ID: COPD-141316051 **NCT02251496**

COPD: Oral Nutrition Supplements vs. Energy- and Protein Dense in Between Meal Snacks.

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METHODS

Study design and participants

This study was a randomised trial and registered at clinicaltrials.gov on September 25, 2014. ClinicalTrials.gov identifier: NCT02251496. The study was approved by the National Bioethics Committee (VSN14-066-S1), Chief medical officer Landspitali (LSH 68-14) and Data Protection Authority (2014/908) and conducted in line with the Declaration of Helsinki. The study follows the CONSORT 2010 statement: extension to randomised pilot and feasibility trials. (Eldridge et al., 2016)

Patients with a clinical diagnoses of COPD who had been recently admitted to the Department of Respiratory Medicine at Landspitali University Hospital were screened for possible nutritional risk (score ≥4) by a trained researcher using a validated nutritional screening tool. (Ingadottir et al.; Thorsdottir, Gunnarsdottir, & Eriksen, 2001) The Icelandic Simple Screening (ISS) used is recommended by the clinical guidelines for hospital nutrition at Landspitali (Friðriksdóttir, 2011) and has been validated against a full nutritional assessment in COPD patients (Thorsdottir et al., 2001) and predicts mortality in COPD patients. (Ingadottir et al.) ISS gathers information on BMI, unintentional weight loss, age, co-morbidities, recent hospitalisation and a range of symptoms that impact nutritional intake during the last weeks or months (vomiting, diarrhoea, loss of appetite or nausea, difficulties in chewing or swallowing).

All eligible patients who were able to eat orally, and had an anticipated length of hospitalisation of >3 days were invited to participate in the study. The most common reason for admission was acute exacerbation of COPD. Written informed consent was obtained from all participants.

Patients diagnosed with cancer, dysphagia, food allergy or intolerance and anatomical obstructions preventing oral food intake were excluded. Patients not able to sign informed consent due to cognitive issues were also excluded.

Socio-demographic data (age, gender and smoking status) were collected from electronic medical records SAGA (TM software 3.1.39.9).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to either an ONS group (ONS) or snacks group. Random sequence generation was performed using randomisation codes produced by Microsoft Excel for Windows 2007. Randomisation, allocation of patients to groups, nutritional intervention and outcome assessments were performed by one researcher

(ARI). Due to the nature of the intervention it was not possible to perform a blinded study. Randomisation took place after screening for nutritional risk and prior to baseline assessment.

Procedures

This study was originally designed as a randomized trial to investigate the effects of snacks on body weight and QoL in COPD patients compared to ONS with a planned enrolment of 200 subjects (ClinicalTrials.gov, number NCT02251496). Despite screening 492 subjects only 76 subjects were eligible indicating that recruitment is challenging in this population and clinical setting. Recruitment rates were lower than expected which led to a change in the study protocol to a randomised feasibility trial as funding was limited to three years. One reason for low recruitment rates might be over strict inclusion criteria. More details on study recruitment are provided in the results.

Nutritional screening was undertaken on admission using the validated screening tool as recommended for use at the Landspitali. (Friðriksdóttir, 2011; Ingadottir et al.; Thorsdottir et al., 2001) A total score of ≥4 is considered 'at nutritional risk'.

After providing informed consent, subjects were randomly allocated to one of two groups. Subjects in group 1 were provided with ONS and subjects in group 2 were provided with snacks (Table 1). The intervention started in hospital and was continued for 12 months after discharge from the hospital.

Table 1 Nutritional content of each intervention products.

Oral nutritional supplement drinks			
Product	Portion size	Energy (kcal)	Protein (g)
Nutridrink compact (Nutricia) e.g. vanilla, banana, strawberry and chocolate	125 ml	300	12
Nutridrink compact fiber (Nutricia) -vanilla, strawberry and mokka	125 ml	300	12
Nutridrink (Nutricia) -vanilla, strawberry, banana, and chocolate	200 ml	300	12
Nutridrink juice style (Nutricia) e.g. blackcurrant, apple and orange	200 ml	300	8
Nutridrink creme (Nutricia) -forest fruit and chocolate	125 g	200	12
Mean		**280**	**11**

In-between meals snack			
Product	Portion size	Energy (kcal)	Protein (g)
Blueberry skyr with cream (MS Dairies)	Skyr 140 g Cream 20 ml	254	17
Two mini skyr with cream (MS Dairies) -vanilla, strawberry and banana	Skyr 167 g Cream 20 ml	274	16
Rye bread (Myllan) with liver paté (Ora) and butter (MS Dairies)	Rye bread 55 g Liver paté 40 g Butter 10 g	313	7
Pan bread (Myllan) with ham- and egg salat (Sómi)	Pan bread 47 g Salat 55 g	262	8
Oat biscuits (Frón) with butter, cheese and glass of milk (MS Dairies)	Oat biscuit 20 g Butter 10 g Cheese 20 g Milk 150 ml	342	12
Nutbar (Himneskt) with milk (MS Dairies)	Nutbar 40 g Milk 150 ml	302	10
Cheesecake (MS Dairies) -raspberry and chocolate	100 g	322	6
Mean		**286**	**11**

