Oral Nutritional Supplementation for the Dietary Management of Malnutrition in Chronic Pulmonary Diseases: Study Protocol of a Randomized, Open-label, Multicentre Clinical Trial

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Abstract

Disease-related malnutrition is frequent in patients with chronic pulmonary diseases. Though there is no doubt about the usefulness of Oral Nutritional Supplements (ONS) in managing malnutrition in such patients, only a handful of publications are available in the literature on clinical trials with ONS in this patient population. Since the digestion of macronutrients results in a strain on the respiratory functions in severe pulmonary diseases, the source of energy may also play a crucial role in the efficacy of nutrition with ONS in such patients. Here we present the study protocol of a randomized, open-label, multicentre clinical trial aimed to determine whether a new, condition-specific ONS (with a composition tailored to the needs of patients with decreased pulmonary functions) is more effective compared to a general ONS in improving the nutritional status in patients with compromised respiratory functions.

Keywords: Disease-related malnutrition, COPD, Cystic fibrosis, Condition-specific, ONS, Clinical nutrition

Abbreviations: ANOVA: Analysis of Variance; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CF: Cystic Fibrosis; ECOG: Eastern Cooperative Oncology Group; EoS: End Of Study; FFM: Fat-free Mass; GFR: Glomerular Filtration rate; Hgb: Haemoglobin; ONS: Oral Nutritional Supplement; OS: Overall Survival; QoL: Quality of Life; ULN: Upper Limit of Normal; UUC: Upper Arm Circumference

Introduction

Most patients with chronic pulmonary diseases such as Chronic Obstructive Pulmonary Disease (COPD) and Cystic Fibrosis (CF) are lean, and often show decreased body weight. Many patients are in a state of marked undernutrition called pulmonary cachexia. Typical metabolic changes associated with the development of cachexia are an increased release of pro-inflammatory cytokines, as well as an overactivity of sympathetic nervous system, as indicated by the increased plasma concentrations of catecholamines. Both pro-inflammatory cytokines and catecholamines promote catabolic processes leading to skeletal muscle and fat mass wasting, such as stimulation of lipid utilization and skeletal muscle protein breakdown while decreasing energy intake and increasing energy expenditure [1].

In total, 25-40% of all COPD patients exhibit weight loss, with 25% of the patients having moderate to severe disease and 35% showing a severe disease with a reduced fat-free mass index [2]. In a large US national outpatient trial, 24% of 779 male COPD patients had a body weight < 90% ideal body weight. In the Netherlands, 35% of 255 consecutive patients admitted for intensive pulmonary rehabilitation weighed < 90% ideal body...
weight. In the UK, 36% of 69 outpatients with moderate to severe COPD weighed < 90% ideal body weight [3]. Decreased body weights have been identified as a factor for poor prognosis in patients with COPD. According to research data, COPD patients with a BMI of < 20 kg/m² have a higher risk of acute exacerbations than patients with a BMI of ≥ 20 kg/m². Moreover, patients who lost weight during a 1-year observation period were more likely to have acute exacerbations than those without weight loss. A negative correlation between the BMI and duration of hospitalization has also been demonstrated. Furthermore, body weight is positively correlated to exercise tolerance and diffusing capacity of the lung [2].

A retrospective study of 400 COPD patients revealed that low BMI ($p < 0.001$), age ($p < 0.0001$) and low arterial $O_2$ tension ($p = 0.05$) were significant independent predictors of increased mortality. After stratification of the group according to BMI, a threshold value of 25 kg/m² was identified below which the mortality risk was clearly increased [4].

Though there is no doubt about the usefulness of Oral Nutritional Supplements (ONS) in managing malnutrition in COPD patients, only a handful of publications are available in the literature on clinical trials with ONS in patients suffering from COPD and CF. Moreover, no clinical trial has so far been published on comparing the effectiveness of different ONS with different compositions. Therefore, a randomized, open-label, multicenter clinical trial will be run to determine, whether a new, condition-specific ONS (with a composition tailored to the needs of patients with decreased pulmonary functions) is more effective compared to a general ONS in improving the nutritional status in COPD and CF patients.

