wheels compared to patients at risk for malnutrition [11].

The studies described above showed that malnutrition in COPD is likely to be associated with longer in-patient hospital stays, a higher probability to be readmitted and an increase in healthcare utilization in comparison with patients without malnutrition.

2. Impact of nutritional counseling and supplements on healthcare utilization and costs

Four randomized controlled trials compared healthcare utilization and/or costs between an intervention group receiving nutritional supplementation and a control group not receiving any supplementation. Two studies did not find a difference in hospital admissions [12-14]. Weekes et al. found no difference in hospital admissions after 6 months (OR: 0.40 95%CI 0.14-1.18) between a group of undernourished COPD patients receiving dietary advice and food fortification (milk powder) and a group of undernourished patients receiving dietary advice on a leaflet [12,13]. Vermeeren et al. also reported no difference in readmissions after three months in patients hospitalized for an exacerbation between the group receiving Respifor© three times per day and a control group [14]. The third trial investigated the effect of eight weeks of supplementation versus no supplementation in malnourished elderly discharged from hospital of which 37% had COPD. Results showed that requirements for healthcare and healthcare costs at 24 weeks did not differ between the supplementation and the no supplementation group. The mean total costs for healthcare professionals’ and social services as recorded in patients’ diaries were €2989 in the intervention group and €2146 in the control group [15]. It could be argued that in all of these studies the duration of follow-up of 6 months or less was too short to detect an effect on healthcare utilization.

A subgroup analysis of the INTERCOM trial reported results over a longer time period, i.e. two-years. In this trial patients were randomly assigned to the INTERCOM program or usual care. The INTERCOM program consisted of exercise training and education for all patients, smoking cessation counseling upon indication and nutritional advice and supplements for muscle-wasted patients (FFMI \leq 15 \text{ (female)} / \leq 16 \text{ (male)} \text{ kg/m}^2) [16]. In the subgroup analysis muscle-wasted COPD patients receiving exercise training in combination with nutritional advice and supplements (15.7% of the total group of patients) were compared to
3. Cost-effectiveness of nutritional counseling and supplements

In a cost-effectiveness study the difference in costs between the nutritional intervention and the control group is divided by the difference in health outcomes to calculate a cost-effectiveness ratio. This ratio is usually the cost per quality-adjusted life year gained, but could also be the cost per additional patient with an improved nutritional status. The nominator of this ratio refers to the difference in total costs, including the costs of the nutritional intervention and all other costs of healthcare utilization.

There is little information in the literature about the costs of nutritional interventions. Sugawara reported the total costs for twelve weeks of supplementation with a nutritional drink supplement to be €270 per patient [18]. In the INTERCOM trial the average total costs per patient according to the official list price for nutritional supplementation with Respifor® were €595 after 4-months and €1260 after 24 months [17]. These costs would have been 25-30% lower if the cost analysis would have been performed from a healthcare instead of a societal perspective, because the price of Respifor is lower for patients entitled to reimbursement. Daily costs of nutritional supplementation varied between €3,20 for two times 200 ml of a nutritional drink [18] and €8,28 for three times 125 ml of Respifor® [16].

According to our knowledge there, the INTERCOM trial is the only study reporting on the cost-effectiveness of a nutritional intervention. In this study nutritional counseling and supplements were given to about 16% of patients in the intervention group who were nutritionally depleted. A post-hoc cost-effectiveness analysis found that despite additional costs of nutritional intervention, total costs were lower for the nutritionally depleted patients in the INTERCOM group compared to the nutritionally depleted patients in the usual care group. This difference was primarily due to a significant reduction in costs related to hospital admissions. Because of these net cost savings no cost-effectiveness ratio was calculated.

4. Future research

There is a clear need for cost-effectiveness studies of nutritional counseling and supplements to support decision making about reimbursement in COPD. There are several possibilities. One is the conventional approach of designing randomized clinical trials in which the additional costs and benefits of adding a nutritional intervention to usual care is investigated. Because usual care is most likely a multimodal pulmonary rehabilitation
program or disease management program that already includes nutritional counseling, the newly designed trials should focus on assessing the added value of the oral supplements or the added value of long-term nutritional counseling. Given the current lack of any cost-effectiveness data, these trials could recruit patients from different target groups including end stage COPD patients with both muscle wasting and weight loss (cachexia) as well as weight-stable COPD patients with muscle wasting (sarcopenia). Second, we need better data on the longitudinal association between changes in the risk factors BMI and FFMI and the risk of COPD exacerbations and hospitalizations. Such data could come from observational studies. They could be used in cost-effectiveness modeling studies to simulate potential long-term effects of changes in BMI and FFM on health status and health care utilization. The latter is necessary because the costs of nutritional intervention in sarcopenic COPD patients are likely to precede the benefits by far.
References