Subjects in group 1 were offered a variety of flavours and pack sizes of ONS free of charge. As the hospital had a contract with Nutricia (Icepharma, Iceland) that was the brand used. Subjects in group 2 were provided with snacks free of charge, based on common Icelandic food products, e.g., Icelandic skyr which is a high protein milk product similar to yogurt. Patients in both groups were encouraged to consume two or more ONS or Snacks daily providing approximately 600 kcal/day and approximately 22 g protein/day in addition to regular food depending on which group they were in.(Collins, Stratton, & Elia, 2012; Ferreira, Brooks, White, & Goldstein, 2012)

The selected ONS were delivered to the patient's home or picked up at the wholesaler and the food packages were delivered to patient's home or collected from the hospital, according to patient preference. It was assumed that each delivery of ONS and Snacks would last for one month and two to three weeks, respectively. A leaflet designed for this study was provided with pictures of different ONS or each snack and written advice regarding their use such as suggestions on timing of intake, choosing a lower volume (125 ml each) when appetite was poor (ONS) and choice of different meals (Snacks). For some items, patients had to portion the snacks themselves, e.g., a whole cheesecake, because the minimal available pack size was more than one portion.

Verbal advice on the use of each intervention was also given to both groups, e.g., ONS should be used from the fridge and snacks with less expiry date should be used first.

All patients could phone the study investigator if they needed more ONS or snacks and every month each patient received a call to ascertain the quantity remaining. If patients were admitted to hospital during the study period they received ONS or snacks according to randomisation during their hospital stay.

During every follow-up appointment and during any hospital readmissions similar time was spent with each group.

Outcomes

Outcomes related to feasibility were percentage of eligible subjects that accepted participation (recruitment), percentage of included subjects that finished the 12 months intervention period (retention), the feasibility of undertaking functional assessment and use of ONS/snacks assessed by 24 hour recalls (compliance).

The primary outcome was efficacy of the interventions assessed as weight change from baseline to one year from admission to the hospital. Assessment of body composition i.e.

fat mass, fat free mass and muscle mass was conducted using a portable, multi- frequency (20kHz, 100kHz) bioelectrical impedance analysis (BIA) device (InBody230 Co., Ltd. Korea). The method has previously been validated in stable COPD patients. (Schols, Broekhuizen, Weling-Scheepers, & Wouters, 2005)

The secondary outcome measures were QoL measured using the St George's Respiratory Questionnaire (SGRQ). This validated questionnaire is based on 76 items used to calculate three component scores: symptoms, activity and impact, and a total score. A score of 100 represents worst possible health status and a score of 0 represents best possible health status. (Jones, Quirk, Baveystock, & Littlejohns, 1992) A change of 4 points in the SGRQ total score is considered the minimum clinically relevant difference. (Jones, 2002)

Other outcomes measures included were forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) measured by spirometry (Jaeger MS-PFT®, Care Fusion, San Diego, USA), (Vogelmeier et al., 2017) functional performance using several tests validated in COPD patients were included: six-minute walk distance (6MWD), (Singh et al., 2014) timed up and go (TUG), (Mesquita et al., 2016) 30 second chair stand (Kato et al., 2014) and hand-grip strength (HGS) (Puhan, Siebeling, Zoller, Muggensturm, & ter Riet, 2013) measured by a handheld dynamometer (Jamar® Sammons Preston Rolyan, Boilingbrook, IL, USA) and energy- and protein intake during hospital stay and at home (two and four weeks after discharge).

Total energy- and protein intake during hospital stay was estimated using a validated plate diagram sheet (Bjornsdottir et al., 2013; Vilhjalmsdottir, Hinriksdottir, Pordardottir, Porsdottir, & Gunnarsdtotir, 2013) for three days, starting on the first day of participation in the study and after the intervention had started.

Energy- and protein intake at home was assessed using the 24-hour recall method, (Salvador Castell, Serra-Majem, & Ribas-Barba, 2015) two and four weeks after hospital discharge and analysed using the ICEFOOD nutritional analysis program. (Thorgeirsdottir et al., 2011) For full details of study assessments (see Appendix 1).

Statistical analysis

All statistical analyses were undertaken using IBM SPSS Statistics 24 and the level of significance was set at 0.05.

Our original power calculations were based on the primary outcome of difference in weight gain between the groups and change in weight to one year. Due to low recruitment rate

and lower participation rates than expected, post-hoc power calculations were performed based on our results.

The Kolmogorov-Smirnov test was used to test data normality. The independent t-test was used to test for differences between continuous data at baseline and the Pearson's chi-squared test was used for categorical data. Intention-to-treat analyses were conducted where the last observations were carried forward and used to assess treatment efficacy. All patients with at least two measures (baseline and one other) were included. Repeated measures ANCOVA was conducted to analyse mean changes in each follow up.

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