**Methods**

**Study design and participants**

The study is designed as a randomized, open-label, multicentre clinical trial with an intervention (n = 50) and a control group (n = 50). Patients at or above the age of 18 years suffering from COPD or CF, with an ECOG 0-2 status will be enrolled into the study. Further inclusion criteria include the ability of consuming oral nutritional supplementation, being managed by an outpatient clinic, life expectancy at least 6 months according to the treating physician, involuntary weight loss > 10% independently of the time frame or > 5% in the past 3 months and one of the following criteria is present: BMI < 20 kg/m² (if age < 70 years) or < 22 kg/m² (if age ≥ 70 years) or fat-free mass (FFM) ≤ 15 kg/m² in females or ≤ 17 kg/m² in males. Exclusion criteria include pregnancy / breastfeeding, previous use of ONS ≥ 1.5 kcal/ml, proven intestinal obstruction, co-morbidity with special dietary requirements (e.g. renal disease, diabetes mellitus), ascites, impaired hepatic functions (> 2x ULN, in case of proven hepatic metastatic, >5x ULN), acute or chronic renal failure (GFR < 30ml/min), severe anemia (Hgb < 80 g/l), uncontrolled nausea and/or vomiting, use of megestrol-acetate and/or steroids that influence metabolism, use of any ONS and/or food supplement in the previous 3 months, known intolerance or allergy to any component of the interventional or control ONS, participation in any clinical trial within 30 days prior to the baseline visit.

Patients will be recruited in 5 pulmonology centers in Hungary. Study visits will be performed at baseline, month 1, month 2 and end of study at month 3. Body weight, body mass index (BMI), FFM, upper arm circumference (UUC) and quality of life will be measured at baseline. At the month 1 and month 2 visits, body weight, BMI, FFM, UUC, and adherence to the prescribed nutritional therapy, while at the end of study visit body weight, BMI, FFM, UUC, quality of life-based on the SF36 questionnaire, and adherence to the prescribed nutritional therapy will be determined (Figure 1).

![Flowchart of study procedures](image)

**Figure 1:** Flowchart of study procedures.

The study has been approved by the Scientific and Research Ethic Committee of the Scientific Health Council of Hungary. Written informed consent will be obtained from all participants.

**Intervention**

Patients will be randomized to a 3-month nutritional therapy with either an ONS designed for the dietary management of disease-related malnutrition in lung diseases with decreased pulmonary functions (interventional group, n = 50), or an ONS recommended for the dietary management of disease-related malnutrition (control group, n = 50). The individual prescribed dose of the interventional and the control ONS will be calculated based on the nutritional needs and the oral food intake.
of the patients. Adherence to the prescribed ONS will be determined by a registry card where the patient documents the ONS consumed each day. The registry card will be checked at each visit and patients will be advised to adhere to the nutritional therapy by the treating physician.

**Randomization**

Patients will be randomized to either the intervention or the control ONS according to their order of appearance at the treating physician. Patients of Chinese origin will be, however, an exception: due to the rarity of such individuals in this patient population in Hungary, they will be handled separately, and they will be enrolled into the interventional and the control group in an equal number in their order of appearance at the clinical trial site.

**Outcomes**

The primary outcome is the body weight change measured in kgs from baseline to the end of study (month 3). Secondary outcomes include change in BMI, FFM, upper arm circumference, and quality of life. Adherence will also be included among the secondary outcomes.

**Sample size calculation**

Sample size calculation was based on the magnitude of type I and II errors, the expected change in the body weight as the primary outcome, and the magnitude of standard error seen in previous clinical studies. The conventional 5% type I error and the 20% type II error have been used in our clinical study ensuring a statistical power of 80%. The expected change in body weight that is able to influence the prognosis of the primary disease and the nutritional status of the patients has been determined as 3 kgs. A similar clinical trial [5] found that the magnitude of standard error of body weight change is 5-6 kgs. Based on these data, the number of patients need to be included in each study group could be calculated according to the following formula:

\[
 n = \frac{2(Z_\alpha + Z_{1-\beta})^2\sigma^2}{\Delta^2}
\]

With a standard error of 5 kg, the number of patients in each study group would be 44, while with a standard error of 6 kg the number of patients in each study group would be 63. According to the practical considerations, the number of patients in both study groups will be 50.

**Statistical analysis**

Descriptive statistics will be used for the presentation of results: mean and standard error in case of continuous variables, and distribution in case of discrete variables. To perform the descriptive statistics-related hypothesis testing, parametric statistical probes, such as independent paired-sample t-test, one-way ANOVA in case of continuous variables, while χ² test and Fisher's exact test in case of discrete variables will be used. Regression analyses will be applied when multiple variables are concerned. The type of regression analysis will be defined on the basis of the outcome tested (e.g. in case of survival-like data, Cox regression model will be used). The applicability criteria will be examined during the statistical hypothesis analyses.

**Discussion**

By population prevalence, one of the most frequent cachexia subtypes is COPD cachexia [6]. Treatment for cachexia has concentrated on increasing food intake, although that alone is unable to reverse the metabolic changes [7]. Due to the hypercatabolic state and increased protein breakdown seen in malnourished / cachectic patients, increased energy and protein intake is vital in slowing down / stabilizing or even reversing weight loss and lean body mass /muscle wasting in cachectic patients [8-10]. However, due to the strain that digestion of the macronutrients causes for the pulmonary functions, the source of energy may also play a crucial role in the efficacy of nutrition with ONS in such patients.

High-calorie intake, especially in the form of carbohydrates, increase carbon-dioxide (CO₂) production and may precipitate respiratory failure in patients with severe lung disease. Energy obtained from fat results in less CO₂ and thus may permit a reduced level of alveolar ventilation for any given arterial CO₂ tension [11]. In a study of 10 patients with severe stable COPD, consumption of a carbohydrate-rich drink resulted in significantly greater increases of minute ventilation, CO₂ level, oxygen consumption, respiratory quotient, arterial CO₂ tension, and a greater fall in the distance walked in 6 minutes, than the consumption of a fat-rich drink. The increase in the CO₂ level correlated significantly with the decrease in the 6-minute walking distance [12]. In a study of 12 clinically stable, ambulatory patients with COPD, compared to the high-fat diet, the high-carbohydrate diet led to a significantly higher production of CO₂, minute ventilation, oxygen consumption, and respiratory quotient 30-60 minutes after the consumption, and the differences could last for about 1.5 hour. According to these results, a high-fat diet is more beneficial to the
COPD patients than a high-carbohydrate diet [13].

Some cytokines are also involved in the development of cachexia: the production of pro-inflammatory cytokines such as CRP, interleukin-6, proteolysis-inducing factor and lipid-mobilizing factor by tumor cells is the initial mechanism [14]. Cachectic and non-cachectic patients had a greater systemic inflammatory response \( (p < 0.05) \) than did healthy controls, as reflected in C-reactive protein, soluble TNF-R75 and IL-6 concentrations [15]. In a study of 64 COPD patients, 400 kilocalories per day of an omega-3 PUFA-rich supplement (0.6 g α-linolenic acid + 0.4 g ω-6 fatty acids) or an omega-6 fatty acids-rich supplement (0.07 g α-linolenic acid 0.93 g ω-6 fatty acids) were administered to the patients for 2 years. In 6-min walk testing, the dyspnea Borg scale significantly improved in the ω-3-supplemented group, while no such effect could be demonstrated in the ω-6-supplemented patients [16].

Data from the literature suggest that muscle-strength preserving agents, such as carnitine, can improve exercise tolerance and inspiratory muscle strength in COPD patients, as well as reduce lactate production [17].

Our study is aimed to demonstrate that clinical nutrition with an ONS designed according to the special nutritional needs of malnourished patients with decreased pulmonary functions may be more effective and may ensure higher adherence than nutrition of these patients with a general ONS.

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References


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